Pharmacoeconomic modelling for policy decision-making: the case of sofosbuvir for hepatitis C infection in South Africa

I Fraser

20098871

MPharm(Pharmacy Practice)

Thesis submitted in fulfillment of the requirements for the degree Doctor of Philosophy in Pharmacy Practice at the Potchefstroom Campus of the North-West University

Promoter: Dr JR Burger

Co-promoters: Prof MS Lubbe

Dr MW Sonderup

Dr MP Stander

May 2016

AKNOWLEDGEMENTS

This thesis would not have been possible without the assistance and support of several individuals. I would especially like to offer my sincere gratitude to the following individuals:

- Dr Johanita Burger, the promoter for this study, for her unremitting motivation and support. As a mentor, she facilitates thinking, encourages risks and supports struggles through guidance and understanding. With grace, humour and enthusiasm you have shared your knowledge and experience. Thank you for encouraging me to pursue excellence. I will never be able to give you enough credit for your support.
- Prof Martie Lubbe, the co-promoter for this study, for sharing her knowledge and valuable time. Sam Walton said: “Outstanding leaders go out of their way to boost the self-esteem of their personnel. If people believe in themselves, it's amazing what they can accomplish”. Thank you for all the years of your continued support and for all you have done for me since I started my post-graduate studies back in 2009.
- Dr Tienie Stander, co-promoter of this study, for his valued support and guidance. You encouraged me to take on this challenge and your confidence in me is deeply regarded. Thank you for sharing your extraordinary expertise and for your untiring commitment to this study.
- Dr Mark Sonderup, co-promoter for this study, for his invaluable knowledge and contribution. Thank you for agreeing to be part of this study and for the time you sacrificed to do so. Your expertise is highly valued and your support and guidance is sincerely appreciated.
- Dr George Dranitsaris for agreeing to be part of this study. I am grateful for your contribution and the time and patience taken to ensure the accuracy of the economic analyses.
- HeXor (Pty) Ltd for financial support. Their investment in me and this study has helped me more than I could ever give them credit for.
- Margreet Bergh, for her assistance with the construction of the model and analyses of the data in TreeAge. Thank you for always being willing to help, your patience, your words of encouragement and your kindness. You have taught me things beyond books and I will never be able to thank you enough.
- Mrs H Hoffman for her knowledge and assistance in the compilation of the reference list and for sending me relevant literature when she came across it.
- Engela Oosthuizen, for her immense assistance during this study and for formatting the final document. Your support and assistance with the administrative tasks surrounding this thesis were invaluable, but do not compare with the value of your friendship. Thank you for your kindness and selflessness.

- Cecile van Zyl for the language editing of the thesis and for the translation of the abstract.
- The members of staff from the Departments of Pharmacy Practice, Clinical Pharmacy, the School of Pharmacy and Faculty of Health Sciences for their encouragement.
- MUSA, the Department of Pharmacy Practice and the North-West University for financial support during the course of this study.
- My parents-in-law, Donald and Hanna, for taking an interest in my studies and always offering kind words of motivation. Thank you for your support and prayers when it was most needed.
- My parents Frannie and Linda, for always being my biggest supporters. Your encouragement and words of wisdom during trying times were invaluable. Thank you for always believing in me and for leading me through all of life's challenges through your exceptional example.
- My husband, Wayne, for helping me to realise this dream. They say the condition of a woman reflects to the world the kind of man her husband is, as it takes a strong man to lead and guide a strong woman, but it takes a stronger man to love and support her. Thank you for loving and supporting me. Thank you for being the one who not only holds me when I am at my best, but also picking me up and hugging me tight at my weakest moments. The achievement of my dream started with you believing in me.

"But they who wait for the Lord shall renew their strength; they shall mount up with wings like eagles; they shall run and not be weary; they shall walk and not faint" — Isaiah 40:31

I am grateful to my heavenly Father for giving me the courage, strength and perseverance to fulfil this dream.

PREFACE

This study is presented in article format.

The chapters in this thesis are outlined as follows:

- Chapter 1 provides an introduction and comprehensive overview of the study. It reflects on the background and motivation for the study, research questions, research objectives and the method of study employed.
- Chapter 2 is the literature review and focused on defining hepatitis C virus infection and researching all relevant aspects on the subject of the disease; including clinical features of the disease, routes of transmission, incubation period, risk factors, prevention, complications, diagnosis and testing, treatment and response.
- Chapter 3 consists of the results and discussions section of the thesis in the form of three manuscripts. Manuscript 1 was accepted for publication by PharmacoEconomics (refer to Annexure C). Manuscript 2 was submitted to Public Health (refer to Annexure C). Manuscript 3 will be submitted to Medical Decision Making.
- Chapter 4 contains the conclusion, recommendations and limitations of the study.
- Annexures and references will be included at the end of Chapter 4.

The co-authors listed in the manuscripts were promoters and co-promoters of this study. All manuscripts included in this thesis have been read and approved by all named authors and the order of authors listed in the manuscripts has been approved by all of the authors. I confirm that there are no other persons who satisfied the criteria for authorship, but are not listed.

The contributions of each author are subsequently outlined.

AUTHORS' CONTRIBUTIONS (MANUSCRIPT 1)

The contribution of each author for manuscript 1 entitled "Cost effectiveness modelling of sofosbuvir-containing regimens for chronic genotype 5 hepatitis C virus infection in South Africa" accepted for publication in PharmacoEconomics, is provided below:

Author	**Role in the study**
Ms I Fraser	Literature review Planning and designing the manuscript Model construction Data analyses Interpretation of results
Dr JR Burger (Promoter)	Supervision of concept of study and manuscript Supervision on writing of manuscript Reviewing the manuscript for final approval
Dr MW Sonderup (Co-promoter) Dr MP Stander (Co-promoter)	Co-supervision of concept of study and manuscript Evaluating model for clinical/technical accuracy Assistance with data collection (efficacy and cost) Reviewing the manuscript for final approval
Prof MS Lubbe (Co-promoter)	Co-supervision of concept of study and manuscript Reviewing the manuscript carefully for final approval
Dr G Dranitsaris (Co-author)	Reviewing the concept of the cost effectiveness model Reviewing the manuscript for final approval

The following statement provided by the co-authors confirms their roles in the study and their permission that the manuscript may form part of the dissertation.

I declare that I have approved the above-mentioned manuscript and that my role in this study, as indicated above, is a representation of my actual contribution, and I hereby give my consent that it may be published as part of the PhD thesis of I Fraser.

Dr JR Burger

Dr MW Sonderup

Prof MS Lubbe

Dr MP Stander

Dr G Dranitsaris

AUTHORS' CONTRIBUTIONS (MANUSCRIPT 2)

The contribution of each author for manuscript 2 entitled "Public health impact of sofosbuvir-based regimens for chronic hepatitis C virus infection in South Africa" submitted to Public Health, is provided below:

Author	**Role in the study**
Ms I Fraser	Literature review Planning and designing the manuscript Model construction Data analyses Interpretation of results
Dr JR Burger (Promoter)	Supervision of concept of study and manuscript Supervision on writing of manuscript Reviewing the manuscript for final approval
Prof MS Lubbe (Co-promoter) Dr MW Sonderup (Co-promoter) Dr MP Stander (Co-promoter)	Co-supervision of concept of study and manuscript Reviewing the manuscript for final approval

The following statement provided by the co-authors confirms their roles in the study and their permission that the manuscript may form part of the dissertation.

I declare that I have approved the above-mentioned manuscript and that my role in this study, as indicated above, is a representation of my actual contribution, and I hereby give my consent that it may be published as part of the PhD thesis of I Fraser.

Dr JR Burger

Dr MW Sonderup

Prof MS Lubbe

Dr MP Stander

AUTHORS' CONTRIBUTIONS (MANUSCRIPT 3)

The contribution of each author for manuscript 3 entitled "Budget impact analysis of sofosbuvir-based regimens for chronic hepatitis C in South Arica" is provided below:

Author	**Role in the study**
Ms I Fraser	Literature review Planning and designing the manuscript Model construction Data analyses Interpretation of results
Dr JR Burger (Promoter)	Supervision of concept of study and manuscript Supervision on writing of manuscript Reviewing the manuscript for final approval
Prof MS Lubbe (Co-promoter) Dr MP Stander (Co-promoter)	Co-supervision of concept of study and manuscript Reviewing the manuscript for final approval

The following statement provided by the co-authors confirms their roles in the study and their permission that the manuscript may form part of the dissertation.

I declare that I have approved the above-mentioned manuscript and that my role in this study, as indicated above, is a representation of my actual contribution, and I hereby give my consent that it may be published as part of the PhD thesis of I Fraser.

Dr JR Burger

Prof MS Lubbe

Dr MP Stander

ABSTRACT AND KEYWORDS

Thesis title: Pharmacoeconomic modelling for policy decision-making: the case of sofosbuvir for hepatitis C infection in South Africa

Keywords: Hepatitis C, sofosbuvir, ribavirin, peg-interferon, pharmacoeconomic modelling, cost-effectiveness, public health impact, budget impact

Abstract

The main purpose of this study was to empower policy-makers to make informed decisions about the treatment of chronic hepatitis C in light of the vast array of novel treatments being developed for this disease. A two-dimensional research method was employed, consisting of a literature review and an empirical investigation. The main objective of the literature review was to provide background to the study by conceptualising chronic hepatitis C and other relevant aspects of the disease. The empirical investigation consisted of constructing a decision-analytic Markov model based on the natural history of chronic hepatitis C virus infection and using the resulting model to determine the cost-effectiveness, the public health impact and the budget impact of sofosbuvir, or sofosbuvir-containing regimens for hepatitis C in South Africa.

The study design was founded on the concept of pharmacoeconomic modelling and the target population of this research project was patients with chronic hepatitis C virus infection living in South Africa. During the modelling phase, a mathematical decision-analytical model was constructed to simulate the progression of hepatitis C virus infection. The model was then populated with data, including annual transition probabilities, cost data, effectiveness data and utility values. Additional data required for the public health analysis and budget impact analysis included South African prevalence and incidence data. Available literature served as the data source for the transition probabilities, treatment efficacy and health state utilities used in this model. Drug costs were taken from the Official Pharmaceutical Bluebook, whereas costs related to disease or treatment management, including outpatient attendance and inpatient palliative care, were taken from the National Health Referencing Price List. Cost estimates for procedures, diagnostic tests and inpatient admissions for complications of CHC were obtained from private sector cost data. Once the model was complete, TreeAge Pro software (TreeAge Pro 2014, R1.2) used the visual model structure to automatically generate the algorithms required to evaluate the model and yield results.

Outcomes from the cost-effectiveness model show that the fixed-dose combination of sofosbuvir-ledipasvir will be cost-effective for South African patients infected with hepatitis C virus genotype 5 at a price of R123 193 (US$10 500) for 12 weeks.

Assuming that only 0.18% of all diagnosed patients with hepatitis C are treated annually, liver-related morbidity and mortality in South Africa will continue to rise over the next two decades; with a 32% increase in the number of hepatocellular carcinoma cases, a 38% increase in decompensated cirrhosis cases and a 58.5% increase in the number of liver-related deaths, irrespective of the treatment option chosen. However, if policy-makers and physicians were to aim to scale up the active treatment of hepatitis C to at least 10% of all diagnosed non-cirrhotic chronic hepatitis C patients annually, the impact of antiviral therapy on chronic hepatitis C virus infections is more demonstrable. Furthermore, if policy-makers were to decide to treat patients with sofosbuvir-based regimens such as sofosbuvir-ledipasvir or sofosbuvir + pegylated interferon and ribavirin, instead of the current standard of care, a total of 185 cases of decompensated cirrhosis, 133 cases of hepatocellular carcinoma and 183 liver-related deaths could be avoided over the next two decades.

Outcomes from the budget impact analysis showed that the estimated expenditure on hepatitis C virus in South Africa is approximately R29 million per annum, assuming that 100 new patients are treated with the current standard of care each year, and those who failed treatment are followed up. Assuming a price of R82 129.32 (US$7 000) for a 12-week course of sofosbuvir and R123 193 (US$10,500) for sofosbuvir-ledipasvir, treating and managing the same number of patients with sofosbuvir-based therapy would result in a cost-saving of more than R5 000 000 (US$426 157) per year, or R26 338 793 (US$2 244 893) over five years. The estimated budget required to treat ~80% of all patients currently infected with hepatitis C virus in South Africa by the end of 2020 is approximately R76 billion.

The next decade will be will be one of rapid innovation in antiviral therapy for chronic hepatitis C. Decision models can help design and evaluate new treatment paradigms that maximise benefits to society as a whole, while promoting a patient-centred healthcare system. Pharmacoeconomic analyses should be used by policy decision-makers as tools to sustain a healthcare system that can continue to reward innovation and afford the next generation of ‘miracle drugs’, such as sofosbuvir.

OPSOMMING EN SLEUTELWOORDE

Titel van proefskrif: Farmako-ekonomiese modellering vir beleidsbesluitneming: Die geval van hepatitis C-infeksie in Suid-Afrika

Sleutelwoorde: Hepatitis C, sofosbuvir, ribavirin, peg-interferon, farmako-ekonomiese modellering, koste-effektiwiteit, publieke gesondheidsimpak, begrotingsimpak

Opsomming

Die hoofdoel van hierdie studie was om beleidmakers te bemagtig om ingeligte besluite te neem oor die behandeling van kroniese hepatitis C, gesien in die lig van die groot verskeidenheid nuwe behandelings wat vir hierdie siekte ontwikkel word. ’n Twee-dimensionele navorsingsmetode is gevolg, bestaande uit ’n literatuuroorsig en ’n empiriese ondersoek. Die hoofdoelstelling van die literatuuroorsig was om ’n agtergrond tot die studie te skep, deur kroniese hepatitis C en ander relevante aspekte van die siekte te konseptualiseer. Die empiriese ondersoek het bestaan uit die samestelling van ’n besluit-analitiese Markov-model gebaseer op die natuurlike geskiedenis van die hepatitis C-virus-infeksie en om die resulterende model te gebruik om die koste-effektiwiteit, die publieke gesondheidsimpak en die begrotingsimpak van sofosbuvir, of sofosbuvir-bevattende regimente vir hepatitis C in Suid-Afrika te bepaal.

Die studie-ontwerp is gegrond op die konsep van farmako-ekonomiese modellering en die teikenpopulasie van hierdie navorsingsprojek was pasiënte met kroniese hepatitis C virus-infeksie wat in Suid-Afrika woon. Gedurende die modelleringsfase is ’n wiskundige analitiese-besluitnemingsmodel gebou wat die vordering van hepatitis C virus-infeksie simuleer. Die model is daarna ingevul met data, insluitend jaarlikse vorderingswaarskynlikhede, koste data, doeltreffendheidsdata en nutwaardes. Addisionele data wat vereis is vir die publieke gesondheidsimpak ontleding en die begrotingsimpak ontleding, het Suid-Afrikaanse voorkomsdata ingesluit. Beskikbare literatuur het gedien as die databron vir vorderingswaarskynlikhede, behandelingsdoeltreffendheid en gesondheidstoestand nutwaardes wat gebruik is in hierdie model. Geneesmiddel pryse is verkry vanuit die Offisiële Farmaseutiese Blouboek, terwyl kostes verwand aan siekte- of behandelingsbestuur verkry is vanuit die Nasionale Gesondheidsverwysings Pryslys. Koste skattings vir prosedures, diagnostiese toetse en binnepasiënt opnames vir komplikasies van kroniese hepatitis C is verkry vanuit privaat sektor koste data. Na afhandeling van die model, het TreeAge Pro sagteware (TreeAge Pro 2014, R1.2) die visuele model struktuur gebruik om outomaties algoritmes te genereer wat nodig was om die model te evalueer en resultate op te lewer.

Uitkomstes van die koste-effektiwiteitsmodel toon dat die vaste dosis-kombinasie van sofosbuvir-ledipasvir koste-effektief sal wees vir Suid-Afrikaanse pasiënte geïnfekteer met die hepatitis C-virus, genotipe 5, teen 'n prys van R123 193 (US$10 500) vir 12 weke.

Indien aanvaar word dat slegs 0.18% van alle pasiënte gediagnoseer met hepatitis C jaarliks behandel word, sal lewerverwante morbiditeit en sterftes in Suid-Afrika voortgaan om oor die volgende twee dekades te styg; met 'n 32%-toename in die aantal HCC-gevalle, 'n 38%-toename in gedekompenseerde sirrose-gevalle en 'n 58.5%-toename in die aantal lewer-verwante sterftes, ongeag die gekose behandeling. Indien beleidmakers en dokters egter poog om die aktiewe behandeling van hepatitis C na ten minste 10% van alle gediagnoseerde nie-sirrotiese kroniese hepatitis C-pasiënte jaarliks te verhoog, sal die impak van antivirale terapie op die hepatitis C-virus-infeksies meer aantoonbaar wees. Verder, indien beleidmakers sou besluit om pasiënte te behandel met sofosbuvir-gebaseerde regimente soos sofosbuvir-ledipasvir of sofosbuvir + peg-interferon en ribavirin, in stede van die huidige behandelingstandaard, sal 'n totaal van 185 gevalle van gedekompenseerde sirrose, 133 gevalle van hepatosellulêre karsinome en 183 lewer-verwante sterftes oor die volgende twee dekades vermy word.

Uitkomste vanuit die begrotingsimpak-analise toon die beraamde besteding op HCV in Suid-Afrika as ongeveer R29 miljoen per jaar, met die aanvaarding dat 100 nuwe pasiënte elke jaar behandel word met die huidige behandelingstandaard, en dat dié wat behandeling nie nagekom het nie, opgevolg word. Indien 'n prys van R82 129.32 (US$7 000) vir 'n 12 weke-kursus van sofosbuvir en 'n prys van R123 193 (US$10,500) vir sofosbuvir-ledipasvir aanvaar word, sal die behandeling van dieselfde aantal pasiënte met sofosbuvir-gebaseerde terapie lei tot 'n kostebesparing van meer as R5 000 000 (US$426 157) per jaar, of R26 338 793 (US$2 244 893) oor vyf jaar. Die beraamde begroting benodig om ~80% van alle pasiënte tans geïnfekteer met HCV in Suid-Afrika teen die einde van 2020 te behandel, is ongeveer R76 miljard.

Die volgende dekade sal een wees van vinnige innovasie in die antivirale behandeling van kroniese hepatitis C. Besluitsmodelle kan help met die ontwerp en evaluering van nuwe behandelingsparadigmas wat die voordele vir die samelewing as geheel maksimeer, terwyl 'n pasiënt-gesentreerde gesondheidsorgstelsel gepromoveer word. Farmako-ekonomiese analises behoort deur beleidmakers as hulpmiddels gebruik te word om 'n gesondheidsorgstelsel te handhaaf wat kan voortgaan om innovasie te beloon en om die volgende generasie wondermiddels, soos sofosbuvir, te kan bekostig.

LIST OF SYNONYMS AND ABBREVIATIONS

A

AASLD	American Association for the Study of Liver Disease
Ab	antibody
AFP	alpha fetoprotein
Ag	antigen
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase

B

BHF	Board of Healthcare Funders
BOC	boceprevir
BRICS	Brazil, Russia, India, Canada, South Africa

C

CADTH	Canadian Agency for Drugs and Technologies in Health
CASL	Canadian Association for the Study of the Liver
CDC	Centres for Disease Control and Prevention
CDEC	Canadian Drug Expert Committee (CDEC) of the (CADTH
CE	cost-effectiveness
CHC	chronic hepatitis C
CLD	chronic liver disease
CLD-Q	Chronic Liver Disease Questionnaire
CMS	Council for Medical Schemes

D

DAAs	direct-acting antiviral
DNA	deoxyribonucleic acid
DoH	Department of Health
DRC	Democratic Republic of the Congo

E

EASL	European Association for the Study of the Liver
ELISA	enzyme linked immuno-absorbent assay
EVR	early virologic response
EOT	end-of-treatment

LIST OF SYNONYMS AND ABBREVIATIONS (continued)

E (continued)

EQ-5D	EuroQol Five Dimension
ETR	end-of-treatment response

F

FBC	full blood count
FDA	Food and Drug Administration

G

GBD	Global burden of disease
GT	genotype
GGT	gamma glutamyl transferase

H

HAART	highly active antiretroviral therapy
HAV	hepatitis A virus
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
Hct	haematocrit
HCV	hepatitis C virus
HCV-G1	hepatitis C virus genotype 1
HCV-G2	hepatitis C virus genotype 2
HCV-G3	hepatitis C virus genotype 3
HCV-G4	hepatitis C virus genotype 4
HCV-G5	hepatitis C virus genotype 5
HCV-G6	hepatitis C virus genotype 6
Hgb	haemoglobin
HIV	human immunodeficiency virus
HQL-Q	Hepatitis Quality-of-life Questionnaire
HREC	Health Research Ethics Committee
HRQoL	health-related quality-of-life
HUI	Health Utilities Index

I

IASL	International Association for the Study of the Liver
ICER	incremental cost-effectiveness ratio
IDSA	Infectious Diseases Society of America

LIST OF SYNONYMS AND ABBREVIATIONS (continued)

I (continued)

IgG	immunoglobulin G
IMPDH	inosine monophosphate dehydrogenase
INR	international normalised ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research

L

LFT	liver function test
LDQoL-Q	Liver Disease Quality-of-life Questionnaire
LDSI	Liver Disease Symptom Index
LDV	ledipasvir

M

MIU	milli international units
MSM	men who have sex with men

N

NHREC	National Health Research Ethics Council
NHRPL	National Health Referencing Price List
NNPI	non-nucleoside polymerase inhibitor
NPI	nucleoside polymerase inhibitor

P

PCR	polymerase chain reaction
PBM	pharmaceutical benefit manager
PEG	polyethylene glycol
peg-INF	pegylated interferon
PI	protease inhibitor
PMB	prescribed minimum benefit
PLT	platelet
PT	prothrombin time

Q

QALY	quality-adjusted-life-years
QoL	quality-of-life

LIST OF SYNONYMS AND ABBREVIATIONS (continued)

R

RBV	ribavirin
RCT	randomised controlled trial
RIBA	recombinant immunoblot assay
RNA	ribonucleic acid
RT-PCR	reverse transcription-polymerase chain reaction
RVR	rapid virologic response

S

sAb	serum antibody
sAg	serum antigen
SAMPR	South African Medicine Price Registry
SEP	single exit price
SF-6D	Short Form Six Dimension
SG	standard gamble
SOC	standard of care
SOF	sofosbuvir
SOF/LDV	sofosbuvir-ledipasvir
SOF-TT	sofosbuvir triple therapy
STATS SA	Statistics South Africa
STM	state transition model
SVR	sustained virologic response

T

TLV	telaprevir
TFT	thyroid function test
TT	triple therapy
TTO	time trade-off

U

U&E	urea and electrolytes
UK	United Kingdom
USA	United States of America
USD	United States Dollar

V

VSR	visual rating scale

W

WHO	World Health Organization
WTP	willingness-to-pay

Z

ZAR	South African Rand

GLOSSARY

For the purpose of this research project, the following concepts are defined:

– Annual transition probability: *"The probability of progressing from a given health/disease state to the next health/disease state in a Markov process in a one-year cycle"* (Ademi *et al*., 2012:947).

– Ascites: *"An abnormal intraperitoneal accumulation of protein and electrolytes"* (Mosby's Dictionary of Medicine, Nursing & Health Professions, 2006:149).

– Breakthrough response: *"Temporary virological and biochemical response occurring during therapy followed by reappearance of HCV RNA and/or abnormal ALT level before the end of treatment"* (Ghany *et al*., 2009:1341).

– Budget: *"An estimate of income and expenditure for a set period of time"* (Oxford University Press, 2016).

– Budget impact analysis: *"A budget impact analyses addresses the expected changes in the expenditure of a health care system after the adoption of a new intervention. It is a means of synthesising available knowledge at the time of a coverage or formulary listing decision to estimate the likely financial consequences of that decision for a health care system"* (Sullivan *et al*., 2014:6).

– Cirrhosis: *"A chronic condition in which the liver parenchyma progressively degenerates"* (Weller, 2005:82).

– Chronic hepatitis: *"A state in which symptoms of hepatitis continue for several months and may increase in severity"* (Mosby's Dictionary of Medicine, Nursing & Health Professions, 2006:382).

– Cost-effectiveness analysis: *"A cost-effectiveness analysis compares the costs and health effects of an intervention to assess the extent to which it can be regarded as providing value for money"* (Phillips, 2009:1).

– Early virological response (EVR): *"a ≥ 2 log reduction in HCV RNA level compared to baseline CHV RNA level (partial EVR) or HCV RNA negative at treatment week 12 (complete EVR). EVR may be utilised to predict a lack of SVR"* (Davis, 2002:S146).

– End-of-treatment response (EOT): *"HCV RNA negative by a sensitive test at the end of 24 or 48 weeks of treatment"* (Ghany *et al*., 2009:1341).

GLOSSARY (continued)

– Formulary: *"A collation of pharmaceutical products that reflect the current verdict of policy-makers of a given organisation and specialists in the diagnosis and treatment of disease"* (Suh *et al*., 2002:162).

– Genotype: *"The genetic constitution of an individual or group, as determined by the particular set of genes it possesses; the genetic information carried by a pair of alleles, which determines a particular characteristic"* (Oxford Dictionary of Nursing, 2003:195).

– Health information: *"Information about all resources, organisations and actors that are involved in the regulation, financing, and provision of actions whose primary intent is to protect, promote or improve health"* (WHO, 2003).

– HRQoL: *"The value assigned to duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy"* (Patrick and Erickson as quoted by Feeny, 2000:II-152).

– Hepatitis: *"Inflammation of the liver characterized by diffuse or patchy necrosis"* (Beers, *et al.*, 2006:219).

– Hepatitis A: *"A virus disease with a short incubation period (usually 15-50 days), caused by hepatitis A virus (family Picornaviridae, genus Hepatovirus) and often transmitted by the fecal-oral route; may be inapparent, mild, severe, or occasionally fatal, and occurs sporadically or in epidemics, commonly in school-age children and young adults; necrosis of periportal liver cells with lymphocytic and plasma cell infiltration is characteristic, and jaundice is a common symptom"* (Stedman's Medical Dictionary for the Health Professions and Nursing, 2005:1563).

– Hepatitis B: *"A virus disease with a long incubation period (usually 50-160 days), caused by hepatitis B virus (Hepaduaviridae, genus Orthohepaduavirus); transmitted by blood or blood products, contaminated needles or instruments, or sexual contact; differs from hepatitis A in having a higher mortality rate and in the possibility of progression to a chronic diseases, a carrier state or both"* (Stedman's Medical Dictionary for the Health Professions and Nursing, 2005:1563).

– Hepatitis C: *"A viral hepatitis caused by the hepatitis C virus; usually mild but often progressing to a chronic stage; the most prevalent type of post transfusion hepatitis"* (Stedman's Medical Dictionary for the Health Professions and Nursing, 2005:661).

GLOSSARY (continued)

– Hepatitis C virus: *"A non-A, non-B virus that causes post transfusion hepatitis"* (Stedman's Medical Dictionary for the Health Professions and Nursing, 2005:661).

– Incremental cost-effectiveness ratio (ICER): *"One-dimensional summary measure of the additional cost of one unit of outcome gained by one strategy compared with another".* The formula for the calculation of the ICER is given by Phillips (2009:1) as:

$$ICER = \frac{\text{difference in cost between programmes P1 and P2}}{\text{difference in health effects between programmes P1 and P2}}$$

– Nonresponse: *"HCV RNA remains detectable and/or ALT fails to normalise throughout the treatment phase. When a conflicting virological and biochemical response occurs, the virological response should take precedence when interpreting the response to therapy"* (Davis, 2002:S146).

– Oesophageal varices: *"A complex of engorged longitudinal veins at the lower end of the oesophagus"* (Mosby's Dictionary of Medicine, Nursing & Health Professions, 2006:676).

– Pharmacoeconomic model: *"An analytic methodology that accounts for events over time and across populations, that is based on data drawn from primary and/or secondary sources and whose purpose is to estimate the effects of an intervention on valued health consequences and costs"* (Weinstein *et al*., 2003:4).

– Pharmacoeconomics: *"The description and analysis of the cost of drug therapy to health care systems and society"* (Bootman *et al*., 1996:8).

– Public health: *"Refers to all organized measures (whether public or private) to prevent disease, promote health, and prolong life among the population as a whole. Its activities aim to provide conditions in which people can be healthy and focus on entire populations, not on individual patients or diseases"* (WHO, 2016).

– Public health impact analysis: *"A systematic process that uses an array of data sources and analytic methods and considers input from stakeholders to determine the potential effects of a proposed policy, plan, program, or project on the health of a population and the distribution of the effects within the population"* (Quigley *et al*., 2006:2).

GLOSSARY (continued)

– Quality-of-life: *"An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"* (WHO, 1997).

– Rapid virological response (RVR): *"When HCV RNA is negative at treatment week 4 by a sensitive PCR-based quantitative assay. RVR may allow shortening of course for genotypes 2 and 3 and possibly genotype 1 with low viral load"* (Fried *et al.*, 2011:69).

– Sensitivity analysis: *"A technique that allows a reviewer to assess the impact that changes in a certain parameter, or parameters, will have on a model's results. It can help the reviewer to determine which parameters are the key drivers of a model's results"* (Taylor, 2009:2).

– Sustained virological response (SVR): *"Clearance of HCV RNA from the blood and persistent normalisation of serum ALT levels observed 6-12 months after therapy has ended"* (Ghany *et al*., 2009:1341).

– Third party payer: *"Insurer, government, or any other organisation that pays for health care expenses for an individual"* (LaFleur Brooks & LaFleur Brooks, 2013:e27).

– Transient or relapsing response: *"Complete virological and biochemical response at end of treatment followed by the re-emergence of virus and/or elevation of ALT levels during follow-up"* (Botha *et al.*, 2010).

– Treatment-experienced: *"A person is considered to be treatment-experienced if they have already taken one or more forms of medication to treat a particular illness"* (Boskey, 2015).

– Treatment-naïve: *"A person is considered to be treatment-naive if they have never undergone treatment for a particular illness"* (Boskey, 2015).

– TreeAge Pro Healthcare 2014 software: *"A visual modelling tool that allows one to build and analyse decision trees and Markov models"* (TreeAge Software, Inc., 2015).

– Triple therapy: Treatment of chronic HCV infection with a combination of pegylated-interferon, ribavirin and sofosbuvir.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1: INTRODUCTION AND STUDY OVERVIEW

This chapter represents the introduction and overview of the study. It reflects on the background and motivation for the study, research questions, research objectives and the method of study employed.

1.1 Background and study rationale

With the introduction of a new drug into the pharmaceutical market, the safety and efficacy thereof are always the primary concerns. Still, it is crucial to determine whether the added benefit of a novel treatment is worth the healthcare resources spent (Pharand, 2002:114).

Healthcare funders are struggling to cover escalating health expenditure and in a financially strained healthcare market, novel medical technology is generally seen as an expensive luxury. The use of the right technology, however, may potentially decrease the overall cost of medical treatment and improve patient outcomes (Lee & Davies, 2013). Consequently, decision-makers at all levels (national, regional, hospital, primary care, and managed care) have the unfortunate task of deciding which therapeutic options to make available to their patients or members. The development of a formulary is one of the tools that healthcare funders can employ to aid in decision-making and ultimately regulate drug costs (Walkom *et al*., 2006:374).

According to Suh *et al*. (2002:162), a formulary is *"a collation of pharmaceutical products that reflects the current verdict of policy-makers of a given organisation and specialists in the diagnosis and treatment of disease".* A medicine formulary results from unambiguous decision-making to include or exclude certain medications from the alternative drugs available to be prescribed. Although expenditure on drug therapy is an indispensable element in formulary development and healthcare decision-making, the value of drug therapy, i.e. a function of its costs as well as its benefits, should be of greatest interest to decision-makers (Walkom *et al*., 2006:374; Walley, 2004:68). Pharmacoeconomics offer a comprehensive analytic framework to evaluate the relative value of treatment alternatives offered to society (Bootman & Skrepnek, 2012:3).

Pharmacoeconomics have been defined as *"the description and analysis of the cost of drug therapy to healthcare systems and society"* and include any study designed to identify, measure and compare the cost and consequences of pharmaceutical products and services (Bootman *et al*., 1996:8). The incentive for pharmacoeconomic evaluations is monetary, as most novel technologies are costly, while resources are scarce (Malone, 2005:S7). However, the cost of drug acquisition should not be the sole determinative factor when selecting medication therapies; rather, various alternatives and their associated outcomes should be considered

(MacKinnon, 2013:151). The main objective of pharmacoeconomics is to provide the most efficient use of available resources, while considering both the cost and the value obtained from a particular medical intervention (Arenas-Guzman *et al*., 2005:34).

The architecture of pharmacoeconomic studies is typically derived from clinical trials conducted as part of the drug-development process. Results from clinical trials define the safety and efficacy of therapy, but it cannot determine whether a given therapy/intervention signifies good value for money for a specific organisation (Miller, 2005:3). Pharmacoeconomic evaluations take into account not only drug safety and efficacy, but also other parameters that finally affect the overall clinical effectiveness of an intervention (Thwaites & Townsend, 1998:175). Pharmacoeconomics deals with decisions on the population rather than patient level (Malone, 2005:S7). There are various research methods included within the framework of pharmacoeconomics, which include (among others) cost-minimisation, cost-effectiveness, cost-benefit, cost-of-illness, cost-utility, cost-consequences and decision-analysis, as well as quality-of-life and other humanistic assessments (Bootman *et al.,* 1996:8; Sharma *et al*., 2014:145, Walley, 2004:71).

In the current climate of rapidly increasing healthcare costs, pharmacoeconomics are becoming increasingly important as the scarcity of resources has demanded the need for more formalised approaches to support decision-making in healthcare (Ademi *et al*., 2012:944; Villa & Skrepnek, 2011:17). Healthcare payers are charged with the responsibility of achieving maximum profits or output with limited budgets. As the demands are often higher than the budget, there is a growing interest in tools that can inform decisions on the allocation of limited resources (Lancry *et al*., 2001:39). Decision-analysis is such a tool — it supports decision-makers in clinical practice to make informed and objective decisions when faced with complex and intricate decisions with important long-term consequences (Aleem *et al*., 2009:137).

Decision-analyses, in particular decision tables and trees, are the most commonly used models in pharmacoeconomic evaluations (MacKinnon, 2013:151). Given certain variables, decision-analysis allows for a systematic approach to decision-making that leads to the generation of economically quantifiable results (MacKinnon, 2013:153). Modelling techniques associated with decision-analysis allow options to be quantified and to be entered directly into the decision process. Modelling furthermore allows for the inclusion of uncertainty, which is an important component of real-world clinical treatment (Hay & Jackson, 1999:79). The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) defines a pharmacoeconomic model as *"an analytic methodology that accounts for events over time and across populations, that is based on data drawn from primary and/or secondary sources and whose purpose is to estimate the effects of an intervention on valued health consequences and costs"* (Weinstein *et al*., 2003:4). In other words, a pharmacoeconomic model is a logical, quantitative combination of

therapeutic and/or effectiveness data and information regarding resource consumption and costs. Models are built to assist decision-makers to estimate the total cost of a therapy (including drugs, diagnostic tests etc.) and its value for money (efficiency) expressed as a benefit-cost, cost-utility or cost-effectiveness ratio (Milne, 1998:121).

The current situation in hepatitis C virus (HCV) infection is an ideal example of where economic analysis may be particularly helpful in supporting decision-makers in quantifying and justifying the value of available treatment options. With an emerging array of potent and expensive therapies and increasingly powerful predictive tools, cost-effectiveness analysis can help provide context regarding the relative cost and health outcomes afforded by a huge array of options (Gellad *et al.,* 2012:1190).

After its formal identification and genome sequencing in 1989, HCV was initially thought to be a chronic viral infection of minimal consequence. Initially overshadowed by human immunodeficiency virus (HIV) infection, HCV has now come to be recognised as an infection with a significant global burden (Gravitz, 2011:S2; Lavanchy, 2011:107). Available estimates indicate that acute HCV infection was responsible for 54 000 deaths and 955 000 disability-adjusted-life-years in 2011 (Khayriyyah *et al*., 2013:1333). However, the main burden from HCV comes from the sequelae from chronic infection. Morbidity and mortality associated with chronic liver disease tend to develop decades after initial infection with HCV (Shepard *et al*., 2005:558). Liver cirrhosis, hepatic decompensation and development of hepatocellular carcinoma (HCC) are some of the consequences of chronic HCV infection, causing significant liver-related morbidity and mortality (Maasoumy & Wedemeyer, 2012:401). Globally, there are approximately 130 to 150 million people who have chronic HCV infection, and each year about three to four million people are newly infected — making it currently one of the most prominent global public health issues (WHO, 2013). More than 350 000 death occur from all hepatitis C-related causes annually (Khayriyyah *et al*., 2013:1333; WHO, 2013).

The prevalence and genotype distribution of HCV infection vary according to geographical area. The most common HCV genotypes in Africa are genotypes 1, 4 and 5. Genotype 4 (HCV-G4) is the most common genotype in Africa and endemic in Central Africa and Egypt, whereas genotype 5 (HCV-G5) is predominantly found in South Africa (Abuelhassan, 2012:93; Karoney & Siika, 2013). Genotypes 1 to 3 are distributed worldwide. In Africa, these genotypes are mostly endemic in West African countries, such as Eritrea, Ethiopia and Kenya (Abuelhassan, 2012:93; Karoney & Siika, 2013:44). Table 1.1 (adapted from Karoney & Siika, 2013) lists the top six WHO regions ranked according to the estimated prevalence of HCV infection.

Table 1.1: Estimated prevalence of HCV by WHO region[a]

WHO region	Total population (in millions)	HCV prevalence rate (%)	Infected population (in millions)
Africa	602	5.3	31.9
Americas	785	1.7	13.1
South-East Asia	1,500	2.15	32.3
Eastern Mediterranean	466	4.6	21.3
Europe	858	1.03	8.9
Western Pacific	1 600	3.9	62.2
TOTAL	5 811	3.1	169.7
[a]*Adapted from Karoney and Siika (2013)*			

As indicated in Table 1.1, Africa has the highest WHO-estimated regional HCV prevalence, with 31.9 million (5.3%) HCV-infected individuals, followed by the Eastern Mediterranean, with an infection percentage of 4.6% and the Western Pacific, of which 3.9% of the total population is infected with HCV.

Table 1.2 (compiled from Karoney & Siika, 2013) lists the countries in Africa with the highest estimated HCV prevalence in the general population. Available estimates for Africa show that beside Egypt in Northern Africa, Central Africa has the highest HCV prevalence in the general population (6.0%), followed by West Africa (2.4%) and South and East Africa (1.6%) (Abuelhassan, 2012). With an estimated prevalence of 17.5%, Egypt not only has the highest HCV prevalence in Africa, but also the world (Karoney & Siika, 2013). Despite the high reported prevalence, data on HCV infection in Africa are extremely limited. This suggests that HCV infection is still being overlooked in this part of the world, resulting in hepatitis C being under-diagnosed and underreported in Africa.

In South Africa, little is known of the epidemiology of HCV. Lack of awareness among the public, healthcare workers, populations at risk and policy-makers have led to researchers referring to HCV as 'the silent volcano' (Prabdial-Sing *et al*., 2013:22). Prevalence of HCV infection in South Africa is estimated to be between low (0.1-1.7%), with the seroprevalence in blood donors and healthcare workers, and HIV positive patients ranging between 1.4 and 1.8% and 13 and 33%, respectively (Abuelhassan, 2012:93; Karoney & Siika, 2013; Prabdial-Sing *et al*., 2013:22; Tucker *et al.*, 1997:605, Vardas *et al.*, 2002:8).

Table 1.2: Top 10 African countries with the highest estimated HCV prevalence[b]

Country	Region	Sample size	HCV prevalence (%) [CI]	Genotype
Egypt	North Africa	unknown	17.5 [13 – 22]	4
Cameroon	Central Africa	6015	13.8 [0 – 40]	4
Burundi	Central Africa	1184	11.3 [4.9 – 33.3]	4
Gabon	Central Africa	1597	9.2 [6.5 – 16.5]	4
Morocco	North Africa	unknown	7.7 [unknown]	1b
Uganda	Central Africa	881	6.6 [0.0 – 14.2]	4
DRC	Central Africa	2572	5.5 [4.3 – 6.6]	4
Guinea	West Africa	2050	5.5 [0.8 – 8.7]	1-3
Burkina Faso	West Africa	965	4.9 [2.2 – 8.3]	1-3

DRC = Democratic Republic of the Congo
[b]Compiled from Karoney and Siika (2013)

The primary goal of treatment of chronic HCV infection, or chronic hepatitis C (CHC) is the prevention of liver-related morbidity and mortality. According to the South African hepatitis C management guidelines, all adults with a confirmed diagnosis of CHC — and especially those patients with an increased risk of developing cirrhosis — should be considered for treatment (Botha *et al*., 2010). The current recommended therapy for treating CHC in South Africa is a combination of weekly subcutaneous pegylated interferon (peg-INF) and daily oral ribavirin (RBV) for periods of either 24 or 48 weeks, depending on the virus genotype (Botha *et al*., 2010).

Table 1.3 lists the drugs currently available for the treatment of CHC in South Africa with their respective prices (MIMS, 2013:399-400). The price indicated for each product is the single exit price (SEP) that has been taken from the South African Medicine Price Registry's (SAMPR) database of medicine prices (28 Jan. 2014) (South African Medicine Price Registry, 2014). Table 1.4 lists the therapeutic regimens for the treatment of the different HCV genotypes in South Africa (compiled from Botha *et al*., 2010). Costs associated with each regimen were calculated by multiplying the cost per week (obtained from Table 1.3) by the treatment duration specified in each regimen (Botha *et al*., 2010). Tables 1.3 and 1.4 indicate that, depending on the weight of the patient and the virus genotype, treatment regimens for CHC can range from R35 563 (peg-INF mono-therapy for 52 weeks) to R111 140 (combination therapy with peg-INF plus RBV for 48 weeks). In addition to treatment with peg-INF/RBV being relatively expensive, it is also lengthy and causes numerous side-effects (Dillon, 2007:27; Gravitz, 2011:S2).

In South Africa, public-sector patients with CHC can access anti-HCV treatment; however, access to treatment remains limited to a handful of patients as treatment is only available at

selected tertiary institutions that offer these services (TAC, 2011). The protocol indicates that patients with hepatitis C can access peg-INF/RBV at state hospitals if it is medically indicated and if, in the opinion of a medical professional, the patient is likely to respond well to the treatment regimen (TAC, 2011). Charges are often low, the amount depending on the patient's salary and how many dependants he/she has. This is a means-based payment system *viz.* those who can afford it will pay the full cost of treatment, whereas those with no or very little income receive treatment free of charge (Harrison, 2009:14).

Those who belong to medical schemes and are above the income threshold are not eligible to receive treatment in a public health facility. Beneficiaries of medical aid schemes in the private healthcare sector often have to pay out-of-pocket if they require treatment for CHC, because hepatitis C is not a prescribed minimum benefit (PMB) (Sonderup *et al*., 2011). PMBs are the minimum benefits that a medical scheme must legally cover, regardless of the benefit option chosen by the beneficiary. PMB conditions are driven by the diagnosis, suggesting that how the member came to have a PMB condition is irrelevant. PMBs are legislated and cover the diagnosis, treatment and care of approximately 300 of the most serious, often life-threatening, and most expensive health conditions, including 270 diseases such as tuberculosis and cancer, any emergency condition, and 25 chronic conditions, including epilepsy, asthma and hypertension (CMS, 2013). The diseases that have been chosen as PMBs are the most common, they are life-threatening, and are those for which cost-effective treatment would sustain and improve the quality of the beneficiary's life (CMS, 2015b).

Because CHC is not included in this list, medication for hepatitis C is paid by most private medical aid schemes only from the day-to-day benefits of the member, subject to available funds (which can range anywhere between R1 000 and R13 600 per year depending on the scheme and the health plan) (Bestmed Medical Scheme, 2015; Discovery Health Medical Scheme, 2015; Momentum Health, 2015). Given the relatively high cost of hepatitis C drugs, however, it is not feasible to fund the treatment using a beneficiary's day-to-day medical savings. Members on lower tier plans that do not include cover for day-to-day medical expenses have to pay for treatment completely out-of-pocket, whereas members on top tier benefit plans of certain schemes can access CHC drugs as a prescribed medication; payable at scheme rates depending on the respective benefit plans (TAC, 2011).

Table 1.3: Cost of drugs used in the treatment of chronic HCV infection in South Africa[c]

Active Ingredient	Trade name	Strength and packaging	SEP* (R)
Peg interferon alfa-2a	Pegasys®	135 µg/0.5 ml, single prefilled syringe	2 709.51
		180 µg/0.5 ml single prefilled syringe	2 092.12
Peg-INF alfa-2b (recombinant interferon alfa-2b + monomethoxy polyethylene glycol)	Peg-Intron®	50 µg single dose pens + diluent	1 075.75
		80 µg single dose pens + diluent	1 893.32
		100 µg single dose pens + diluent	2 003.27
		120 µg single dose vials + diluent	2 403.92
		150 µg single dose vials + diluent	3 227.26
Lyophilised interferon alfa-2a	Roferon-A®	3.0 million IU/0.5 ml prefilled syringe	227.97
		4.5 million IU/0.5 ml prefilled syringe	316.06
		6.0 million IU/0.5 ml prefilled syringe	413.43
		9.0 million IU/0.5 ml prefilled syringe	612.01
Ribavirin	Copegus®	200 mg tablets; 42's	267.98

**SEP = single exit price as indicated by South African Medicine Price Registry's Database of medicine prices (28 Jan. 2014)*

[c]Compiled from MIMS (2013:399-400) and South African Medicine Price Registry (2014)

Up to 2011, the global standard of care (SOC) for CHC was combination therapy with peg-INF and RBV. Treatment with peg-INF/RBV generally produces sustained virologic response (SVR) rates of 40 to 80%, depending on factors such as the HCV genotype, viral load and degree of liver fibrosis (Alexopoulou & Papatheodoridis, 2014:6062). In 2011, two direct-acting antivirals (DAAs) with specific activity against HCV were approved as add-on therapy for chronic HCV genotype 1 (HCV-G1) infection (Kanda *et al.,* 2013:1). These DAAs — telaprevir and boceprevir — proved to be potent inhibitors of HCV replication and improve treatment success rates; however, they also accentuate adverse events and have to be used in combination with peg-INF/RBV (Kanda *et al*., 2013:1). Several second-generation DAAs have been developed since the approval of telaprevir and boceprevir and several more are currently being investigated in on-going clinical trials (Alexopoulou & Papatheodoridis, 2014:6062). None of the DAAs, however, are currently registered in South Africa. The hope for HCV-infected patients is that all-oral, interferon-free regimens will become the standard of care in the future — answering the pressing need for drug therapies that are potent inhibitors of HCV infection, but have fewer adverse events (Kanda *et al*., 2013:1).

Table 1.4: Therapeutic regimens per HCV genotype in South Africa[d]

Therapeutic options	Susceptible genotypes	Treatment duration	Dosage		Calculated costs* (ZAR)	Total treatment cost** (ZAR)
Peg-interferon α-2a *(Pegasys®)* + Ribavirin *(Copegus®)*	1,4,5,6	48 weeks	Peg-interferon α-2a	180 µg per week	100 421.76	
			Ribavirin	1 000 mg/day (≤75 kg)	10 718.40	**111 140.16**
				1 200 mg/day (>75 kg ≤90 kg)	12 862.08	**113 283.84**
				1 400 mg/day (>90 kg)	15 005.76	**115 427.52**
	2 & 3	24 weeks	Peg-interferon α-2a	180 µg per week	49 490.88	**-**
			Ribavirin	800 mg per day	R4 287.36	**53 778.24**
Peg-interferon α-2b *(PegIntron®)* + Ribavirin *(Copegus®)*	1,4,5,6	48 weeks	Peg-interferon α-2b[ii]	1.5 µg/kg per week	96 156.96	
			Ribavirin	800 mg/day (<65 kg)	8 574.72	**104 731.68**
				1 000 mg/day (≥65 kg ≤85 kg)	10 718.40	**106 875.36**
				1 200 mg/day (>85 kg ≤105 kg)	12 862.08	**109 019.04**
				1 400 mg/day (>105 kg)	15 005.76	**111 162.72**
	2 & 3	24 weeks	Peg-interferon α-2b[ii]	1.5 µg/kg per week	48 078.48	**-**
			Ribavirin	800 mg/day	4 287.36	**52 365.84**
Lyophilised peg-INF α-2a *(Roferon-A®)*	1-6	52 weeks		3 MIU 3 x per week[iii, iv]	227.97 x 3 x 52	**35 563.32**

MIU = milli international units; peg-INF α = pegylated interferon alpha

**Calculated costs: calculated by multiplying cost per week (Table 1.3) by treatment duration*

***Total treatment regime cost: calculated by adding calculated cost* of peg-INF to calculated cost* of different dosages of ribavirin*

[i] Calculated as R6.38 per 200 mg tablet [R267.98 for 42 tablets (South African Medicine Price Registry, 2014)]

[ii] Calculations based on price of 100 µg pen (patient weight >70 kg)

[iii] Recommended adult dosage (MIMS, 2013:400)

[iv] Calculations based on price of 3 MIU/0.5 ml prefilled syringe (South African Medicine Price Registry, 2014)

[d] Compiled from Botha et al. (2010)

1.2 Problem statement

The recent announcement of a new drug to treat chronic HCV infection made headlines through the medical world. Sofosbuvir (formerly known as GS-7977), a direct-acting nucleotide NS5B polymerase inhibitor developed as an oral drug for the treatment of CHC, has been described as a 'game changer' in the management of HCV (Bourlière *et al.*, 2011:S38). The safety and effectiveness of sofosbuvir have been evaluated in interferon-based and interferon-free regimens in several clinical trials, with excellent results (Lawitz *et al.*, 2013:34).

According to Zeuzem *et al*. (2014), the phase 3 VALENCE study (ClinicalTrials.gov number, NCT01682720) indicated a sustained virologic response 12 weeks after treatment (SVR12) in 85% (n=212/250) of both treatment-naïve and treatment-experienced patients with HCV genotype 3 (HCV-G3), all of whom received a 24-week regimen of sofosbuvir plus RBV. The phase 2 LONESTAR-2 study (ClinicalTrials.gov, number NCT01726517) reported SVR12 rates of 83% (n=20/24) in cirrhotic and non-cirrhotic patients with HCV-G3 who had previously been treated with a combination of peg-IFN/RBV, but whose treatment had been unsuccessful after 12 weeks of sofosbuvir plus peg-IFN/RBV (Lawitz *et al*., 2014:515). The NEUTRINO clinical trial (NCT01641640) was a phase three, multicentre, open-label, single-group study that evaluated the safety and effectiveness of sofosbuvir in combination with peg-INF/RBV in patients with HCV genotypes 1, 4, 5 or 6 (Lawitz *et al*., 2013:1881). All patients participating in the trial received sofosbuvir plus peg-INF/RBV for 12 weeks. Overall, 90% of patients enrolled in the study achieved SVR after 12 weeks of treatment. Results from the study indicated that there was no great difference in the SVR rate among different HCV genotypes: the SVR rate was 89% for patients with HCV-G1 (92% for G1a and 82% for G1b) and 96% for those with HCV-G4. The single patient with HCV-G5 and all six patients with genotype 6 (HCV-G6) in the NEUTRINO trial also achieved SVR. Responses also did not vary substantially according to race or ethnic group (Lawitz *et al.,* 2013:1881). Since SVR after 12 weeks of treatment is considered to be a cure for HCV infection, the results of these trials indicate that sofosbuvir could potentially cure more than 90% of HCV infections (Lawitz *et al*., 2014:515).

Sofosbuvir received approval from the United States of America's (USA) Food and Drug Administration's (FDA) advisory panel in December 2013, after it was found that the drug not only cured more patients with hepatitis C than current treatments, but it did so in a shorter period of time (FDA, 2013). Besides the apparent proof of superior efficacy, studies have also shown that adverse events (including fatigue, headache, nausea and neutropenia) were less common with sofosbuvir-based treatment (Lawitz *et al*., 2013:1881). Shortly after the approval of sofosbuvir, the FDA approved an interferon-free regimen of sofosbuvir (400 mg) in a fixed dose combination with ledipasvir (90 mg) for chronic HCV-G1 infection, in the form of a single tablet (Afdhal *et al*., 2014a, Afdhal *et al*., 2014b, Kowdley *et al*., 2014). Just like sofosbuvir, the

sofosbuvir-ledipasvir (SOF/LDV) combination is dosed once daily, is generally well-tolerated (compared to interferon-containing regimens), offers a shorter duration of therapy for most patients and has reported high cure rates (Afdhal *et al*., 2014a). In clinical trials, SOF/LDV yielded high SVR rates, ranging from 93 to 99% in treatment-naïve and treatment-experienced patients with HCV-G1, with or without cirrhosis (Afdhal *et al*., 2014a, Kowdley *et al*., 2014). Investigators reported the option of utilising a shorter 8-week course of therapy in treatment-naïve and treatment-experienced patients if the baseline HCV ribonucleic acid (RNA) is <6 million IU/mL, but that a 12-week regimen of SOF/LDV once daily is optimal in patients with an initial HCV RNA of >6 million IU/mL, as shorter durations are associated with a higher relapse rate (Kowdley *et al*., 2014). The phase 3, ION-4 study (ClinicalTrials.gov number, NCT02073656) evaluated SOF/LDV in the treatment of genotypes 1 or 4 HCV infection among patients co-infected with HIV. In the trial, 96% (n=321/335) of HCV patients achieved SVR 12 weeks after completing therapy (Naggie *et al*., 2015:705). In a small, open-label study conducted in France, SOF/LDV yielded high SVR rates in treatment-naïve and treatment-experienced patients with HCV-G5. SVR rates of 95% were reported for HCV-G5 infection, irrespective of the patient's cirrhosis status (Abergel *et al*., 2015). Based on these results, the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) amended their guidelines to include sofosbuvir + peg-INF/RBV and SOF/LDV for HCV-G5 infection (AASLD, 2015; EASL, 2015).

Described as the most advanced hepatitis C drug at the moment, sofosbuvir comes at a time where there is a pressing need for hepatitis C treatments that are less burdensome to the patient (Akpan, 2013; Rivas, 2013; Williams, 2013). Sofosbuvir certainly has the potential to revolutionise patient care, but the pertinent question is: "At what price?"

Sofosbuvir (marketed as *Sovaldi*® and *Virunon*® in the USA) has been launched in the USA for the treatment of chronic HCV infection at a wholesale price of $1 000 per daily dose, or a total cost of $84 000 (~R909 988.80)[1] for a 12-week treatment regime (Pollack, 2013). The SOF/LDV combination (*Harvoni®)* is priced at US$94 500 (~R1 108 746) for a treatment course for 12 weeks, eliciting a global debate on the pricing of new HCV drugs (Barrett & Langreth, 2015). These apparent high prices are driving debates between the biotechnology company that manufactures *Sovaldi*® and *Harvoni*®, and health activists, notably those fighting to prevent the registration of a global patent (Jack, 2013). According to Flinn and Armstrong (2012), several large USA pharmaceutical benefit managers (PBMs) are pushing back against the high prices of these drugs, discussing different strategies to constrain costs while further refusing to pay a premium based on a drug's administration convenience — confirming fears that the high price of sofosbuvir and SOF/LDV will cause insurers to compel patients to use the older, less

[1]1USD = 10.8332ZAR. 2014 XE currency converter (Date of access: 21 Jan. 2014)

expensive HCV treatments first. These drugs, however, are also less effective (Alexopoulou & Papatheodoridis, 2014:6062).

Further concerns are that the price for sofosbuvir and other sofosbuvir-containing regimens will render these drugs completely inaccessible to the vast majority of HCV-infected patients residing in low- and middle-income countries. Unaffordable prices for these drugs will consequently become a huge burden for healthcare funders and governments who will need to start providing and financing treatment (Jack, 2013).

In answer to global outcries, in September 2014, Gilead signed an agreement with seven India-based generic pharmaceutical manufacturers to develop sofosbuvir and SOF/LDV for distribution in 91 developing countries (Gilead Sciences, Inc., 2014a). Under the licensing agreement, the generic pharmaceutical manufacturers have the right to develop and market generic sofosbuvir and SOF/LDV in certain developing countries, including South Africa. These drug companies will receive a complete technology transfer of the Gilead manufacturing process, enabling them to scale up production. A further stipulation of the licensing agreement allows generic companies to set their own prices for the generics (Gilead Sciences, Inc., 2014a).

As sofosbuvir and SOF/LDV is yet to be registered in South Africa, it is unclear what prices will be considered cost-effective for these drugs. According to the World Bank (2014), the *per capita* health expenditure for South Africa (calculated as the sum of public and private health expenditures as a ratio of the total population) was $689, translating to R7 464 per person per annum, compared to $8 608 (R93 252) per person per annum in the United States (The World Bank, 2014). According to the CMS, medical schemes in South Africa paid R103.3 billion for health benefits to their 8.7 million beneficiaries in 2012 (CMS, 2013). This translates to an average of R11 874 per beneficiary per year. Considering the SEP of hepatitis C drugs, most of the treatment regimens are ten-fold the health expenditure *per capita* for South Africans. Bearing in mind that the international launch price of sofosbuvir and SOF/LDV is noticeably higher than the current hepatitis C drugs, cost-effectiveness analyses on the use of sofosbuvir and SOF/LDV in South Africa are crucial.

Modelling suggests increasing numbers of CHC cases are manifesting their most serious symptoms, *viz.* cirrhosis and its complications and will continue to rise, peaking in approximately 2030. The problem is turning into a pressing public health concern that threatens to pressurise already stretched healthcare system, patients and researchers (Dillon, 2007:25; Gravitz, 2011:S2; Poll, 2012:396; Wilkie, 2013:22).

Considering the lack of prospective, long-term studies on the new DAAs that include cost data in South Africa and the fact that decisions about treatment are dominated by concerns about cost; further economic modelling of treatment strategies might assist decision-makers in allocating resources for maximal collective health benefits (Koff & Seeff, 1995:1882; Gellad *et al*., 2012:1189). The limitations of economic modelling in hepatitis C notwithstanding, pharmacoeconomic models can provide an alternative perspective on the potential value of available treatment strategies. The main purpose of this study was therefore to empower policy-makers to make informed decisions about the treatment of chronic HCV infection in light of new and more effective treatments being developed for this disease.

1.3 Research questions

The research questions that established the undertaking of this study were:

- Will sofosbuvir (either in combination with peg-INF/RBV or ledipasvir) be cost-effective compared to the current standard of care for treating HCV-G5 infected individuals in the private healthcare sector of South Africa?
- What will the public health impact of the use of sofosbuvir-containing regimens compared to current HCV treatments be?
- What will the budget impact of sofosbuvir-containing regimens in the South African market as part of the total healthcare budget be?

1.4 Research aim and objectives

1.4.1 General research aim

The general aim of this research project was to determine the cost-effectiveness of sofosbuvir-containing regimens for the treatment of chronic HCV infection in South Africa by constructing a decision-analytical model utilising TreeAge Pro Healthcare 2014 software (TreeAge Pro 2014, R1.2).

1.4.2 Specific research objectives

The research project was conducted in two phases; a literature review (phase one) and an empirical study (phase two). The project had both literature and empirical objectives.

1.4.2.1 Literature phase objectives

The specific objectives of the literature review included:

(i) Defining HCV infection and researching all relevant aspects on the subject of the disease; including clinical features of the disease, routes of transmission, incubation period, risk factors, prevention, complications, diagnosis and testing, treatment and response;
(ii) investigating the current status of CHC by determining global and national prevalence and epidemiology of chronic HCV infection;
(iii) investigating different HCV genotypes and their geographical distributions;
(iv) characterising the patient journey of an individual with hepatitis C infection, by determining the main disease states of chronic HCV infection, as well as the annual transition probabilities from one disease state to the next;
(v) determining the medical expenses involved (direct medical) during each disease state;
(vi) determining the effectiveness of the competing treatment strategies by means of published clinical trial data, and
(vii) describing the concept of health-related quality-of-life (HRQoL) and determining health state utilities in patients with CHC.

1.4.2.2 Empirical phase objectives

Following the objectives already met in the literature phase, the specific objectives of the empirical phase included:

(i) Building a Markov model using TreeAge Pro Healthcare 2014 software (TreeAge Pro 2014, R1.2), based on the natural history/disease states of chronic HCV infection identified in the literature review;
(ii) populating the model with data, including annual transition probabilities, cost data, effectiveness data, health state utility values and background mortality rates;
(iii) running the model through TreeAge Pro Healthcare 2014 software (TreeAge Pro 2014, R1.2) to yield results based on cost-effectiveness and analysing these results;
(iv) using the results to compare the alternative HCV treatment strategies based on cost-effectiveness and incremental cost-effectiveness ratios;
(v) using a willingness-to-pay (WTP) threshold of R200 000; determining if sofosbuvir and/or SOF/LDV will be cost-effective for HCV-G5 infection in South Africa at the modelled prices;
(vi) quantifying the public health impact of the use of sofosbuvir-containing regimens compared to current HCV treatments from a South African private sector third-party payer's perspective, and
(vii) determining the budget impact of sofosbuvir-containing regimens in South Africa as part of the total healthcare budget.

Table 1.5: Empirical phase objectives

Objective	Manuscript
Building a Markov model on TreeAge Pro Healthcare 2014 software (TreeAge Pro 2014, R1.2), based on the natural history/disease states of chronic HCV infection identified in the literature review	Manuscript 1
Populating the model with data, including annual transition probabilities, cost data, effectiveness data, health state utility values and background mortality rates	Manuscript 1
Running the model through TreeAge Pro Healthcare 2014 software (TreeAge Pro 2014, R1.2) to yield results based on cost-effectiveness and analysing these results;	Manuscript 1
Using the results to compare the alternative HCV treatment strategies based on cost-effectiveness and incremental cost-effectiveness ratios	Manuscript 1
Determining if sofosbuvir-containing regimens will be cost-effective for HCV infection in South Africa based on the WTP threshold of R200 000	Manuscript 1
Quantifying the public health impact of the use of sofosbuvir-containing regimens compared to current HCV treatments from a South African private sector third-party payers' perspective	Manuscript 2
Determining the budget impact of sofosbuvir-containing regimens in South Africa as part of the total healthcare budget	Manuscript 3

1.5 Research methodology

The study consisted of a literature review (phase one) documented in Chapter 2 and an empirical investigation (phase two), documented in Chapter 3 of this thesis.

1.5.1 Literature review methodology

The purpose of conducting a literature review is to identify, analyse and interpret information and knowledge related to a specific topic (Jones, 2007:33). For the purpose of this study, it aimed to set the context for the study and provide a foundation to address the stated research questions. It also served to rationalise the research in terms of the gap(s) in existing knowledge. Figure 1.1 illustrates the steps followed in the literature review based on the specific research objectives set for this research phase.

Literature was retrieved from PubMed, ScienceDirect, Scopus and EBSCOhost. In EBSCOhost, searches were limited to Academic Search Premier, AHFS Consumer Medication Information, CINAHL, Health Source, International Pharmaceutical Abstracts and MEDLINE. A Boolean/phrase search was conducted using the following terms: [Search (liver) OR (hepatic) AND (anatomy) OR (function*) OR (test*) OR (pathology) OR (disease*) OR (disorder*);

[Search (hepatitis C) OR (HCV) OR (non-A non-B hepatitis)]. Searches relating to HCV (or hepatitis C) could include phrases such as (natural history) OR (treatment) OR (diagnosis) OR (epidemiology) OR (prevalence) to narrow down searches when literature relating to a specific topic was not included in the initial search. To identify literature on health-related quality-of-life, search terms included [Search (health-related quality-of-life) OR (HRQoL) OR (utility measurement) AND (hepatitis C) OR (HCV).

Searches were limited to English articles published from 1990 to the present. There was no discrimination between publication types (i.e. periodical, newspapers, books, electronically available theses and dissertations) or document types (i.e. abstracts, articles). Manuscripts were reviewed and evaluated for inclusion in the literature review. The bibliographies of these manuscripts were also examined for relevant papers that had not been identified through the initial search strategy. As this is not a systematic review or a meta-analysis, specific criteria for inclusion or exclusion of literature were not set.

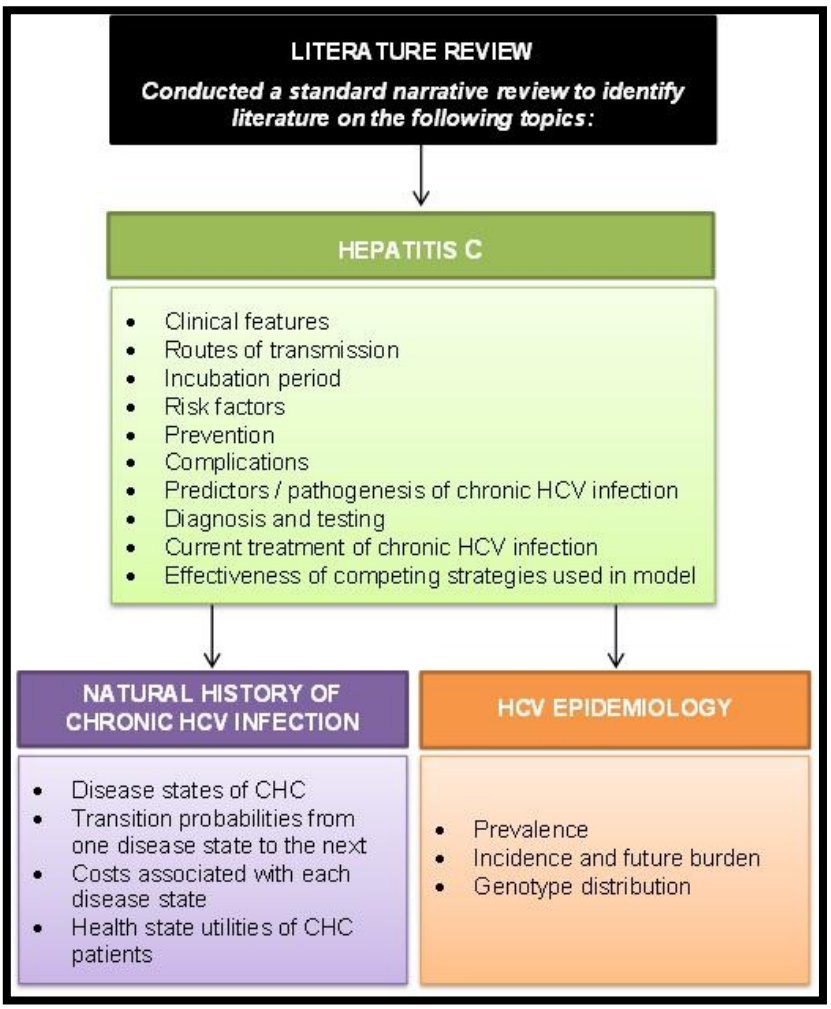


Figure 1.1: Schematic of the steps followed during the literature review

1.5.2 Empirical research methodology

This section describes the study design, setting, data source(s), target population, study population, data collection tools and data analysis relating to the empirical research phase.

1.5.2.1 Study design

The study design was founded on the concept of pharmacoeconomic modelling. A pharmacoeconomic model is defined as *"an analytic methodology that accounts for events over time and across populations, that is based on data drawn from primary and/or secondary sources and whose purpose is to estimate the effects of an intervention on valued health consequences and costs"* (Weinstein *et al.,* 2003:4). The application of pharmacoeconomic modelling as an analytical decision-making tool and the concept of pharmacoeconomics and its utilisation in formulary decision-making have been discussed in section 1.2.

1.5.2.2 Target and study population

The target population of this research project was patients with chronic HCV infection living in South Africa. The study population for the cost-effectiveness model consisted of a hypothetical cohort of patients with chronic HCV-G5 infection. The study population for the public health impact- and budget impact analyses represented patients with chronic HCV infection in South Africa (based on available epidemiological data).

1.5.2.3 Setting and study perspective

The South African pharmacoeconomic guidelines recommend a funder's perspective for pharmacoeconomic analyses (Medicines and Related Substances Act (101 of 1965)). Therefore, this study was conducted from a third party payer's perspective in the private healthcare sector of South Africa.

1.5.2.4 Model construction, data source and data analyses

The methods employed in model construction, data collection and results analysis are described based on the specific objectives set for the empirical research phase. Figure 1.2 illustrates the steps followed during the empirical phase.

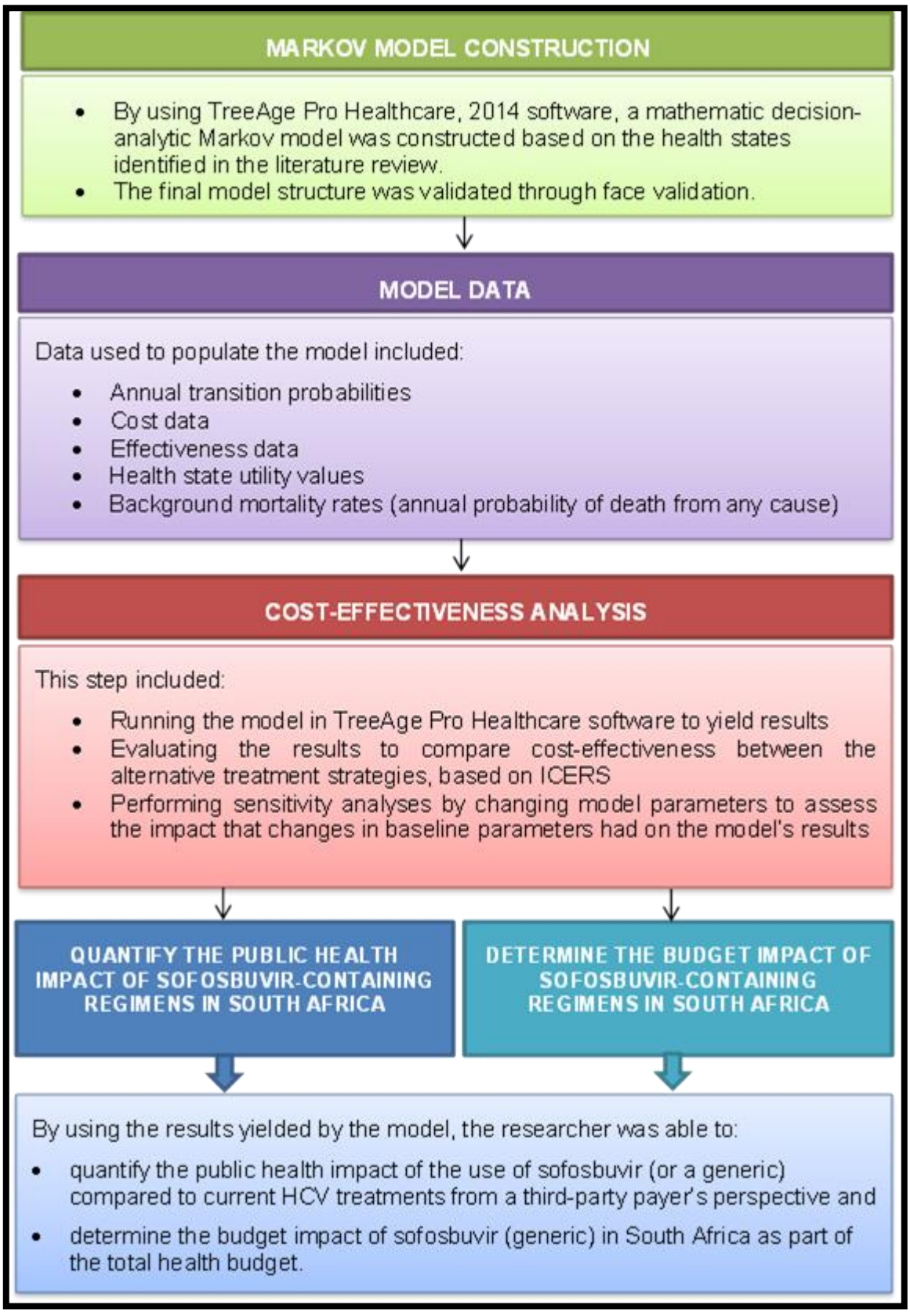


Figure 1.2: Schematic of steps followed during the empirical investigation

(i) Building a Markov model on TreeAge Pro Healthcare 2014 software, based on the natural history/disease states identified in the literature review

To determine the expected health-economic outcomes in patients with chronic hepatitis C (CHC), a decision analytic model was developed to simulate the disease progression of chronic hepatitis C virus (HCV) infection. TreeAge Pro Healthcare 2014 software (TreeAge Pro 2014, R1.2) was used to build a model based on the disease progression of chronic HCV infection in a hypothetical cohort of people, over a lifetime horizon.

Healthcare models often need to follow a disease process into the future. The most common approach to this is to create a state transition model (STM) (Milne, 1998:126). Because it is the most common type of 'state transition' pharmacoeconomic model and because it is appropriate to describe the progression of chronic illness with recurring health states or events (Sonnenberg & Beck, 1993:322), a Markov model was used to simulate the patient journey of HCV-infected individuals. A Markov model allows for a clinical condition to be described in terms of the health states a person can be in, how they can move from one health state to another (transitions) and the likeliness of such transitions (transition probabilities) in either the absence or presence of an intervention, including the interventions' effects on transition probabilities (Ademi *et al.*, 2012:947).

The conceptualisation of a Markov model begins by understanding the natural history of the disease being modelled and identifying the specific health states that reflect that disease, i.e. characterising the patient journey of an individual with the modelled disease (Roberts *et al*., 2012:804). The health states (or disease states or 'Markov states') are mutually exclusive and collectively exhaustive, meaning that any individual in the modelled cohort can be in only one state during each cycle and every individual in the initial cohort must be in a state during each cycle (Sonnenberg & Beck, 1993:322).

TreeAge Pro (TreeAge Pro 2014, R1.2) supports Markov models through the decision tree structure and a decision tree model can contain many Markov models for specific strategies. A model built with TreeAge software typically begins with a decision node with a branch for each treatment strategy for the specific disease/ health condition being modelled. The sub-tree for each strategy follows the disease through treatment, including any number of possible outcomes. In the decision tree structure, the Markov model consists of the Markov node and everything to its right. Health states are represented by the direct branches of the Markov node. The cohort starts each cycle distributed among these health states. For every health state, there is a separate transition sub-tree, which stipulates the events that can occur within a cycle. Events that occur within each cycle are modelled as transitions from one state to another, with a series of chance nodes representing the events.

At each point where the transition sub-tree ends, the cohort returns to one of the states to begin the next cycle, which results in an altered distribution of the cohort between the health states to start each cycle.

The model consisted of an initial decision tree, followed by a state-transition Markov model. In the decision tree, patients were eligible to receive treatment. Treatment strategies included: i) SOC [pegylated-interferon (peg-INF) + ribavirin (RBV)]; ii) SOF-triple therapy (sofosbuvir + peg-INF + RBV) and iii) SOF/LDV. The state-transition model simulated the natural history of CHC. A cohort simulation model was used, because it allows for tracking infected cohorts over time and also permits simulation of events in a population as they occur (Sonnenberg & Beck, 1993:326). Through a Markov simulation, a hypothetical cohort of male and female patients with chronic HCV infection moved through defined health states in the model. Main health states included were: CHC without cirrhosis (treatment naive *vs*. treatment failed); compensated cirrhosis (treatment naive vs. treatment failed); decompensated cirrhosis; hepatocellular carcinoma (HCC); sustained virologic response (SVR) without cirrhosis; SVR with cirrhosis; liver-related death and non-liver related death. Time was represented by annual cycles, i.e. one cycle was 12 months, during which patients could remain in the same histologic or clinical state; progress to another histologic or clinical state; die of liver-related causes; or die of other causes (non-liver related).

All patients in the cohort entered the model with a confirmed diagnosis of CHC and initiated treatment upon entering the model. A three-armed study was developed — patients in the first arm of the model received SOF/LDV, while patients in the second arm received SOF-TT and patients in the third arm received SOF/LDV. For all three treatment strategies, the aim of treatment was SVR and, based on the efficacy rates of each treatment option modeled, treatment could either be successful (achieved SVR) or unsuccessful (failed to achieve SVR). Patients only received treatment during the first model cycle and patients were assumed to complete only one course of treatment before achieving SVR. Patients who achieved SVR were assumed to maintain SVR and not experience further disease progression until they died, thus, we assumed that SVR eliminates the risk of progressive liver disease. Patients who did not achieve SVR, on the other hand, were assumed to be at risk of progressive liver disease. No response after 12 weeks (SOF-containing regimens) or 48 weeks (SOC) was considered as treatment failure and patients progressed to the next health state. Retreatment, relapse or recurrence was not considered.

For each treatment arm, the cohort was divided according to the presence or absence of cirrhosis and at the start of the state-transition model patients were placed in one of two disease states: “CHC without cirrhosis” or “compensated cirrhosis”. The initial distribution of patients without cirrhosis (80%) and those with cirrhosis (20%) is representative of the South African

HCV population. This is also closely related to the distribution of patients with cirrhosis and those without in the NEUTRINO trial (cirrhotic patients, 17%; non-cirrhotic patients, 83%) and the French study conducted by Abergel *et al*. (2015) (presence of cirrhosis in treatment naive patients, 14%; presence of cirrhosis in treatment experienced patients, 30%). Based on this initial distribution assumed, 80% of the cohort in each treatment arm started in the "CHC without cirrhosis (treatment naive)" state for the first cycle of the Markov model. In this model, patients without cirrhosis were assumed to have advanced fibrosis (METAVIR score ≥F2).

The current South African hepatitis C management guidelines state that "treatment should be considered in all adults with confirmed chronic hepatitis C and particularly in those who are at increased risk of developing cirrhosis. For patients, in whom liver histology is available, treatment is indicated if advanced fibrosis (F2 or F3 according to the METAVIR scoring system) is present" (Botha *et al*., 2010). Even though fibrosis is not a prerequisite for treatment, ≤F1 fibrosis stages F0 and F1 were excluded because as it stands, these patients do not automatically qualify for treatment in the peg-INF/RBV era. Furthermore, funders in South Africa only pay for >F1 fibrosis. It is generally accepted that in the era of direct acting antivirals, all patients qualify for treatment — even so, treatment prioritization must occur and in both EASL and AASLD guidelines, patients with ≤F1 fibrosis are not prioritized unless another indication for treatment exists e.g. cryoglobulinemia, extreme fatigue etc. (AASLD, 2015; EASL, 2015). However, it is difficult to model for this scenario as clear data does not exist to include such estimates.

It is further assumed that spontaneous clearance of HCV is only possible from F0 and therefore not a possibility in this model. CHC patients without cirrhosis who achieved SVR (treatment successful) moved to the "SVR without cirrhosis" state at the end of the first cycle and remained there until death (non-liver related). Patients without cirrhosis who failed treatment, moved to the "CHC without cirrhosis (treatment failed)" state at the end of the first cycle. During the subsequent cycles, patients in the "CHC treatment failed" state could either remain in that state or progress to the "compensated cirrhosis (treatment failed)" state according to the annual transition probabilities.

The remaining 20% of the modeled cohort started in the "compensated cirrhosis (treatment naive)" state. Those who achieved SVR moved to the "SVR with cirrhosis" state — a state for patients who are cured of HCV, but who have a lower utility than full health because of the advanced stage of fibrosis. Patients with cirrhosis who failed treatment moved to the "compensated cirrhosis treatment failed" state at the end of the first cycle. During subsequent cycles, all patients in the "compensated cirrhosis treatment failed" state, including those who transitioned from "CHC without cirrhosis treatment failed", could either remain in that state,

progress to “decompensated cirrhosis” or progress to “HCC”, based on annual transition probabilities.

“Decompensated cirrhosis” included ascites, esophageal varices and hepatic encephalopathy as serious hepatic manifestations. From the “decompensated cirrhosis” state, patients could progress to “HCC”, die from liver-related causes, or remain in the decompensated state, depending on the transition probabilities. Recovery from decompensation to compensated cirrhosis is only possible from a liver transplant. This model did not include liver-transplant as a possible treatment option, because in 2011 there were 31 liver transplants in South Africa, of which only two were due to HCV (Saraswat *et al*., 2015). Given that it is not common practice in South Africa to manage end stage liver disease due to HCV with liver transplantation, liver transplants were not considered as an intervention in this model, and recovery from decompensated cirrhosis to a recovered health state was not possible. Patients who have progressed to HCC could either remain in the “HCC” state at the end of a 12 month cycle or die a liver-related death. Death from any cause was possible from all health states and background mortality for all patients in the model was assumed to be the same mortality rate as for the general population. The simulation was carried out until the cohort reached an age of approximately 100 years (cycle length, 50 years). The model structure, inputs and assumptions were validated by South African clinical hepatologists (refer to Appendix A.1.1).After the model structure is completed and main disease states and disease progression have been established, the model is populated with data to perform a cost-effectiveness analysis.

(ii) Populating the model with cost data, effectiveness data, health state utility values, annual transition probabilities and background mortality rates

Data required for the cost-effectiveness analysis include: a) natural history parameters; b) cost data; c) effectiveness data; and d) health state utility data. Table 1.6 is a summary of the data used to populate the model with the respective data sources.

(a) Natural history parameters

Natural history parameters refer to the annual transition probabilities and were based on published literature. Within the context of modelling, the annual transition probability is *“the probability of progressing from a given health/disease state to the next health/disease state in a Markov process in a one year cycle”* (Ademi *et al*., 2012:947).

The natural history of chronic HCV infection has been described many times in literature and the transition probabilities of disease progression have been documented and published in the public domain (Alawazi *et al.*, 2013:344; Alberti *et al*., 1993:19; Ascione *et al*., 2007:S5; Chen & Morgan, 2006:50, Davis *et al*., 2003:333; Thein *et al*., 2005:643). Available literature on this

subject served as the data source for the transition probabilities used in this model (refer to Chapter 2, Table 2.6).

(b) Cost data

In order to do a cost-effectiveness evaluation, all relevant costs associated with the treatment of chronic HCV infection were included in the model. Each stage of the disease has specific costs associated with it and accumulates over the modelled period. Since this study was conducted from a third-party payer's perspective in the private healthcare sector, only direct medical costs were considered, i.e. diagnostic tests, drug costs, hospitalisation, out-patient procedures, follow-up costs and any other costs associated with the treatment/management of HCV.

Table 1.6: Required data types for model population

Data type	Variable	Data source	Example
Natural history parameters	Annual transition probabilities	Published literature	CHC → cirrhosis: 20% over 20 years
Cost data			
Drug costs	SOC (PEG-INF + RBV)	Official Pharmaceutical Bluebook	COPEGUS® 200 mg tablets R425.37 per 42 tablets PEGASYS® 180 mcg sc injection R3 558.69 ea.
	Sofosbuvir (SOF)	Published literature	~R11 700 ($1 000) /daily dose
	Sofosbuvir-ledipasvir (SOF/LDV)	Published literature	~R13 199 ($1 125) /daily dose
Disease management	Outpatient attendance	NHRPL for services by medical practitioners	NHRPL codes: 0190; 0191; 0192
Inpatient costs, including palliative care	General ward, high care ward, intensive care unit, gasses and disposables, ward medicine, theatre fees, confinements, pathology, radiology, physiotherapy, day clinics Home healthcare per visit	Private sector cost data and NHRPL in respect of hospice or similar approved facilities with a practice number commencing with "79"	Ward fee, per day: 30.552 units = R671.10 Home health care, per visit = 10 units = R219.70
Diagnostic tests/pathology	HCV assay, HCV PCR, viral load, HCV genotyping LFT, FBC, U&E, clotting studies, iron studies, TFT HBV serology, HIV-test, HAV-immunity Liver biopsy Abdominal ultrasound Screening for HCC using AFP & ultrasound	Private sector cost data	HCV antibody = R198.74; HCV PCR & viral load = R2 850.60; HCV genotyping = R1 606.90; HBV serology = R596.22; HIV-test = R1 164.55; HAV-immunity = R113.63; TFT = R508.68; LFT = R517.22; FBC = R174.80; U&E = R49.72; INR = R82.36; AFP = R170.37; Iron studies = R423.41; Liver biopsy = R86 653.00; Abdominal US = R678.75
Effectiveness data	Cure rate of SOC	Meta-analysis of BERNAR-1 and BERNAR-2 RCTs	SVR rate: no cirrhosis = 55%; compensated cirrhosis = 40%
	Cure rate of SOF	NEUTRINO RCT	SVR rate: no cirrhosis = 92%; compensated cirrhosis = 80%
	Cure rate of SOF/LDV	French phase 2 open-label study by	SVR rate: no cirrhosis = 95%; compensated cirrhosis = 95%
Health state utilities	Utility value (or HRQoL) of HCV patients during each disease state	Published literature	Healthy = 1; CHC = 0.82; Compensated cirrhosis = 0.78; Decompensated cirrhosis = 0.65; HCC = 0.25

AFP = alpha fetoprotein; FBC = full blood count; HAV = hepatitis A virus; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRQoL = health-related quality-of-life; LFT = liver function test; PCR = polymerase chain reaction; peg-INF = pegylated interferon; RBV = ribavirin; RCT = randomised controlled trial; SOC = standard of care; SOF = sofosbuvir; SOF/LDV = sofosbuvir-ledipasvir; TFT = thyroid function test; U&E = urea and electrolytes, US = ultrasound

A literature review identified the resources used during each health state of CHC. The treatment and -management patterns identified from literature were confirmed by South African hepatologists. Based on these guidelines, a South African-specific cost for each CHC health state in the model was calculated. These included drug costs, cost of disease management, and costs of diagnostic tests/pathology. A detailed description of the costs used in this model is presented in Manuscript 1 (refer to Chapter 3) and the supplementary material for Manuscript 1 (refer to *"Online Resource A: Cost-effectiveness modeling of sofosbuvir-containing regimens for chronic genotype 5 hepatitis C virus infection in South Africa"* in Chapter 3).

- Drug costs

Drug costs included the costs of peg-INF, RBV, sofosbuvir and SOF/LDV. Unit costs of peg-INF and RBV were taken from the Official Pharmaceutical Bluebook (The Pharmaceutical Bluebook, 2015). The price modelled was taken as the SEP (including VAT) plus dispensing fee.

There is not currently a South African market price for sofosbuvir (*Sovaldi®)* or SOF/LDV (*Harvoni*®). However, in order to do a cost-effectiveness analysis, the cost of all three interventions being compared should be modelled. In 2015, generic manufacturers began selling sofosbuvir generics in India for approximately US$960 for a 12-week regimen (NATCO Pharma Ltd., 2015). In Pakistan and Brazil, governments opted to negotiate prices exclusively with Gilead and entered into agreements with the manufacturer to distribute *Sovaldi*® at subsidised rates of approximately US$1 500 and US$7 000, respectively (FEROZSONS Laboratories Ltd., 2014; GTPI, 2014). In 2014, Gilead initiated a partnership with Egypt, agreeing to provide *Sovaldi*® and *Harvoni*® to the country at a significantly reduced cost. In Egypt *Sovaldi*® and *Harvoni*® is currently sold at a price of US$900 and US$1 200, respectively for 84 tablets (12-week treatment), the lowest available prices in the world (Fick & Hirschler, 2014).

Although South Africa might not be able to obtain these drugs at prices similar to Egypt, Egypt has demonstrated that with effective leadership and government support, price reductions are achievable. Because South Africa is included in the list of countries for distribution of the generic version of sofosbuvir and SOF/LDV, it will almost certainly be able to have access to the drugs at lower prices. At the time of this analysis, SOF/LDV generics and information on their pricing were not yet available anywhere in the world. Furthermore, neither sofosbuvir, nor SOF/LDV (brand name or generic) is yet registered in South Africa and their pricing have not been established. However, indications are that South Africa will be benchmarked with the BRICS (Brazil, Russia, India, Canada and South Africa) countries (South Africa, 2015). Therefore, a cost of R82 129.32 (US$7 000) for a 12-week course of sofosbuvir was assumed

— the same price offered to Brazil — and a cost of R123 194 (US$10 500) for a 12-week course of SOF/LDV in the base case scenario (GTPI, 2014).

- Cost of disease management

Costs related to disease or treatment management, including outpatient attendance and inpatient care, were taken from the National Health Referencing Price List (NHRPL). The NHRPL is a schedule of health service procedure codes administered by the Department of Health (DoH) and linked to reference prices. The Council for Medical Schemes (CMS) designed the NHRPL on behalf of the Department of Health. The first publication came out in 2004. This list does not contain negotiated prices; it is compiled by gathering submissions from all disciplines of health service with suggestions regarding the actual cost of running a practice. The NHRPL is in the public domain and published by the Board of Healthcare Funders (BHF) of Southern Africa.

The NHRPL pricelist was last published in 2009. All prices used in the model need to be normalised to one specific year, i.e. 2015. The most recent NHRPL values (2009) were medically inflated to 2015 values using Statistics South Africa's (STATS SA) annual statistical release reports (P0141) from 2009 to 2010 (STATS SA, 2009; STATS SA, 2010; STATS, SA; 2011, STATS SA, 2012; STATS SA, 2013; STATS SA, 2014 and STATS SA, 2015). The statistical release report gives a percentage change of consumer price indices for all urban areas. Each report contains a table with the heading "Consumer price indices for the total country". Medical inflation is regarded as the year-on-year percentage change in medical services. The year-on-year percentage change values were taken to calculate an inflation factor for each year from 2009 to 2015 (Inflation factor = 1 + (% change / 100). An inflation multiplier was then calculated as the product of the inflation factors from the year in which the prices were obtained (2009) to the current year (2015).

- Costs of diagnostic tests/pathology

The NHRPL makes available a standardised billing structure for use in the medical schemes industry. This empowers healthcare providers and medical schemes to autonomously set benefits and prices that match their own affordability constraints and cost structures. Procedure codes used in the NHRPL are numeric or alphanumeric codes that are used to identify medical services, treatment and procedures performed by healthcare providers. These codes provide a standardised method to describe medical, surgical and diagnostic services and facilitate communication between healthcare providers, medical schemes and medical scheme beneficiaries. Several procedure codes are currently in use in the private sector, of which RPL codes are among the most common (Matshidze & Hanmer, 2007:96).

The NHRPL rates are thus a guideline for practitioners and medical aid schemes around which they can calculate tariff structures and design benefit structures. It does not necessarily reflect the actual prices that may be charged at medical practices and private sector laboratories. Therefore, costs associated with these aspects of CHC treatment were rather obtained from private sector data. Cost estimates for procedures, diagnostic tests and inpatient admissions for complications of CHC were obtained from private sector cost data. The private sector cost data consisted of medicine claims data from the private healthcare sector in South Africa. Data was provided by an external party. This party, who's identity is to remain confidential, administrates the medical aid claims of approximately 40% of the medical aid scheme beneficiaries in the South African private healthcare market. From literature and expert opinion, all relevant diagnostic, management or treatment procedures associated with the treatment of CHC were identified. The RPL codes for these procedures (not including drug costs, outpatient management and inpatient palliative care) were then taken from the NHRPL and were submitted to the company supplying the cost data, who, in turn, provided the estimated private sector costs for each code. Data used for this model were from medical aid claims between February 2014 and February 2015, extracted on 30 April 2015.

The model accounted for three types of HCV-related cost, i.e. drug regimen, treatment monitoring and health state (downstream liver-disease complications). Costs of treatment cycles were expressed in South African Rand (ZAR) and United States Dollars (US$) at 2015 value. According to the South African third-party payer's perspective, only direct costs were considered — in particular, the drug costs (peg-INF, RBV, SOF) and the costs associated with disease management (i.e. diagnostic tests, routine blood tests, outpatient visits, hospitalisation etc.) Patients initiated treatment at the start of the model. In addition to receiving drug-treatment, all patients underwent baseline testing and diagnosis upon entering the model. Patients in both arms of the model acquired a once-off cost for pathology (including HCV antibody, HCV PCR & viral load, HCV genotyping, HBV sAg, HBV sAb, HBV core antibody (total), HIV-test (rapid and Western Blot technique), HAV-immunity (HAV IgG), TFT, LFT, FBC, U&E, INR, AFP and iron studies, abdominal ultrasound), the cost of a liver biopsy and the cost of a consultation with a specialist (hepatologist), irrespective of the treatment option chosen (refer to Table S2 on Online Resource A in Chapter 3). A detailed description of drug and monitoring costs are shown in Table S1 of the Online Resource in Chapter 3.

Patients only received treatment during the first model cycle, as no response after 48 weeks (SOC) or 12 weeks (SOF) was considered as treatment failure. After treatment failure patients progressed to the next health state in the model during the following cycle, as no retreatment was offered. During the first model cycle, patients received either SOF/LDV for 12 weeks (arm 1), SOF-TT for 12 weeks (arm 2) or SOC for 48 weeks (arm 3). The same treatment was

offered to patients with and without cirrhosis in each arm respectively. During treatment, patients are subjected to routine monitoring and screening. Therefore, in addition to the cost of drugs, patients in both treatment arms also acquired treatment and monitoring costs. The frequency of these test were dependant on the treatment regime and the disease state the patient is in when he/she receives treatment. Treatment management and monitoring of patients during treatment was based on the typical South African management of HCV, confirmed by South African hepatologists. The total cost of drug treatment and total monitoring costs were added to calculate a total treatment cost for cirrhotic and non-cirrhotic patients in each treatment arm.

(c) Effectiveness data

Effectiveness data was obtained from published literature. The purpose of effectiveness data in cost-effectiveness analyses is to indicate the effect of an intervention of the disease progress (i.e. does it slow down the disease process or return a patient to the healthy state?). Data on the response rate to antiviral therapy of HCV-G5 is limited as the global HCV-G5 population and is relatively small and large single studies are difficult to perform (D'Heygere *et al*., 2011:817). Most available studies on HCV-G5 are based on retrospective data in small groups of patients; i.e. 26 patients living in the Midi-Pyrenees region of France (Legrand-Abravanel *et al.,* 2004:1398), 16 patients in Southern Belgium (Delwaide *et al.,* 2005:2348) and 87 HCV-G5 patients from 12 centres in France (Bonny *et al*., 2006:593). There is also substantial heterogeneity in the management of HCV-G5 between studies with regard to the types of interferon used, the dosages of drugs administered and treatment length, which makes it difficult to properly document the characteristics and response rate to interferon-based treatment of CHC patients infected with HCV-G5 (Legrand-Abravanel *et al.,* 2004:1398; Delwaide *et al.,* 2005:2348; Bonny *et al*., 2006:593).

D'Heygere *et al.* (2011) pooled the results of two large phase III/IV randomised controlled trials (RCTs) conducted in Belgium in patients with chronic hepatitis C (n = 1 073 patients). The BENAR-1 and BENAR-2 randomised controlled trials were both designed to test safety and efficacy of peg-INF/RBV in patients with CHC and included efficacy data on all six genotypes (Langlet *et al.,* 2009:352; Nevens *et al*., 2010:223). The meta-analysis was performed to compare the efficacy of peg-INF in combination with RBV on HCV-G5 with other genotypes. Efficacy data for the standard of care, i.e. peg-INF/RBV was thus taken from the meta-analysis conducted by D'Heygere *et al.* (2011). The NEUTRINO trial is the only sofosbuvir trial to date that includes efficacy data for HCV-5 (Lawitz *et al.,* 2013:33). This open-label, single-arm trial evaluated 12 weeks of sofosbuvir in combination with peg-INF/RBV in chronic HCV patients with genotypes 1, 4, 5 or 6 (ClinicalTrials.gov, 2013). As a result, efficacy data for triple therapy, i.e. sofosbuvir + peg-INF + RBV was taken from the NEUTRINO trial. To date, there have been

no large RCTs that include efficacy data for SOF/LDV in HCV-G5, however, a small open label study conducted in France found that sofosbuvir-ledipasvir administered as monotherapy for 12 weeks in treatment-naïve and treatment-experienced patients infected with HCV-G5 yielded an SVR rate of 95%, irrespective of cirrhosis status (Abergel *et al.*, 2015). A full critical appraisal of both trials including SOF (NEUTRINO trial and open-label, multicentre, single-arm, phase 2 trial conducted in France) was done using the Consolidated Standards of Reporting Trials (CONSORT) checklist (refer to Appendix A). Baseline characteristics for the participants in the NEUTRINO trial and the French study conducted by Abergel *et al*., (2015) are shown in Tables 1.7 and 1.9.

Table 1.7: Baseline characteristics: NEUTRINO trial

Characteristic	SOF + peg-INF + RBV for 12 weeks
Mean age – years (range)	52 (19-70)
Mean body-mass index (range)	29 (18-56)
Male sex – no. (%)	209 (64)
Race or ethnic group – no. (%)	
White	257 (79)
Black	54 (17)
Asian	7 (2)
Other	9 (3)
Hispanic or Latino	46 (14)
HCV subtype – no. (%)	
1a	225 (69)
1b	66 (20)
2	0
3	0
4	28 (9)
5	1 (<1)
6	6 (2)
Mean HCV RNA – $\log_{10}$ IU/ml	6.4±0.7
HCV RNA ≥800 000 IU/ml – no. (%)	267 (82)
IL28B genotype – no. (%)	
CC	95 (29)
CT	181 (55)
TT	51 (16)
Cirrhosis – no. (%)	54 (17)
Alanine aminotransferase >1.5xULN – no. (%)	166 (51)
IL = interleukin; IU = international units; HCV = hepatitis C virus; RNA = ribonucleic acid	

Investigators in the NEUTRINO study determined that the enrolment of 300 patients with HCV genotype 1, 4, 5, or 6 infection would provide a power of 90% to show a rate of SVR with the sofosbuvir regimen that was higher than 60%, a calculated control rate based on previous efficacy after adjustment for the presence of cirrhosis and expected safety benefit. There was a joint decision with regulatory authorities not to include a currently available protease-inhibitor regimen as an active control, based on the expectation of high response rates, improved safety, and shorter treatment duration (Lawitz *et al*., 2013:1886).

Participants received sofosbuvir + peg-INF + RBV for 12 weeks and were followed for 24 weeks following treatment. Participants received 400 mg sofosbuvir as an oral tablet, 180 µg of peg-INF as a subcutaneous injection, and 1000-1200 mg RBV as 200 mg oral tablets. In the NEUTRINO trial, 12 weeks of treatment with SOF + peg-INF/RBV had high efficacy in previously untreated patients with genotype 1 or 4 infection, with apparent reductions in adverse events (Lawitz *et al*., 2013:1887).

Table 1.8: Outcomes of NEUTRINO trial: response during and after treatment

Response	SOF + peg-INF/RBV for 12 weeks
HCV RNA <25 IU/ml – no./total no. (%)	
During treatment	
At 2 weeks	299/327 (91)
At 4 weeks	321/325 (99)
At last observed measurement	326/327 (>99)
After end of treatment	
After 4 weeks	302/327 (92)
After 12 weeks	295/327 (90)
Virologic breakthrough during treatment – no. (%)	0
Relapse in patients with HCV RNA <25 IU/ml at end of treatment	
Patients who completed treatment	25/320 (8)
Patients who did not complete treatment	3/6 (50)
HCV = hepatitis C virus; IU = international units; RNA = ribonucleic acid	

In the NEUTRINO trial, 92% of patients achieved SVR four weeks after treatment had ended, and 90% of patients had SVR 12 weeks after treatment had ended. Since virologic suppression was achieved by week 4 in almost all patients and was maintained until the end of treatment, response-guided treatment was not required. Although no data from randomized comparisons were available, findings from the NEUTRINO trial suggest that adverse events associated with the SOF + peg-INF/RBV regimen are similar to those associated with peg-INF/RBV alone.

Abergel *et al.* (2015) assessed the efficacy and safety of combination therapy with the NS5A inhibitor LDV and SOF in patients with HCV genotype 5. This open-label, multicentre, single-arm, phase 2 trial was conducted at five hospitals in France. Eligible patients were at least 18 years old and had chronic infection with HCV genotype 5, with plasma HCV RNA of at least 10 000 IU/mL. BLAST analyses of NS5B partial sequences were used to establish the genotype and subtype at screening. Participants received a fixed-dose combination tablet of 400 mg SOF and 90 mg LDV as an oral tablet, once per day for 12 weeks. The primary endpoint was the proportion of patients with a SVR, defined as HCV RNA concentration less than 15 IU/mL at 12 weeks after the end of treatment. Investigators analysed the efficacy and safety in all patients who received at least one dose of LDV/SOF. The baseline characteristics of participants in this trial are shown in Table 1.9.

Table 1.9: Baseline characteristics: French LDV/SOF study

Characteristics	**HCV-G5**	
	Naïve (n = 21)	**Experienced (n = 20)**
Mean age, years (range)	61 (40-78)	64 (50-79)
Male, n (%)	11 (52)	10 (50)
White, n (%)	21 (100)	20 (100)
Mean BMI, kg/m^2 (range)	24 (18-30)	27 (19-39)
Cirrhosis, n (%)	3 (14)	6 (30)
IL28B non-CC, n (%)	8 (38)	14 (70)
Mean HCV RNA, log$_{10}$ IL/ml (range)	6.2 (5.3-6.9)	6.6 (5.7-7.1)
BMI = body mass index; HCV = hepatitis C virus; IL = interleukin; RNA = ribonucleic acid		

All 41 patients who started treatment completed the full 12 weeks of treatment and had undetectable HCV RNA at their final treatment visit. Results for patients with HCV-G5 are shown in table 1.10.

In the overall study population, 39 of 41 patients achieved SVR12 (SVR rate 12 weeks after treatment = 95%; 95% CI: 83–99). SVR12 was achieved by 20 (95%; 95% CI: 76–100) of the 21 patients who were treatment naive and 19 (95%; 95% IC: 75–100) of the 20 patients who were treatment experienced. Of the nine patients with cirrhosis, eight (89%) achieved SVR12; whereas 31 (97%) of the 32 patients without cirrhosis achieved SVR12. The two patients who did not reach SVR12 both had IL28B TT genotype and had viral relapse within 4 weeks of the end of treatment (Abergel *et al*., 2015). Results from this trial suggested that the oral regimen of LDV/SOF is an effective and well-tolerated treatment for both treatment-naïve and treatment-experienced patients with HCV-G5 infection.

Efficacy data for the new DAAs for HCV-G5 remains based on small patient numbers, which is evident in the fact that the NEUTRINO trial only included one patient with HCV-G5, and 41 patients with HCV-G5 in the open-label, multicentre, single-arm phase 2 trial conducted in France. The lack of efficacy data for HCV-G5 has been a significant challenge as to date, sub-Saharan African countries, including South Africa, have been excluded from clinical trials for new HCV DAAs, It is a glaring omission by trial designers and multinational pharma to have significantly excluded these regions of the world, with differing genotypes from registration trials. It places researches at a significant disadvantage and this thesis is a concerted attempt to try and address major gaps in data. It is, however, recognised that interferon-free drugs for HCV are a reality and that there is a movement towards an era of all-oral therapies for all HCV genotypes and the cost-effectiveness of these new drugs for HCV in South Africa is very relevant and an important topic for further research.

Nevertheless, based on the results of the Abergel *et al.* study and the NEUTRINO trial, both the AASLD and EASL amended their HCV treatment guidelines in 2015 to include sofosbuvir + peg-INF/RBV and SOF/LDV for HCV-G5 infection. Dosing and administration of both sofosbuvir-containing regimens modelled in this study were based on the EASL and AASLD guidelines (AASLD, 2015; EASL, 2015). The EASL clinical practice guidelines (CPGs) have been developed by a CPG panel of experts chosen by the EASL Governing Board. The recommendations are peer-reviewed by external expert reviewers and approved by the EASL Governing Board. The CPGs are based (as far as possible) on evidence from existing publications, and, where evidence is unavailable, the experts draw on personal experience and opinion. Where possible, the level of evidence and recommendation are cited. The evidence and recommendations in the EASL guidelines are graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system. The strength of recommendations thus reflects the quality of underlying evidence. The quality of the evidence in the EASL guidelines are classified in one of three levels: high (A); moderate (B) or low (C). The GRADE system also offers two grades of recommendation: strong (1) or weak (2). The EASL guidelines therefore consider the quality of evidence: the higher the quality of evidence, the more likely a strong recommendation is warranted; the bigger the variability in values and preferences, or the bigger the uncertainty, the more likely a weaker recommendation is warranted.

The AASLD and EASL clinical practice guidelines for treating HCV-G5 include SOF + peg-INF/RBV for 12 weeks based on the NEUTRINO trial, and SOF/LDV for 12 weeks based on the French Abergel *et al.* study (EASL, 2015:217). The NEUTRINO trial was graded B1 by EASL: B = moderate quality (further research is likely to have an important impact on the panel's confidence in the estimate of effect and may change the estimate); 1 = strong recommendation

(factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost). The French SOF/LDV study was graded A1: A = high quality (further research is very unlikely to change the panel's confidence in the estimate of effect); 2 = weak recommendation (variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption) (EASL, 2015:201).

The AASLD treatment recommendations are based on scientific evidence and expert opinion. Each recommended statement includes a Roman numeral (I, II, or III) that represents the level of the evidence that supports the recommendation, and a letter (A, B, or C) that represents the strength of the recommendation. Both SOF/LDV and SOF-TT considered class IIa, level B. Class IIa means that the weight of evidence and/or opinion is in favour of usefulness and efficacy; whereas level B means that the data was derived from a single randomized trial, nonrandomized studies, or an equivalent (AASLD, 2015). Thus, even with the limitation only a single patient with HCV-G5 included in the NEUTRINO trial and the small HCV-G5 patient population included in the French SOF/LDV study, both AASLD and EASL still consider the evidence of these trials to be of moderate to high quality.

The National Institute for Health and Care Excellence (NICE) considered SOF in combination with RBV — with or without peg-INF — to be clinically effective compared with peg-INF/RBV in people with treatment-naïve and treatment-experienced HCV genotypes 4, 5 and 6. NICE recommends this combination for HCV-G5 only in patients who have cirrhosis, because it is not considered to be a cost-effective regime in the absence of cirrhosis (NICE, 2015a). The SOF/LDV combination has a marketing authorisation in the United Kingdom for treating CHC in adults, however, the marketing authorisation recommends specific treatment durations for HCV genotypes 1, 3 and 4 only, and states that SOF/LDV should not be used in people with HCV genotypes 2, 5 and 6 (NICE, 2015b).

In their 2015 guidelines, the Canadian Drug Expert Committee (CDEC) of the Canadian Agency for Drugs and Technologies in Health (CADTH) considered there to be insufficient evidence to make any recommendation for patients with CHC genotype 5 or 6 infection (CADTH, 2015). It is important to note that none of the DAA regimens available in Canada are approved for use in CHC genotype 5 or 6 infection, however, the Canadian Association for the Study of the Liver (CASL) guidelines recommend SOF + peg-INF/RBV for 12 weeks for the treatment of HCV-G5 infection, and SOF/LDV for 12 weeks (preferred) or SOF + peg-INF/RBV for 12 weeks (alternative) for the treatment of HCV-G6 infection (Myers *et al*., 2015).

(d) Utility values

Utility measures originated in health economics, and form an important subgroup of generic measures that are used in cost-effectiveness studies and medical decision-making analyses (Kind *et al.,* 2009:S27). Utility measures can be used to compute quality-adjusted life years (QALYs), which provide an indication of the benefits gained from different medical procedures in terms of quality-of-life (QoL) and survival of the patient (Torrance, 1986:2).

Utilities are cardinal values that reflect an individual's preferences for a specific level of health status or different health outcomes. They are measured on an interval scale with zero reflecting states of health equivalent to death and one reflecting perfect health (Whitehead & Ali, 2010:96). Utilities are normally combined with survival estimates in health economic analysis and aggregated across individuals to generate QALYs for use in cost-utility analyses of healthcare interventions (Torrance, 1986:2). Within the context of modelling, each health state of the Markov model is assigned a utility — a cardinal value representing the strength of a person's preference for a particular health outcome (Tolley, 2009:1). By multiplying utility values with the average number of cycles that individuals reside in each state, QALYs and, consequently, expected costs, can be estimated. For example: if a utility value of 0.8 is assigned to the 'moderately ill' state, and a person remains in that state for 10 years, and then spends three years in the 'severely ill' state, which has a utility value of 0.5, the person will have accumulated 9.5 QALYs at the end of these time frames [(10 x 0.8) + (3 x 0.5) = 9.5 QALYs]. Health utilities for HCV-infected patients were obtained from published literature.

(iii) Running the model through TreeAge Pro Healthcare 2014 software to yield results based on cost-effectiveness and analysing these results

As the cohort cycles through the health states and transition sub-trees, cost, effectiveness and/or other value measures (i.e. QALYs) are accumulated, both based on the starting health state and on the events that occur within the cycle. After all cycles are completed, the overall accumulated cost and/or effectiveness generates the expected value for the Markov model in its entirety — this accounts for all combinations of events over any number of cycles.

(iv) Using the results to compare the alternative HCV treatment strategies based on cost-effectiveness and incremental cost-effectiveness ratios

Once the model was complete, TreeAge Pro software (TreeAge Pro 2014, R1.2) used the visual model structure to automatically generate the algorithms required to evaluate the model and choose the optimal strategy. Standard algorithms give weight to each possible outcome within the strategy, based on its probability and the combined weighted average generates an overall expected value for each strategy. The model estimated (deterministic) life years (LY) and

lifetime costs for the following strategies: (i) peg-INF + RBV, (ii) sofosbuvir + peg-INF + RBV, and (iii) SOF/LDV monotherapy. By applying a health utility value to life years gained, QALYs were calculated for each alternative treatment strategy.

Incremental costs were divided by incremental QALYs and cost-effectiveness was expressed as 'cost per QALY' or 'incremental cost-effectiveness ratio' (ICER). TreeAge Pro's healthcare module (TreeAge Pro 2014, R1.2) allows the researcher to compare the modelled strategies on the basis of cost-effectiveness via ICERs and/or net benefits. The ICER can be compared to a WTP threshold to determine whether healthcare funders can afford the more effective treatment on the basis of cost-effectiveness.

Sensitivity analyses were conducted to study the effects of uncertainty on the results and conclusions. Deterministic and probabilistic sensitivity analyses were conducted. Deterministic (one-way) sensitivity analysis was used to identify thresholds for individual parameters and to assess the impact of individual changes to model inputs and assumptions on model results. Key parameters varied included SVR rates (±10% to a maximum of 99%), transition probabilities (95% CI), costs for health states (±20%) and utility values (range, minimum and maximum values taken from literature). We conducted the probabilistic sensitivity analysis by running 1,000 simulations, varying costs by gamma-distribution (±10%) and transition probabilities (±10%), SVR rates (±10%) and utility values (±20%) by beta-distribution. Both future costs (in rand, year 2015 values) and health outcomes (QALYs) were discounted at an annual discount rate of 5%.

(v) Determining whether the modelled price for sofosbuvir and SOF/LDV will be cost-effective for HCV infection in South Africa based on the willingness-to-pay threshold of R200 000

Results from the cost-effectiveness analysis were used to determine if the chosen prices for sofosbuvir and SOF/LDV will be cost-effective in South Africa. If the prices modelled in the base-case scenario were not cost-effective, it would be adjusted in sensitivity analyses until it yielded an ICER below the willingness-to-pay threshold of R200 000 to determine at which price sofosbuvir and/or SOF/LDV will be cost-effectiveness in South Africa compared to the current standard of care.

(vi) Quantifying the public health impact of the use of sofosbuvir-containing regimens compared to current HCV treatments from a third-party payer's perspective

(vii) Determining the budget impact of sofosbuvir-containing regimens in South Africa as part of the total health budget

Using the results from the cost-effectiveness model, the public health impact of the use of sofosbuvir-containing regimens compared to current HCV treatments in South Africa was quantified. A third party payer's perspective was followed to determine the budget impact of sofosbuvir-containing regimens in South Africa.

1.5.2.5 Validity and reliability

1.5.2.5.1 Validity and reliability of data used in the model

- Pharmaceutical Bluebook and NHRPL data

In 1958, an entrepreneurial chemist identified the need to provide a reliable pharmaceutical price guideline for fellow pharmacists, which led to the development of the Pharmaceutical Bluebook. Today, the Pharmaceutical Bluebook is a publication renowned for its accurate and up-to-date information and it remains the single most trusted pharmaceutical product data and price reference for members of the medical and pharmaceutical profession. Doctors, pharmacists and medical aids can subscribe to the on-line version of the Pharmaceutical Bluebook and on-line subscribers gain access to a searchable database of information that is updated as soon as changes are received from the pharmaceutical manufacturers, who supply the information directly to Pharmaceutical Bluebook cc. The Pharmaceutical Bluebook contains the most complete reference list of ethical products in South Africa and the database is kept up to date on a daily basis — reducing the possibility of medical aid rejections through incorrect pricing (The Official Pharmaceutical Bluebook, 2015).

The NHRPL is a schedule of health service procedure codes administered by the DoH and linked to reference prices. It was designed by the Council for Medical Schemes on behalf of the DoH and was first published in 2004. NHRPL schedules are in the public domain and can be found on the Council for Medical Scheme's website (CMS, 2015a).

- Private sector cost data

There are different definitions for 'health information' depending on the setting or context it is used in. However, it is agreed that a good working definition of health information is that it is information about "...all resources, organisations and actors that are involved in the regulation, financing, and provision of actions whose primary intent is to protect, promote or improve health" (WHO, 2003).

Role players at all levels of the healthcare spectrum utilise health information for planning and decision-making. The type of information collected by various role players depends on what they want to use the information for, and hence there is a difference in the reliability, level of detail, and diversity of topics between information collected by different health sectors (Matshidze & Hanmer, 2007:91). The Council for Medical Schemes has developed an essential dataset for the private health sector. The essential dataset describes the essential information that all medical schemes must collect and includes three primary information areas, i.e. access, cost, and utilisation of healthcare services (CMS, 2003).

- Effectiveness data and health utilities data

Effectiveness data and health utilities data were obtained from published, peer-reviewed literature. Effectiveness data was taken from published results of the NEUTRINO clinical trial (ClinicalTrials.gov number NCT01641640) (Lawitz *et al.,* 2013), the phase two open-label study conducted in France on SOF/LDV for HCV-G5 infection (Abergel *et al.,* 2015) and the BERNAR-1 and -2 trials (D'Heygere *et al.,* 2011).

1.5.2.5.2 Validity and reliability of model structure

The credibility of any model rests on its validity, i.e. the extent to which a model measures what it is supposed to measure. Validation is a process of determining whether the model and its associated data are an accurate representation of the real world and whether the results allow policy-makers or healthcare researchers to draw the inferences they have to make (MacKinnon, 2008:34). The types of model validation used in this study included face validation, internal validation (verification), cross-validation (between-model validation) and external validation.

Face validity describes the extent to which a model, its assumptions and applications correspond to current science and evidence. Face validity is subjective as it is judged by people who have clinical expertise in the problem being addressed (Eddy *et al.,* 2012:845). In the case of this study, face validation was performed by clinical experts — independent hepatologists — who evaluated how well each model component reflects its understanding of the pertinent medical science, available evidence and clinical question at issue. Internal

validity, or model verification, addresses whether the model's parts perform as intended and the model has been implemented appropriately, i.e. it examines the extent to which the mathematical calculations are performed correctly and are consistent with the model's specifications (Eddy *et al*., 2012:845).

For the purpose of this study, internal validity was verified by conducting sensitivity analyses on model parameters. Through the evaluation of a broad range of input values, the investigator was able to determine whether the direction and magnitude of model outputs behave as anticipated. Cross-validation, or between-model validation, was conducted by comparing the model with others that address the same problem and determining the extent to which they calculate similar results. External validation involves comparing a model's results with actual events data (Eddy *et al*., 2012:845). For the purpose of this study, the researcher simulated events that have occurred, such as those in the NEUTRINO trial and examining how well the results correspond. Uncertainty in the model was dealt with by performing extensive sensitivity analyses of key clinical and economical parameters. These sets of techniques were used to test the robustness of the conclusions (Milne, 1998:131). One-way sensitivity analysis was used to assess the impact that changes in a certain parameter will have on the model's conclusions. Sensitivity analysis can help the researcher to determine which parameters are the key drivers of a model's results (Taylor, 2009).

1.6 Ethical considerations

The guiding principles of health research formulated by the National Health Research Ethics Council (NHREC) reflect the basic ethical values of beneficence, non-maleficence, equality, dignity and autonomy (Greeff, 2014). The purpose of these principles is to protect the interest of both research participants and researchers within a variety of research contexts.

This was considered to be a no-risk study since the model only employed a hypothetical cohort of HIV-naïve HCV patients. Permission to conduct this study was obtained from the Health Research Ethics Committee (HREC), Faculty of Health Sciences, North-West University (NWU-00035-15-A1).

1.7 Chapter summary

This chapter provided an introduction and overview of the study. It reflected on the background and motivation for the study, research questions, research objectives and the method of study employed. The next chapter represents the literature review of this study and will cover all of the topics included in the literature research phase objectives set out in paragraph 1.4.2.1. Chapter three and four represent the results and discussions and conclusions of the study, respectively.

CHAPTER 2: LITERATURE REVIEW

Chapter 2 represents the literature review of this study. The aim of this chapter was to characterise the patient journey of an individual infected with the hepatitis C virus, focusing on defining HCV infection and researching all relevant aspects on the subject of the disease; including clinical features of the disease, routes of transmission, incubation period, risk factors, prevention, complications, diagnosis and testing, treatment and response.

2.1 Hepatitis C virus

The decade of the 1980s saw the emergence of two major blood-borne viruses. The discovery and unrestrained spread of HIV in the early 1980s obscured the presence of another infectious agent that generally affected intravenous drug users and recipients of blood products (Gravitz, 2011:S2). The HCV remained unidentified until 1989 when it was identified and cloned (Choo *et al*., 1989:359). Notably, it was the first biologic infectious agent to be patented given the collaborative work in its discovery between the public and private sectors.

HCV is one of five 'hepatitis viruses' (hepatitis A, B, C, D and E). Hepatitis A and B were discovered in 1973 and 1967, respectively. The hepatitis A virus (HAV) causes an acute infection with diffuse liver inflammation that mostly settles within weeks to months, while the hepatitis B virus (HBV) has a significant risk of chronicity with exposure in childhood (30-60%) and less than 10% in adults (Williams, 2006:521). More than a decade after the discovery of HAV and HBV, researchers established that another infectious agent was responsible for causing liver disease. Initially called non-A-non-B hepatitis virus, it was named hepatitis C after its formal identification in 1989 (Houghton, 2009:83).

HCV is an enveloped single-stranded RNA virus that belongs to the *Flaviviridae* family of RNA viruses (Lindenbach & Rice, 2001:992). It is hepatotropic rather than directly cytopathic — suggesting that it has a special affinity for exerting a particular effect on the liver, instead of directly damaging liver cells during virus invasion (Bertoletti & Ferrari, 2003:4). HCV consists of a family of highly related, yet distinct genotypes. These genotypes are genetic variants of the same virus, with differing geographical distribution and with a complex nomenclature. Six major genotypes of HCV have been identified (genotypes 1 to 6), as well as several subtypes (Choo *et al*., 1991:2451).

The significance of HCV, however, does not reside in the virus itself, but rather in the fact that it may cause hepatitis C; a slowly progressing liver disease histologically defined as *"inflammation of the liver characterized by diffuse or patchy necrosis"* (Beers *et al*., 2006:219). Hepatitis C can range in severity from mild illness (lasting a few weeks) to a serious, lifelong disease in those

who are infected with the virus (Pears, 2010:49). Although hepatitis C is generally considered to be a progressive disease — with the rate of progression varying widely from one person to another — the disease has two distinct phases, *viz*. acute and chronic (Parini, 2001:20).

2.1.1 Acute hepatitis C

Acute hepatitis C is invariably a subclinical process and diagnosis is seldom made during the acute infection stage. The clinical appearance of acute hepatitis C is not well described for all modes of transmission, as the course of the acute phase has primarily been described in the post-transfusion scenario (Marcellin, 1999:9). As noted, in most cases, acute hepatitis C is asymptomatic. In the 10 to 15% of newly infected persons who are symptomatic during acute infection, clinical illness is usually mild and lasts no longer than six months (Maheswari *et al*., 2008:323).

After viral transmission, HCV RNA becomes detectable in the serum within seven to 21 days. Longer incubation periods can occur, especially in cases where only small amounts of viral loads have been transmitted (Ozaras & Tahan, 2009:351). Specific HCV antibodies usually present 12 to 16 weeks after the initial infection, although in some cases, it may take up to six months before the antibodies can be detected (Ozaras & Tahan, 2009:351). Despite the highly variable course of acute hepatitis C, its most characteristic feature is fluctuating elevations in serum alanine aminotransferase (ALT) levels. Normalisation of ALT levels might occur and suggest full recovery, but this is often followed by elevations in ALT levels that indicate progression to chronic disease (CDC, 1998:13). Four to 12 weeks after infection, a rapid raise in HCV RNA levels is followed by a delayed increase in serum ALT levels — that can reach values of more than nine-fold the upper limit of normal with simultaneous elevation of serum bilirubin — indicating hepatic injury (Cox *et al*., 2005:957).

In some patients, HCV infection is a self-limiting illness. In these patients, serum ALT levels return to normal and serum HCV RNA becomes undetectable within approximately three months after the onset of acute infection (Santantonio & Fasano, 2008:627). However, spontaneous elimination of the virus is uncommon and very few persons infected with HCV will 'naturally' clear the virus at the acute stage. Those who fail to clear the virus, develop chronic HCV infection (Poll, 2012:396).

2.1.2 Chronic HCV infection

Patients, in whom HCV infection persists for longer than six months, are considered to have chronic HCV infection. Chronic HCV infection is recognised by persistently abnormal serum ALT levels and characteristic histological findings; although it may be clinically indistinguishable from chronic hepatitis due to other causes (Hoofnagle, 1997:15S). Chronic hepatitis is defined

as *"a state in which symptoms of hepatitis continue for several months and may increase in severity"* (Mosby's Dictionary of Medicine, Nursing & Health Professions, 2006:382).

Approximately 75 to 85% of newly infected patients will progress to chronic HCV infection, which causes low-grade necro-inflammation of the liver and progressive liver fibrosis over many years, increasing the risk of liver failure and liver cancer in those persons affected (Seeff, 1997:19). Similar to acute hepatitis C, chronic hepatitis C (CHC) is generally asymptomatic, although patients may complain of non-specific symptoms, such as fatigue, muscle aches, anorexia, right upper quadrant pain or nausea. These symptoms are, however, not exclusive to CHC and are also not associated with the severity of liver injury (Hoofnagle, 1997:15S).

2.1.3 Predictors of chronic HCV infection

The rate of chronic infection is affected by many factors, including the age at time of onset of infection, gender, ethnicity and immunosuppression (Chen & Morgan, 2006:48). The following are risk factors for developing chronic HCV infection: age, gender, ethnicity/race, and immunosuppression. These factors are discussed briefly in subsequent paragraphs.

2.1.3.1 Age

The NHANES study found that the chronicity rate was less likely in subjects younger than 20 years than for persons older than 20 years; the chronicity rate was estimated at 30% in persons below the age of 20 years, and 76% for those older than 20 years, which suggests that persons infected with HCV during their late teen years are less likely to have chronic HCV infection than those affected at older ages (Alter *et al*., 1999:558).

2.1.3.2 Gender

The rate of chronicity in HCV infection appears to be lower in women than in men (Kenny-Walsh, 1999:1229). Evidence for this largely comes from retrospective analyses of two major outbreaks of HCV that occurred among pregnant women who received contaminated Rh immune globulin: in a 17-year follow-up study in Ireland, the chronicity rate was 55% of 704 women with anti-HCV after receipt of contaminated immune globulin (Kenny-Walsh, 1999:1229). A similar HCV chronicity rate (55%) was found in a 20-year German follow-up study of 917 women who had received Rh immune globulin contaminated with HCV (Wiese *et al*., 2000:91).

2.1.3.3 Ethnicity/race

There are differences among different racial and ethnic groups with HCV infection; not only in the rate of chronicity of HCV infection, but also in response to treatment and the development of

complications. It has been reported that African Americans have a higher rate of chronic HCV infection than Caucasians and Hispanic whites (Seeff *et al*., 2001:457).

2.1.3.4 Immunosuppression

Because the risk of chronicity of HCV infection is higher in patients who are co-infected with HIV than in those who are HIV negative, it appears that the competency of the immune response is an important factor in the development of chronic HCV infection and the progression of liver fibrosis (Thomas *et al*., 2000:450). Studies have indicated a significantly higher prevalence of HCV among HIV infected patients as compared to HIV negative patients (13.4% vs. 1.73%) (Parboosing, 2008). This might be important for South Africa, as an estimated 12.2% of the South African population (6.4 million persons) are HIV positive (Shisana *et al*., 2014).

2.1.4 Risk factors for advanced progression of liver fibrosis

The rate of progression of liver fibrosis in chronic HCV infection varies extensively. Fibrosis is an important consideration in the disease pathogenesis of hepatitis C, as fibrosis implies possible progression to cirrhosis. In mild cases, fibrosis is limited to the portal and periportal areas of the liver. More advanced changes are defined by fibrosis that extends from one portal area to another, also known as 'bridging fibrosis' (Chen & Morgan, 2006:49). The following are factors that have been identified as risks for the advanced progression of liver fibrosis: alcohol consumption, age, and co-infection with HIV, HBV and other comorbidities.

– **Alcohol consumption**

Alcohol consumption appears to be one of the most influential factors driving fibrosis in patients with CHC infection, as higher levels of alcohol consumption contribute to the development of progressive liver disease (Poynard *et al*., 2001:734; Wiley *et al.,* 1998:805). The interaction between alcohol and HCV in chronic liver disease is not fully understood, but appears to involve earlier onset and more rapidly progressive fibrosis even with levels of alcohol consumption as low as 20 g/day (Alawazi *et al.*, 2013:353). Detrimental effects have been reported at 30 g/day in men and 20 g/day in women (Wiley *et al.,* 1998:805).

– **Age**

A significant association has been reported between the rate of fibrosis and the age at time of onset of HCV infection. The progression of liver disease is non-linear and may develop at a faster rate as the patient gets older (Deuffic-Burban *et al*., 2002:116; Poynard *et al*., 2001:733).

– **Co-infection with HIV or hepatitis B virus and comorbid conditions**

The role of co-infections and comorbid conditions is another important component in the natural history of HCV infection, because immunosuppression has been associated with more aggressive liver disease (Soriano *et al.,* 2002:813). Comorbid conditions such as obesity, diabetes mellitus (to which HCV infection itself appears to predispose) and insulin resistance (which appears to be associated with worsening liver fibrosis and decreased response to HCV therapy) all increase the risk for advances progression of liver fibrosis (Chen & Morgan, 2006:49; Wilkie, 2013:23). Furthermore, immunosuppressed persons with chronic HCV infection seem to progress more quickly to cirrhosis than those who are immunocompetent.

2.1.5 Clinical features of hepatitis C

All types of viral hepatitis have a similar symptom profile. Patients infected with any one of the virus genotypes can present with one or more of the following signs or symptoms:

- Fever
- Fatigue
- Loss of appetite
- Nausea
- Vomiting
- Abdominal pain
- Grey-coloured bowel movements
- Dark urine
- Joint pain, and
- Jaundice (Immunization Action Coalition, 2007).

Individuals with hepatitis C are less likely to experience symptoms than patients with other types of viral hepatitis and approximately 80% of people infected with HCV are asymptomatic following initial infection (CDC, 2012).

The onset of flu-like symptoms may be abrupt or insidious, with general malaise, myalgia, arthralgia, easy fatigability, upper respiratory symptoms and anorexia. Distaste for smoking may occur early and nausea and vomiting are fairly common. Abdominal pain is mostly mild and constant in the right upper quadrant or epigastrium. Low-grade fever is generally present, although defervescence and a lowered pulse rate often correspond with the onset of jaundice.

Jaundice generally occurs within five to 10 days in approximately only 10% of patients, but may appear at the same time as the initial symptoms (Parini, 2001:20; Poll, 2012:397).

The most common clinical signs of viral hepatitis include mild hepatomegaly (which is present in more than half of all cases) and liver tenderness. Splenomegaly is reported in approximately 15% of patients and soft, enlarged lymph nodes, especially in the cervical or epitrochlear areas, may also occur. Minor neurocognitive impairment has also been described in patients with chronic HCV infection (Pears, 2010:50). Noteworthy signs and symptoms of liver disease do not, however, occur until fibrosis has developed to such an extent that the liver function is compromised, at which stage, cirrhosis may already be present (Pears, 2010:50).

2.1.6 Routes of transmission

HCV is a blood-borne virus generally transmitted through exposure to infected blood (Villena, 2006:S12). Although anyone can, theoretically, contract HCV, it is largely associated with previous or current drug users, particularly injecting drug users, as over 50% of cases of HCV are transmitted by injection drug use (Wilkie, 2013:23). Other routes of transmission include infected blood transfusions, blood products and organ transplants, unsafe medical injection practices and needle-stick injuries in healthcare settings, or being born to an HCV-infected mother (Alter, 2011:340). Although less common, HCV may also be transmitted through sharing personal items contaminated with infectious blood. In sub-Saharan Africa, traditional practices may play a role (Alter, 2011:340).

The risk of sexual and maternal-neonatal transmission is low (and much less likely than for HIV) and may be greatest in a subset of patients with high circulating levels of HCV RNA (Tong *et al*., 1995:40). Sexual transmission risk in the men who have sex with men (MSM) population, however, is considerably higher. Transmission *via* breastfeeding, on the other hand, has not been documented (Villena, 2006:S13). In poorer countries, the reuse of medical supplies is still common and, in combination with a lack of screening of blood donations, is fuelling the virus's spread (Gravitz, 2011:S2). In many patients, though, the source of infection is unknown (Wilkie, 2013:23).

2.1.7 Risk factors for contracting HCV

As HCV is most commonly transmitted through exposure to infectious blood, the following groups of people are at risk of contracting HCV:

– Current or former injecting drug users;

– Recipients of clotting factor concentrates before 1987;

– Recipients of blood transfusions or donated organs before July 1992;

– Long-term haemodialysis patients;

– Persons with known exposures to HCV (e.g. healthcare workers after needle stick injuries, recipients of blood or organs from a donor who later tested positive for HCV), and

– Infants born to infected mothers (CDC, 2012).

Intranasal cocaine use, body piercing, tattoos and having multiple sexual partners may all also increase the risk of HCV infection (even though the virus is not commonly spread through sexual intercourse) (Yee *et al*., 2001). Furthermore, HIV-infected persons are also at an increased risk of contracting HCV, as co-infection with HCV is found in at least 30% of persons infected with HIV. Not only does HIV infection lead to an increased risk of hepatic failure and a more rapid progression of chronic HCV infection to cirrhosis, but it also increases the hepatotoxicity of highly active antiretroviral treatment (HAART) (Thein *et al.*, 2008:1988).

2.1.8 Incubation period

It has been suggested that the duration of the incubation period of HCV may vary between different routes of transmission (Maasoumy & Wedemeyer, 2012:402). Typically, the incubation period for HCV infection is 14 to 140 days with a mean of 45 days (Ozaras & Tahan, 2009:351). Seroconversion normally occurs 32 to 46 days after viraemia, although prolonged periods (up to 12-48 weeks) before seroconversion are not uncommon in immunocompromised persons (Maasoumy & Wedemeyer, 2012:403).

2.1.9 Prevention of HCV infection

At present, there is no vaccine and no post-exposure prophylaxis available for HCV (vaccines have been developed for hepatitis A, B and E) (WHO, 2013). It has been suggested that the greatest stumbling block to vaccine development is the virus's ability to mutate rapidly and the existence of numerous subtypes, along with its ability to neutralise naturally-produced antibodies (Chen & Morgan, 2006:47). Education, prevention and effective management of those infected are fundamental to reducing transmission of the virus. It is also imperative to recognise the need for safer blood supply and injection practices in healthcare in developing countries (CDC, 2012).

2.1.10 Diagnosis and testing

Diagnosis of chronic HCV infection is made when HCV RNA persists for more than six months. There is no distinct serologic marker for acute infection and the differentiation of acute from chronic HCV infection primarily depends on the clinical presentation, *viz*. the presence of jaundice or other symptoms of hepatitis C and whether or not there was a prior history of ALT elevation and the duration of the elevation (Ghany *et al*., 2009:1338).

2.1.10.1 Liver function tests

The 'traditional' liver function tests (LFTs) are alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT) and bilirubin (total and conjugated). Table 2.1 (Turner *et al*., 2009:224-225) lists the traditional LFTs with their normal values. Elevated ALT and AST levels suggest cellular injury and result from hepatocellular necrosis or inflammation (Aragon & Younossi, 2010:196). Elevations in ALP and GGT levels are seen in infiltrative liver disease (such as tumour or granuloma), cholestasis or obstruction (Kang, 2013:226). In those who are jaundiced, bilirubin levels are elevated.

LFTs can be used in detecting and diagnosing liver disease (Pratt, 2010:1230). In the case of HCV infection, up to 80% of patients have abnormal ALT values and in approximately half of these patients, the values fluctuate. Chronic HCV infection can increase ALT and AST up to 20 times the normal value and when values are evaluated, ALT levels are usually higher than AST levels. ALP, GGT, lactate dehydrogenase and creatine kinase are usually normal, whereas iron and ferritin levels may be slightly elevated (Pradat *et al*., 2002:976). Albumin levels and prothrombin time are usually normal until significant liver damage occurs (Pradat *et al*., 2002:976). Elevation of ALP and GGT in combination with low white blood cell and low platelet counts also suggests advancing fibrosis or established cirrhosis. AST levels are usually higher than ALT in cirrhosis, but less than a 2:1 ratio (Murali & Carey, 2014). Although LFTs are useful in detecting liver disease, it is not specific to the diagnosis of HCV infection; since other liver diseases also increase certain liver enzymes. Furthermore, it is not unusual for patients infected with HCV to have fluctuating liver enzyme levels. Despite chronic HCV infection, LFTs may remain normal for over a year in some patients (Pratt, 2010:1227). As a result, an HCV antibody diagnostic test was developed specifically for the diagnosis of chronic active HCV infection.

2.1.10.2 Antibody diagnostic tests

HCV infection is diagnosed by two classes of assays — serologic assays that detect specific antibodies to the HCV (anti-HCV) and molecular assays that detect viral nucleic acid, or hepatitis C viral ribonucleic acid (HCV RNA) (Botha *et al*., 2010). Neither serologic nor

molecular assays have a role in the assessment of disease severity or prognosis (Ghany *et al*., 2009:1337). The enzyme linked immuno-absorbent assay (ELISA) and recombinant immunoblot assay (RIBA) are both serologic assays, of which the latter is a more specific test that can be used to confirm a positive ELISA result (Dillon, 2007:26). According to the 2010 South African hepatitis C management guidelines, anti-HCV testing should be performed in all persons suspected of having acute or chronic HCV infection, or who are at increased risk of HCV infection, whereas HCV RNA testing is recommended in:

– all anti-HCV-positive patients,

– any anti-HCV-negative patients with unexplained liver disease or who are suspected of having acute hepatitis C or who are immunocompromised, and

– patients in whom antiviral treatment is being considered (Botha *et al*., 2010).

Table 2.1: Traditional liver function tests[e]

Marker	Description	Normal values[♣]
ALT	Primarily found in hepatocytes, and is released in liver damage.	5-40 units/L
	ALT is a sensitive indicator of liver injury.	
AST	Not very specific for liver disease, as it is found in many sources, including the liver, heart, muscles, intestine and pancreas.	5-40 units/L
	Both ALT and AST may be very high in hepatitis.	
ALP	Found in the liver (especially in the biliary tract), bones, intestines and placenta.	40-115 units/L
	ALP rises with obstruction or infiltrative diseases, i.e. stones or tumours.	
GTT	Microsomal enzyme present in hepatocytes and biliary epithelial cells, renal tubules, pancreas and intestine. Also present in cell membranes for transporting of peptides into the cell across the cell membrane. Also involved in glutathione metabolism.	9-85 units/L
Bilirubin	Bilirubin is the pigment in bile produced from the breakdown of haemoglobin. Bilirubin has two primary sources; namely indirect and direct. Indirect (unconjugated) bilirubin is derived from old red blood cells and is lipid soluble. It is removed by the spleen and sent to the liver. Direct (conjugated) bilirubin is water soluble and is formed when the liver complexes glucuronic acid to unconjugated bilirubin to enable excretion. Hyperbilirubinemia results from increased bilirubin production, decreased liver uptake, or decreased biliary excretion.	Indirect: 5-18 µmol/L Direct: 0-8 µmol/L

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma glutamyl transpeptidase

[e]Compiled from Turner et al. (2009:224-225)

Table 2.2 (compiled from CDC, 2013) summarises the interpretation of results of tests for HCV infection and the further actions recommended for clinicians and laboratories by the US Centers for Disease Control and Prevention (CDC) (Ghany *et al*., 2009:1338).

When a patient is anti-HCV negative, the sample can be reported nonreactive for HCV antibody and no further action is required. If it is suspected that the person being tested has recently been exposed to HCV, a molecular assay can be performed to test for HCV RNA. If, however, HCV RNA testing is not feasible and the patient is not immunocompromised, a follow-up anti-HCV assay can be conducted to demonstrate seroconversion (CDC, 2013). A recurrently reactive anti-HCV result is consistent with HCV infection, but does not distinguish between current infection, past resolved infection or biologic false positivity for HCV antibody. A positive antibody test thus only indicates exposure to the virus; it does not differentiate between active or resolved infection. The presence or absence of active HCV infection is established in those with positive serology by using a molecular assay to test for HCV RNA (CDC, 2013). *In vitro* reverse transcription-polymerase chain reaction (RT-PCR)-based assays are molecular assays that assess active viral replication in human serum and plasma from HCV-infected individuals (Vandesompele *et al*., 2002).

Table 2.2: Interpretation of HCV test rest results[f]

Test outcome	Interpretation	Further actions
HCV antibody nonreactive	No HCV antibody detected	No further action required
HCV antibody reactive	Presumptive HCV infection	Test for HCV RNA to identify current infection
HCV antibody reactive, HCV RNA detected	Current HCV infection (acute or chronic depending on the clinical context)	Provide patient with appropriate counselling and link patient to care and treatment
HCV antibody reactive, HCV RNA not-detected	No current HCV infection or resolution of HCV or acute HCV during period of low-level viremia	No further action required (in most cases)
HCV antibody negative, HCV RNA detected	Early acute HCV infection, or chronic HCV in setting of immunosuppressed state; false positive HCV RNA test	Distinguish between true positivity and biologic false positivity for anti-HCV by testing with another HCV antibody assay. When HCV also test subsequent blood sample to confirm HCV RNA positivity prior to initiating antiviral therapy
HCV = hepatitis C virus; RNA = ribonucleic acid *[f]Compiled from CDC (2013)*		

In the event that HCV RNA is not detected, a distinction between true positivity and biologic false positivity for anti-HCV can be made by testing with another HCV antibody assay (Wilkie,

2013:23). When HCV RNA is detected, it is recommended that a subsequent blood sample be tested to confirm HCV RNA positivity prior to initiating antiviral therapy (CDC, 2013). There is no true difference between qualitative and quantitative molecular assays to establish current HCV infection; however, it is important to use the same laboratory test before and during drug therapy for monitoring purposes (Botha *et al.,* 2010).

The optimal approach to detecting HCV infection is to screen persons for a history of risk of exposure to the virus and to test selected individuals who have an identifiable risk factor (Ghany *et al*., 2009:1335). In addition to the groups of people at risk of contracting HCV, testing is also recommended for:

- persons born from 1945 to 1965 (so called 'baby-boomer' generation);
- persons with haemophilia;
- persons with signs or symptoms of liver disease, undiagnosed abnormal LFTs, abnormal liver function or unexplained jaundice;
- blood donors; and
- persons who have previously been diagnosed with non-A and non-B hepatitis, but have not been tested for hepatitis C infection (Poll, 2012:398).

It should be emphasised that all former injection drug users should be tested, even if they only used once or many years ago. Furthermore, children born to infected mothers should be tested before the age of 18 months (Poll, 2012:398).

2.1.10.3 The use of a liver biopsy in the diagnosis of chronic liver disease

Liver biopsy is the gold standard for staging liver disease in individuals with chronic liver disease. It is used selectively given its high cost and risk, as well as poor patient acceptance because of the risk of bleeding and post-procedural pain (Saadeh *et al*., 2001:197). The three main reasons for performing a liver biopsy are that biopsies:

- provide supportive information on the current status of the liver injury or fibrosis;
- identify features informative to the decision to start therapy; and
- reveal advanced fibrosis or cirrhosis that demands surveillance for HCC and/or other complications.

Table 2.3 lists the factors to consider before performing a biopsy.

Table 2.3: Factors to consider before doing a biopsy[g]

Factor	Normal limit		Value	Action
	Adult male	*Adult female*		
Hgb (g/dl) **Hct (%)**	Hgb = 13-18 Hct = 40-52	Hgb = 11.7-16 Hct = 35-47	Within normal limits or an acceptable risk	May proceed with biopsy
PLT count (thous/µl)*	140-440	140-440	>60,000/mm^3	May proceed with biopsy
			40,000/mm^3-60,000/mm^3	Physician to order PLT transfusion to increase count to a safe level
			<40,000/mm^3	Use alternative biopsy method
PT	INR = 1.0 – 1.4		< 4 seconds prolonged	May proceed with biopsy
			4-6 seconds prolonged	Physician may order transfusion of fresh frozen plasma to increase time to a safe level
			>6 seconds prolonged	Use alternative biopsy method

Hct = haematocrit; Hgb = haemoglobin; PLT = platelet; PT = prothrombin time
**thous/µl = thousand per microliter; 1 µl = 1 mm^3*
[g]Compiled from Saadeh et al. (2001:199)

Liver biopsies also provide information on other histological features that might have an influence on liver disease progression (Saadeh *et al*., 2001:199). A liver biopsy, in essence, remains the gold standard to evaluate disease severity and progression in chronic HCV infection, through grading and staging of liver damage (Corbett *et al*., 2005:5). The grade (necro-inflammatory activity) and stage (degree of fibrosis) of liver damage can assist in the assessment and prediction of disease progression (Corbett *et al*., 2005:5).

2.1.10.4 Grading and staging a liver biopsy

Several scoring systems for histological stages have been conceived; the most common being the French METAVIR, the Scheuer, the Batts-Ludwig, the International Association for the Study of Liver Disease (IASL) and the Ishak scoring systems (Theise, 2007:S3). Table 2.4 (compiled from Franciscus, 2007:1 and Ghany *et al*., 2009:1139) compares some of the most frequently used scoring systems.

Table 2.4: Comparison of scoring systems for histological stage[h]

Stage	IASL	Batts-Ludwig	METAVIR	Ishak
0	No fibrosis	No fibrosis	No fibrosis	No fibrosis
1	Mild fibrosis	Fibrous portal expansion	Periportal fibrotic expansion	Fibrous expansion of some portal areas with or without short fibrous septa
2	Moderate fibrosis	Rare bridges or septae	Periportal septae 1 (septum)	Fibrous expansion of most portal areas with or without short fibrous septa
3	Severe fibrosis	Numerous bridges or septae	Porto-central septae	Fibrous expansion of most portal areas with occasional portal to portal bridging
4	Cirrhosis	Cirrhosis	Cirrhosis	Fibrous expansion of most portal areas with marked bridging (portal to portal and portal to central)
5				Marked bridging (portal to portal and portal to central) with occasional nodules (incomplete cirrhosis)
6				Cirrhosis

IASL = International Association for the Study of Liver Disease
[h]Compiled from Franciscus (2007) and Ghany et al. (2009:1339)

From Table 2.4 it is evident that most scoring systems ultimately use the same principles to record liver disease stage. It is clear that the 'stage' or 'fibrosis' score is composed of a mixture of features, none of which specifically depends on the amount of fibrous tissue in a liver biopsy sample (Standish *et al*., 2006:571). Variability between scoring systems, sampling methods, observer agreement and expertise renders the grading and staging of fibrosis by means of liver biopsy an inexact science (Koukoulis, 2001:901). Acknowledgment of a 'built-in' variability in grading and staging chronic HCV infection by both the clinician and the pathologist is essential to manage the individual patient with CHC (Skripenova *et al*., 2007:323).

2.1.11 Complications of chronic hepatitis C

CHC is typically asymptomatic and may remain undiagnosed for decades. Many patients are diagnosed coincidentally after donating blood or by systematic screening and more often than not, at a late stage in the disease (Marcellin, 1999:9). Of all the possible outcomes of chronic HCV infection, the most feared complication is liver-related mortality due to liver cirrhosis and HCC (Maasoumy & Wedemeyer, 2012:404).

2.1.11.1 Cirrhosis

Cirrhosis is a chronic condition in which the liver parenchyma progressively degenerates (Weller, 2005:82). Fibrous tissue surrounds regenerating liver cells, thereby impeding hepatic

blood flow (Tso & McGill, 2003:514). This obstruction of blood flow through the liver causes back pressure, which, in turn causes portal hypertension. Portal hypertension can result in various disorders, including oesophageal varices, ascites, hepatic encephalopathy and hypersplenism.

2.1.11.2 Oesophageal varices

Oesophageal varices are potential manifestations of portal hypertension and are frequently seen in cirrhosis (in approximately 80% of patients). The term refers to a complex of engorged longitudinal veins at the lower end of the oesophagus (Mosby's Dictionary of Medicine, Nursing & Health Professions, 2006:676). These veins are especially vulnerable to haemorrhage and can result in bleeding from oesophageal blood vessels (Zein & Edwards, 2009:133). Approximately 30% of patients who develop an oesophageal variceal haemorrhage can die during the episode of bleeding, highlighting the incumbent mortality associated with this condition (Tso & McGill, 2003:514).

2.1.11.3 Ascites

Ascites is defined as *"an abnormal intraperitoneal accumulation of protein and electrolytes"* (Mosby's Dictionary of Medicine, Nursing & Health Professions, 2006:149). Ascites is a consequence of portal hypertension — usually secondary to cirrhosis. In some cases, ascitic fluid may become infected, with subsequent pain and fever (Zein & Edwards, 2009:132).

2.1.11.4 Hepatocellular carcinoma

HCC is the formation of a malignant tumour in the liver and is the most common type of primary liver cancer. HCC is a devastating complication of cirrhosis (Weller, 2005:82). Even though small localised tumours can occasionally be cured by surgical resection or liver transplantation, the prognosis for patients with HCC remains poor (Beers *et al*., 2006:236).

2.1.11.5 Extrahepatic Manifestations

The liver is not the only organ affected by HCV infection. A range of extra-hepatic manifestations are described in chronic HCV infection. There is a strong association between HCV infection and mixed essential cryoglobulinemia, membranoproliferative glomerulonephritis, sicca syndrome and polyarteritis nodosa. Other manifestations such as porphyria *cutanea tarda*, non-Hodgkins lymphoma, auto-immune thyroiditis, lichen planus, aplastic anaemia, thrombocytopenia, erythema nodosum, diabetes mellitus and neuropathy are less well documented and further research is needed (Marcellin, 1999:9). Many of these conditions are thought to arise from an auto-immune mechanism (García-Carrasco & Escárcega, 2006:161,

Marcellin, 1999:9). Mixed cryoglobulinemia is the most well-described extrahepatic manifestation of HCV infection. Cryoglobulins consist of immune complexes of HCV and its antibody, rheumatoid factor, immunoglobulins and complement, which usually cause no symptoms, although rarely, arthralgia, Raynaud's disease, vasculitis, glomerulonephritis and purpura result (García-Carrasco & Escárcega, 2006:161). Table 2.5 further defines some of the other disorders that may result from cirrhosis or portal hypertension.

Table 2.5: Definitions of complications due to cirrhosis

Condition	Definition
Oedema	"The abnormal accumulation of fluid in interstitial spaces of tissues, such as in the pericardial space, intra-pleural space, peritoneal cavity, or joint capsules". Oedema may be caused by various conditions including hepatic cirrhosis (Mosby's Dictionary Of Medicine, Nursing & Health Professions, 2006:613).
Caput medusae	"A pattern of dilated cutaneous veins radiating from the umbilical area of a new-born. The feature is also observed in adults with cirrhosis of the liver" (Mosby's Dictionary Of Medicine, Nursing & Health Professions, 2006:294).
Spider naevi or Spider angioma	"A form of telangiectasia (the permanent dilation of groups of superficial capillaries and venules) characterized by a central elevated red dot the size of a pinhead from which small blood vessels radiate". Spider naevi can occur when the liver is diseased and unable to detoxify oestrogens (Mosby's Dictionary Of Medicine, Nursing & Health Professions, 2006:1747;1825).
Jaundice	"A yellow discoloration of the skin and conjunctiva, due to the presence of bile pigment in the blood" (Weller, 2005:217).
Splenomegaly	"An abnormal enlargement of the spleen, as is associated with portal hypertension" (Mosby's Dictionary Of Medicine, Nursing & Health Professions, 2006:1754)
Hepatic encephalopathy	"A neuropsychiatric manifestation of extensive liver damage caused by chronic or acute liver disease. Either endogenous or exogenous waste toxic to the brain is not neutralised in the liver before being shunted back into the peripheral circulation of the blood, or substances required for cerebral function are not synthesized in the liver and therefore are not available to the brain" (Mosby's Dictionary Of Medicine, Nursing & Health Professions, 2006:875).
Hepatomegaly	"Abnormal enlargement of the liver" (Mosby's Dictionary Of Medicine, Nursing & Health Professions, 2006:878).
Palmar erythema	"An inflammatory redness of the palms of the hands" (Mosby's Dictionary Of Medicine, Nursing & Health Professions, 2006:1381).
Testicular atrophy	Testicular: "pertaining to the testicle" Atrophy: "Wasting of any part of the body, due to degeneration of the cells" (Weller, 2005:35).
Gynecomastia	"An abnormal enlargement of one or both breasts in males" (Mosby's Dictionary Of Medicine, Nursing & Health Professions, 2006:841).
Pectoral alopecia	Pectoral: "the region of the chest" (Stedman's, 2005:1095). Alopecia: "Complete or partial absence or loss of hair" (Stedman's, 2005:51).

2.1.12 Natural history of HCV

The individual course of CHC is highly variable; and so, the natural history of HCV infection is not well defined (Chen & Morgan, 2006:47). There are exceptional variations in the severity of HCV-related liver disease between infected individuals; and this, together with the substantial contribution of various co-factors to the severity of liver disease, has challenged the development of a universal model describing the natural history of HCV infection (Alberti *et al*., 1993:17; Marcellin, 1999:9).

In their meta-analysis, Alberti *et al*. (1993:18) list several reasons for the uncertainty about the long-term course of HCV infection. These reasons include that:

– an accurate confirmation of the time of onset of CHC is difficult, because acute infection is mostly asymptomatic and remains unrecognised in the majority of patients;

– disease progression is slow and is only detectable at histological level, often only decades after acute infection; and

– the relatively recent discovery of HCV has limited the follow-up of HCV infection in prospective studies, and the availability of effective HCV treatments has made it unethical to prospectively follow infected patients untreated for prolonged periods.

Despite these limitations, however, many attempts have been made to describe the natural history of HCV infection. Literature indicates that after acute infection, only 15 to 25% (median 20%) of patients exposed to HCV will resolve their infection without sequela. The remaining 75 to 85% (median 80%) will progress to chronic HCV infection (Davis *et al*., 2003:333). Of those chronically infected, approximately 20 to 40% of patients will have persistently normal serum ALT levels — these patients will not progress to more advanced liver disease. The remaining 60 to 80% (median 70%) will have abnormal serum ALT levels and/or progress to chronic active liver disease (CHC) (Alberti *et al*., 1993:19; Ascione *et al*., 2007:S5; Davis *et al*., 2003:333). The distinction between infected patients with normal and abnormal ALT levels respectively is important, though, since models disregarding this distinction will overestimate disease progression in patients with normal ALT levels if modelled at the same rate as patients with elevated ALT levels (Davis *et al*., 2003:333). Additionally, approximately 1 to 2% of patients with a chronic HCV infection develop extrahepatic complications, i.e. cryoglobulinemia, glomerulonephritis, porphyria *cutanea tarda*, vasculitis, uveitis or thrombocytopenia (Parini, 2001:20). It is unclear whether these complications/associated diseases are caused directly from HCV infection or from the underlying immune stimulation caused by chronic infection (Chen & Morgan, 2006:50).

Studies indicate that 10 to 30% (median 20%) of patients with CHC will develop cirrhosis over a period of 20 years (Alberti *et al*., 1993:17; Alawazi *et al.*, 2013:344; Chen & Morgan, 2006:50, Thein *et al*., 2005:643). If cirrhosis develops, additional symptoms may include muscle weakness, nausea, weight loss, itching, dark urine, fluid retention and abdominal swelling (Parini, 2001:20). Signs of cirrhosis also include splenomegaly, low platelets, poor synthetic function (low albumin, raised bilirubin, abnormal clotting) and clinical features such as jaundice, ascites, encephalopathy and spider naevi (Wilkie, 2013:22). A small percentage of patients with cirrhosis will progress to decompensated cirrhosis, where complications of liver dysfunction start to become evident. Some patients with decompensated cirrhosis may require liver transplantation (Sweeting *et al*., 2007:572).

Despite the lack of an explicit natural history diagram for chronic HCV infection, the understanding of morbidity and mortality among people with HCV infection has greatly improved over the past several years. The mortality distribution among people with HCV infection was reported in a systematic review of four large population-based studies (Grebely & Dore, 2011:331). Results from the systematic review indicated that liver-related and drug-related causes accounted for approximately half of all deaths among people with HCV infection. Liver disease-related mortality — including decompensated cirrhosis and HCC — accounted for 20.4%, 18.6%, 23.5% and 24.2% of all the deaths registered in population-based HCV notification death-registries in Australia, Sweden, Scotland and Denmark, respectively. South African-specific mortality rates related to HCV are not available; however, it is clearly important to monitor progressive trends in mortality rates and distribution among people with HCV infection and attention should be given to these trends in the South African setting (Grebely & Dore, 2011:331).

Available information indicates that even though the natural history of HCV infection is not completely understood, there are some certainties about chronic HCV infection, including that:

- chronic HCV infection can persist for approximately two decades with limited morbidity and mortality, but problems may occur between the second to fourth decade after infection;
- progression of liver damage or fibrosis is not linear;
- patterns of disease progression are very different, the progression to cirrhosis is typically clinically silent and some patients are not known to have hepatitis C until they present with the complications of end-stage liver disease or HCC;
- CHC reduces quality and/or quantity-of-life in 15% of infected persons;

– the time from HCV infection to cirrhosis is dependent on multiple factors and cannot be predicted in an individual patient (Alazawi *et al.*, 2010:353; Ascione *et al*., 2007:S6; Chen & Morgan, 2006:49).

The variations in the individual course of HCV infection notwithstanding, one certainty is that chronic HCV infection can induce progressive liver fibrosis that may advance to cirrhosis and various other complications over a period ranging from a few years to a couple of decades (Zarski *et al*., 2003:307). Based on reviewed literature, the main disease states in the natural history of HCV infection and the approximate annual transition probabilities for progressing from each disease state to the next were identified. Figure 2.1 (compiled from Alawazi *et al.*, 2013:344; Alberti *et al*., 1993:11; Hutchinson *et al.*, 2005:712; Saab *et al*., 2010:750 and Sweeting *et al.*, 2006:145) presents main disease states in the natural history of HCV infection and the annual transition probabilities for transitions from one disease state to the next are listed in Table 2.6.

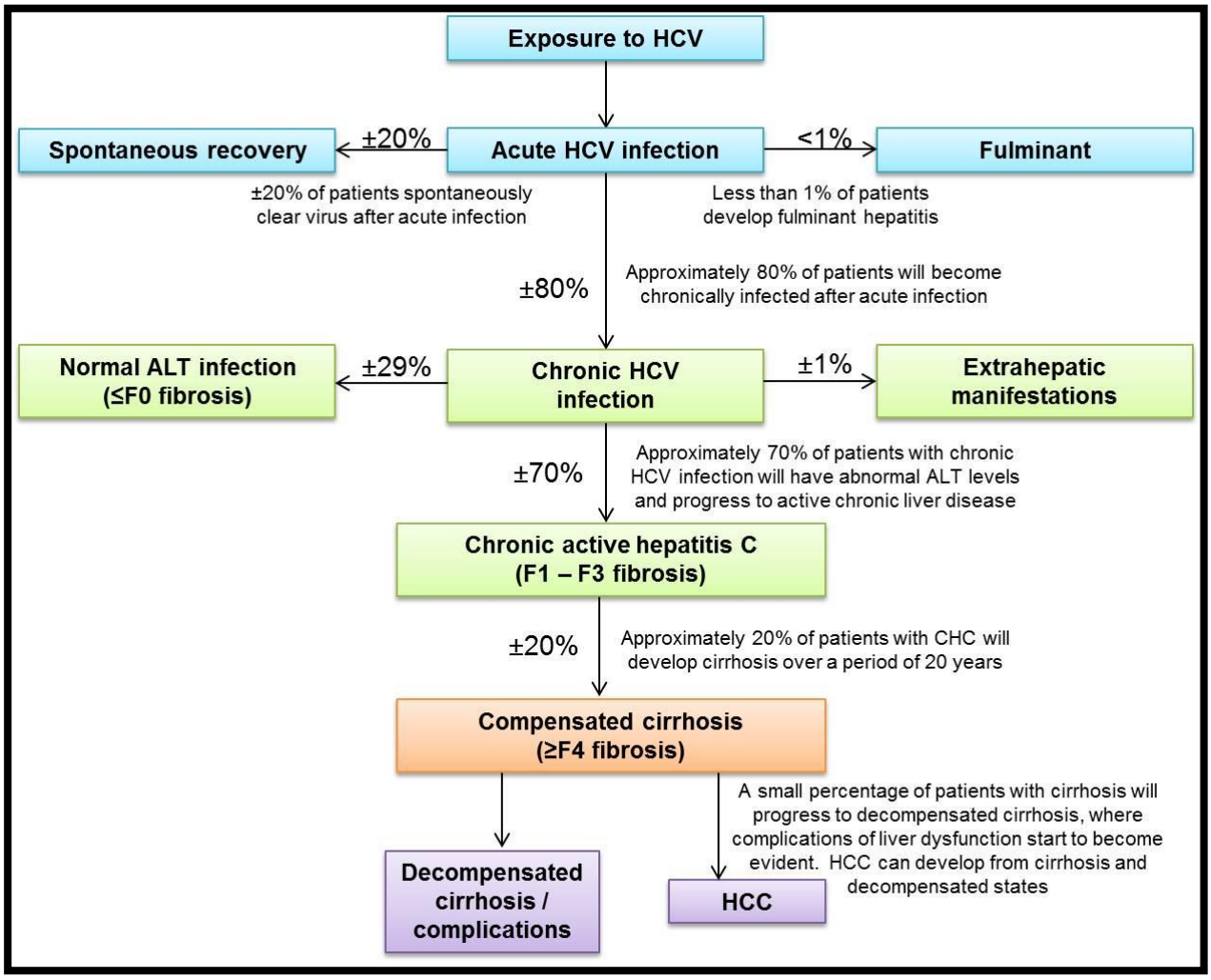


Figure 2.1: Natural history of HCV infection

Table 2.6: Annual transition probabilities in chronic (active) HCV infection

HCV natural history	Annual probability	Range (%)	Reference
CHC → cirrhosis*	1.1%	(0.5-1.8)	Alberti *et al*. (1993)
Cirrhosis → decompensated cirrhosis	6.4%	(3.0-7.0)	Alawazi *et al.* (2013)
Cirrhosis → HCC	3.6%	(1.5-4.0)	Alawazi *et al.,* 2013
Decompensated cirrhosis → HCC	6.8%	(4.1-9.9)	Saab *et al.* (2010); Sweeting *et al*. (2006)
Decomp. cirrhosis → liver-related death	16.8%	(12-40)	Hutchinson *et al.* (2005)
HCC → liver-related death	60.5%	(30-80)	Hutchinson *et al.* (2005)
**Annual probability of CHC to cirrhosis was calculated from assumed probability of 20% over 20 years*			

2.2 Epidemiology of hepatitis C virus infection

HCV is endemic worldwide and affects people of all ages, genders and races. Global HCV epidemiology data is generally derived from the result of regional or national cross-sectional seroprevalence studies. Most of these studies, however, are conducted in select populations that do not necessarily represent the greater community in which they reside (Shepard *et al*., 2005:558). Based on published seroprevalence studies and submitted epidemiological data, the WHO estimates that approximately 130 to 150 million people globally are chronically infected with HCV, reflecting a global HCV prevalence of 3% (WHO, 2013). The population of chronic HCV carriers around the world represents a reservoir sufficiently large for HCV to persist (WHO, 2002:33). Table 2.7 (compiled from Lavanchy, 2011:110) shows the prevalence of chronically HCV-infected patients in six geographical world regions.

Table 2.7: Regional prevalence of chronic HCV infection: 2010[i]

Region	Anti-HCV (%)	No. chronically HCV-infected
Africa	3.2	28 100 000
Americas	1.5	14 000 000
Asia	2.1	83 000 000
Australia and Oceania	1.2	400 000
Europe	2.3	17 500 000
Middle East	4.7	16 000 000
Total	2.4	159 000 000
[i]Compiled from Lavanchy (2011:110)		

These estimates indicate a high percentage of chronically infected patients in the Middle East (4.7%) and Africa (3.2%). Asia (2.1%) and Europe (2.3%) have moderate percentages of HCV

chronicity, whereas the Americas (1.5%) and Australia and Oceania (1.2%) have the lowest percentages of people with chronic HCV infection. Instead of reporting on the prevalence of disease according to continent or country, the Global Burden of Disease study 2010 (GBD 2010) defined 21 world regions that were as 'epidemiologically homogenous' as possible, to facilitate the reasonable extrapolation of information from detailed studies done in one country, to other countries in the region (Lim *et al.*, 2012:2224-2260). Figure 2.2 represents the HCV prevalence rates according to these 21 regions as reported in the GBD 2010 study.

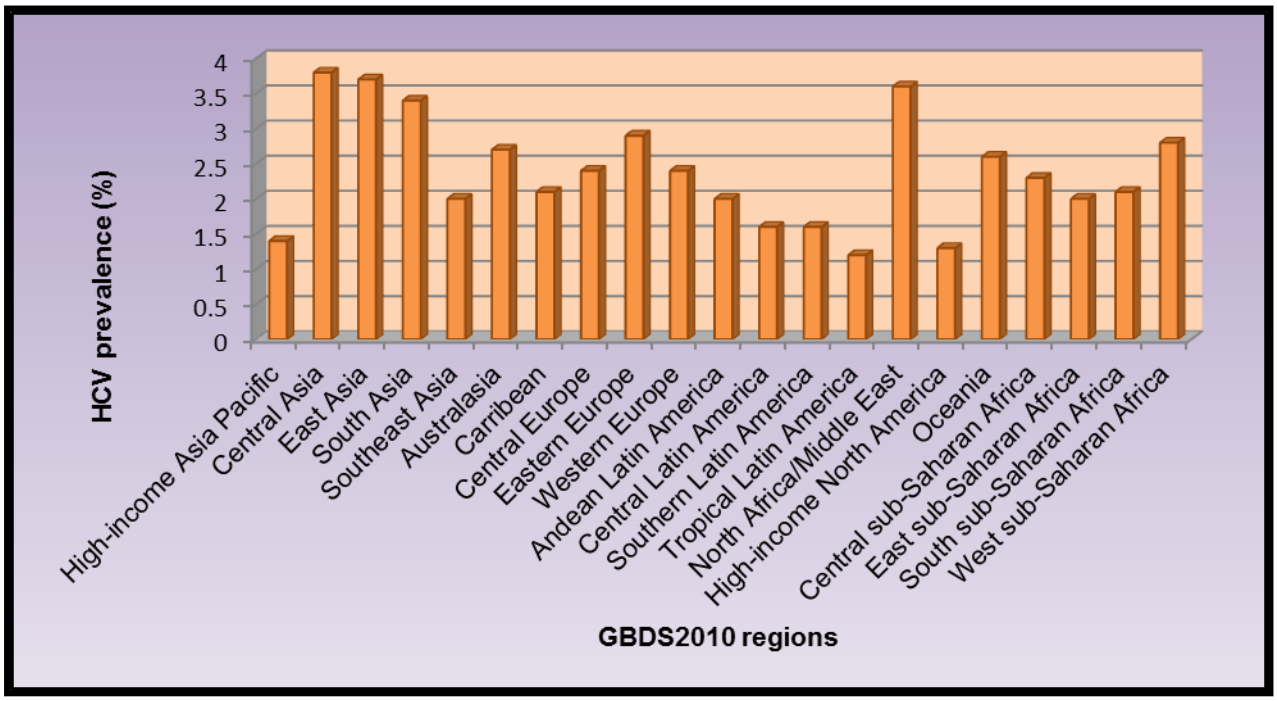


Figure 2.2: HCV prevalence rates according to GBDS regions - 2010

Similar to reports from other epidemiology studies (Averhoff *et al*., 2012:S11, Hanafiah *et al*., 2013:1333; Lavancy, 2011:110), results from the GBD 2010 study indicated that HCV prevalence is generally low (<1.5%) in regions such high-income Asia Pacific, high-income North-America and Tropical Latin America. Prevalence is a little higher (≤2%) in Andean, Central and Southern Latin America, Southeast Asia and East sub-Saharan Africa. Europe, Central-, South- and West sub-Saharan African countries, Australasia, Oceania and the Caribbean have a moderate HCV prevalence (>2%; <3%), whereas Central- East- and South Asia, North Africa and the Middle East are estimated to have high HCV prevalence rates (>3.5%). Prevalence rates of HCV for the Western Pacific region range from 2.5 to 4.9% (Averhoff, 2012:S11; Hanafiah *et al*., 2013:1333; Lavancy, 2011:110). Egypt has the highest HCV prevalence in the world (>14.7%) (Mohamoud *et al*., 2013:288). Unsafe injections using contaminated equipment are thought to be the main mode of transmission in these countries with high HCV prevalence rates (WHO, 2013).

2.2.1 Epidemiological trends

Although HCV has a global distribution, there is a large degree of geographic variability in its spread and every country faces its own distinct challenges when dealing with the HCV epidemic (Gravitz, 2011:S12).

2.2.1.1 The United States of America

HCV is the most common chronic blood-borne infection in the USA (Shepard *et al.,* 2005:558). Between 2.7 and 3.9 million people in the USA are chronically infected with HCV and an estimated three- to four million people become newly infected with hepatitis C every year (WHO, 2013). The highest HCV prevalence in the USA is in people born from 1945 to 1964 (CDC, 2012). The prevalence of HCV among 'baby boomers' is five times higher than among persons born in other years, indicating that a significant number of infections most likely occurred in the 1970s and 1980s (Smith *et al*., 2011). In fact, 'baby boomers', who make up approximately 27 to 30% of the US population, account for 75% of the people in the United States with HCV (Gravitz, 2011:S2).

2.2.1.2 Europe and the United Kingdom

In Europe, as in many other countries, HCV prevalence data is often out-dated and lacking. Still, current estimates for the European continent indicate that 17.5 million individuals are chronically infected with HCV and an increased prevalence is anticipated over the next decade (Lavanchy, 2011:110). Injecting drug use is still the most significant risk factor for HCV infection in the United Kingdom (UK) and an estimated 215 000 people in the UK are chronically infected with HCV, predominantly (~90%) with HCV-G1 and HCV-G3. Liver disease is the fifth largest cause of death in the UK, and the average age of death from this cause is 59 years (Wilkie, 2013:23).

2.2.1.3 Asia

In China, the geographical distribution of HCV infection is varied and patterns differ between rural and urban settings. However, with the significant increase in intravenous drug use, it is expected that the prevalence will generally increase in China (Xia *et al*., 2008:1000). The same is true for the Middle East (Lavanachy, 2011:11).

As for China, HCV is also an emerging infection in India — already responsible for a significant proportion of liver disease in various states. Again, prevalence appears to be highly variable according to the geographical site or the population group analysed, but it can be assumed that

substantial increases in morbidity and mortality in India will be the sequelae of chronic HCV infection in years to come (Mukhopadhya, 2008:471).

In Japan, 70% of cases of HCC are attributable to HCV and HCC is the fourth and fifth leading cause of death in males and females, respectively. The prevalence of HCV is much lower in the younger generation than in the older generation, indicating a steadily decreasing incidence of HCV in Japan (Chung *et al*., 2010:39).

2.2.1.4 Africa

HCV prevalence data for Africa is extremely limited. In spite of its high prevalence, diagnosis and reporting of HCV in Africa are still far from adequate. With the exception of Egypt, data on HCV in Africa is lacking and most of the available data are old and out-dated (Karoney & Siika, 2013:2). Furthermore, through much of Africa, HCV is mainly obscured by widespread HIV and HBV infections (Gravitz, 2011:S1).

In their meta-analysis, Karoney and Siika (2013:2) reported on the prevalence of HCV in Africa after reviewing relevant literature. The review indicated that, depending on the country, the prevalence of HCV in the general population in Africa ranges between 0.1 and 17.5%. Egypt, Cameroon, Rwanda and Burundi are some of the African countries with the highest HCV prevalence; whereas Zambia, Kenya, Malawi and South Africa are the countries with the lowest HCV prevalence in Africa (Karoney & Siika, 2013:2) (also refer to Table 1.2). Egypt has the highest HCV prevalence and transmission rate in the world, approximately 14.7%, three times the global infection rate (Mohamoud *et al.*, 2013:288).

2.2.2 Incidence and future burden

Data on the incidence of new cases of HCV infection are difficult to obtain, as most acute infections are asymptomatic. Furthermore, because of the asymptomatic form of acute infection, measurement of incidence fails to produce reliable prevalence statistics and most approximations are based on reviews of published data (Lavanchy, 2011:108).

A recent meta-analysis reported on the new estimates of the global age-specific epidemiology of HCV infection. According to Hanafiah *et al*. (2013:1338-1339), the HCV prevalence trend in sub-Saharan Africa reflects an increase in prevalence with an aging population. The study reported a peak prevalence of 5.3 to 6.7% at 55 to 64 years old, where after there is a slight decrease in prevalence, reaching a peak of 4.4 to 5.3% in elderly patients over the age of 85 years. In the Western region of sub-Saharan Africa, total HCV prevalence decreased from 4.0% in 1990 to 2.8% in 2005. The Americas similarly showed an increase in prevalence as a function of age, where population prevalence in Latin America and the Caribbean also peaked

at ages 55 to 64 years, followed by a gradual decrease after the peak was reached. North America displayed a shift in age-specific population peaks from 1990 to 2005, where prevalence peaked at 2.5% at ages 35 to 44 years in 1990, and at 2.7% at ages 55 to 64 years in 2005. Prevalence trends showed an insignificant decrease in total prevalence in North Africa / Middle East from 1990 to 2005; peak prevalence reaching 9.5% and 8.2% at ages 55 to 64 years in 1990 and 2005 respectively, followed by a decline. The Western Pacific region showed a slight, insignificant increase in HCV prevalence between 1990 and 2005, whereas prevalence trends in Europe and Asia also indicated an increase in prevalence with an increase in age with the population prevalence peaking at 55 to 64 years and declining or plateauing afterwards. In Europe, the highest peak prevalence was observed in the Eastern region (5.2%), followed by Central Europe (4.7%). The total prevalence in Asia is highest in the Central region (3.1% and 3.8% in 1990 and 2005, respectively). The most significant increase in population prevalence in Asia was observed in East Asia, where anti-HCV seroprevalence increased from 2.2% in 1990 to 3.7% in 2005. These numbers indicate that, although not as rapidly as in the past, the prevalence of HCV infection is still increasing.

HCV infections are on the rise in older teenagers and young adults (Gravitz, 2011:S2). Rates of transmission in the United States, Europe and Japan have declined since the virus was identified as a result of disposable medical instruments and a screened blood supply. However, the virus continues to dominate in developing nations that lack the resources to treat those infected (Gravitz, 2011:S2).

A major determinant of the future burden of disease is the past and present incidence of infection (Armstrong, 2003:725). Acute disease reporting systems can underestimate the incidence of HCV infection, even in countries with well-established surveillance systems (Hagan *et al.,* 2002:579). Because the direct measurement of HCV infection incidence is impractical, researchers have relied upon mathematical models to infer trends in incidence. All published models predict that the incidence of HCV-related sequelae will rise in their respective countries in the coming decades (Shepard *et al*., 2005:559).

2.2.3 The status of hepatitis C in South Africa

The exact extent of the burden of HCV in South Africa is not well known; however, it is estimated to be low (0.1-1.7%). Some studies in South African patients have reported an HCV prevalence of up to 2.6% (Ellis *et al*., 1990:249). The seroprevalence of HCV in South Africa furthermore differs between low- and high-risk groups, averaging 2.6% in urban and 3.8% in rural populations (Ellis *et al.,* 1990:249). A study conducted at a KwaZulu-Natal hospital found HCV prevalence rates of 23%, 24% and 33% in patients with cirrhosis, HCC and chronic active hepatitis, respectively (Soni *et al*., 1996:80). On the other hand, a study conducted at the Chris

Hani Baragwanath Hospital in Gauteng found an HCV prevalence of only 1% in patients with HIV or acquired immune deficiency syndrome (AIDS) (Lodenyo *et al*., 2000:13). HCV seroprevalence in South African healthcare workers has also been found to be quite low (1.8%) (Vardas *et al*., 2002:11). A higher HCV prevalence has, however, been reported in high-risk individuals, e.g. 39.4% and 4.8% in haemophiliacs and chronic dialysis patients, respectively (Gededzha *et al.,* 2010:814).

2.2.3.1 HCV and HIV co-infection

Co-infection with HCV and HIV is not uncommon (as they share similar modes of transmission) and approximately four to five million people globally are co-infected with HCV and HIV (Gededzha *et al*., 2010:815).

South Africa has one of the highest numbers of people living with HIV (Shisana *et al*., 2014). An estimated 12.2% of the South African population (6.4 million persons) are HIV positive (Shisana *et al*., 2014). Studies have also indicated a significantly higher prevalence of HCV among HIV infected patients as compared to HIV negative patients (13.4% *vs.* 1.73%) (Parboosing, 2008; Sorbi *et al*., 1996:295).

Early gains obtained from the restructuring of the South African public health sector post-1994 have been undermined by a massive increase in the burden of HIV/AIDS-related disease, resulting in poor health outcomes relative to total health expenditure. Healthcare feats of the past 20 years are largely eclipsed by the burden of AIDS on mortality and the health system (Palella *et al.*, 2006:33). Even though HAART programmes for the treatment of HIV/AIDS in the public healthcare sector have been heightened by South African health departments since 2003, there are still no research programmes to monitor the efficacy of HAART in patients co-infected with HBV and HCV (Lukhwareni *et al*., 2009:410).

CHC is an often unmentioned disease in many parts of Africa, including South Africa. A lack of awareness, together with issues relating to poverty, socio-economic status and access to medical care, contribute to a reduced opportunity for patients to receive clinical work-up and treatment for HCV (Gededzha *et al*., 2010:815). Many experts and decision-makers even consider providing antiviral therapy for conditions such as HCV in patients with HIV (Muller *et al*., 1998:351). Although there are extensive hindrances to providing antiviral therapy for viral hepatitis in the presence of competing priorities, it will be impossible to defy the consequences of chronic liver disease without treatment (Cooper *et al*., 2009:303). And even though liver-related death is not generally considered a major cause of mortality in patients with HIV in South Africa and other developing countries, it may become a pressing issue in years to come (Bica *et al*., 2001:492). It is important to bear in mind that patients with HIV/HCV co-

infection have less immune reconstitution than those with an HIV mono-infection. Furthermore, due to enhanced drug-induced hepatotoxicity, HAART may actually worsen the outcome of HCV disease (Miller *et al.,* 2005:713).

Research predicts that delivery of antiviral therapy will become a more demanding issue as more HIV-infected patients are spared a death from HIV/AIDS after receiving lifesaving HAART, only to succumb from complications of advanced, untreated viral hepatitis-induced liver disease thereafter (Palella *et al.*, 2006:33). Continuing to manage the HIV and AIDS epidemic, together with efforts to sustain financing for the prevention and treatment of HIV and AIDS will dictate the next decade or so. The most critical objective will be to reduce the rate of new HIV infection in South Africa; however, failure to also establish knowledge and infrastructure for viral hepatitis care and antiviral therapy now may diminish the milestones and the advances made with antiretroviral therapy in the developing world (Cooper *et al*., 2009:303).

2.2.4 Hepatitis C virus genotypes

After the discovery of the complete HCV genome in 1989 (Choo *et al*., 1991:2451), several HCV isolates from different parts of the world were obtained and sequenced. This has led to the identification of various different strains, or genotypes, which may differ from each other by as much as 33% over the whole viral genome (Zein, 2000:223).

At least six major genotypes (with several subtypes) have been identified throughout the world. Characterisation of the different genotypes — genotypes 1 to 6 — and identification of the differences among HCV genotypes is of clinical, epidemiological and surveillance importance (Zein, 2000:224). From a clinical perspective, HCV genotyping is a fundamental concern, as HCV genotype is a significant predictor of treatment response (Dillon, 2007:28). Most studies, however, suggest that there is not a significant clinical difference in the virulence or pathogenicity between different genotypes in general, and that genotypes do not influence the severity of disease progression (Dillon, 2007:28; WHO, 2002:35; Zein, 2000:224).

From a public health perspective, HCV genotyping may provide vital epidemiological information (Prabdial-Sign, 2008:36). Knowledge of the rate of occurrence of a genotype and the differences in geographic distribution among HCV genotypes may inform screening and preventative public programmes in different countries (Zein, 2000:224).

2.2.4.1 Genotype distribution

Although HCV has a worldwide distribution, there are substantial regional differences in the distribution of the different HCV genotypes. The majority of epidemiological studies focus on

genotypes 1 to 3, since they are most prevalent in rich and developed countries, whereas HCV circulation patterns in developing countries are less documented (Pybus *et al*., 2001:2324).

Genotype 1a is common in the United States and Northern Europe. Genotype 1b has a worldwide distribution and is often found to be the most common genotype. Genotypes 2a and 2b are also found worldwide and are relatively common in North America, Europe, and Japan, whereas genotype 3 is found in India, the USA and Europe. Genotype 4 is most common in North Africa and the Middle East, with a proportion ranging from 36 to 100% of all HCV cases, while genotype 6 occurs in Hong Kong and Southeast Asia (Antaki *et al.*, 2009a:343). Table 2.8 (compiled from Verbeeck *et al.*, 2008:170 and Wilkie, 2013:24) summarises the regional distribution of the HCV strains.

Table 2.8: Global distribution of the hepatitis C genotypes[j]

HCV genotype	Regions commonly found in
1,2,3	Widely distributed throughout Western countries and Far East (Japan, China, Taiwan, Thailand)
4	Predominant in North and sub-Saharan Africa and the Middle East
5,6	Predominant in South Africa and southeast Asia respectively. High prevalence of genotype 5 also recently reported in Spain, Belgium and France.
[j]*Compiled from Verbeeck et al. (2008:170) and Wilkie (2013:24)*	

There is an apparent lack of data particularly on the epidemiological history of HCV-G5. HCV-G5 is relatively uncommon and has been thought to be confined to the northern part of South Africa for many years (Verbeeck *et al*., 2008:170). New evidence, however, suggests that the epidemiology of HCV-G5 is more diverse than originally thought, as pockets of HCV-G5 can be found worldwide (Verbeeck *et al*., 2008:170). According to Verbeeck et al. (2006:4221), HCV-G5 is sporadically found in Australia, Brazil, the Netherlands, Canada, Spain and Ireland.

Several European studies reveal a high and very local prevalence of HCV-G5 in Spain, Belgium and France, ranging from 10.3 to 27.7% (Henquell *et al.,* 2001; Jover *et al*., 2001; Verbeeck *et al*., 2006:4221). Even though the cause of the pockets of HCV-G5 in these regions remains largely unknown, transmission routes related to blood transfusions or haemodialysis have been suggested (Verbeeck *et al*., 2008:170). Studies in Belgium and France found that patients infected with genotype 5 were significantly older than patients infected with other genotypes, whereas further analyses of the French and Belgium strains suggested that sexual intercourse and intra-familial transfer of this particular genotype are possibly underestimated (Henquell *et al.,* 2001; Jover *et al*., 2001; Verbeeck *et al*., 2006:4221). Furthermore, Verbeeck *et al*. (2006:4221) suggest that the Belgian and South African populations have

sustained independent populations of HCV-G5 for at least a century. Table 2.9 (compiled from Antaki *et al*., 2009a:343) shows the proportion of HCV-G5 in HCV patients worldwide.

Table 2.9: Proportion of HCV-5 in HCV patients worldwide[k]

Region	Countries	HCV-5 (%)
Africa	South Africa	40
Middle East	Syria	10
Europe	France	3
	Belgium	1-5
	United Kingdom	0.7
	Spain	0-10.3
	Italy	0-0.1
America	Canada	0.1-4.5
Compiled from Antaki et al. (2009a:343)		

A study conducted by Gededzha *et al*. (2012:601) investigated the sequence diversity and genotypes of HCV in South Africa. This study indicated that even though HCV-G5a remains the predominant genotype in South Africa, HCV-G1 and HCV-G4 are encountered in a significant proportion (38%) of the population. The study also indicated that there is definitely an introduction of new subtypes of HCV-GT4 in South Africa (Gededzha *et al*., 2012:601).

According to Gededzha *et al*. (2012:603), 54% of their study population were infected with HCV-G5; 19% were infected HCV-G1 and another 19% with HCV-G4, while only 2% were infected with HCV-G3. This supported findings a previous study (Prabdial-Sing *et al*., 2008:38) that reported that HCV-G5a is the most predominant HCV genotype in South Africa. Results from another South African study established that HCV-G5 is the predominant genotype in South Africa (56.3%), followed by HCV-GT1 (28.7%), HCV-GT3 (9%), HCV-GT4 (5%) and HCV-GT2 (15%) (Prabdial-Sing *et al.*, 2013:24). A more recent study indicated a slightly different distribution of the HCV genotypes in South Africa (HCV-GT5 ~36%, HCV-GT1b ~22%, HCV-GT3a ~11.7%, HCV-GT4 ~8.91%, HCV-GT2 <2%) (Prabdial-Sing *et al.*, 2013:24). These results, however, still support HCV-GT5 being the dominant genotype in South Africa.

2.3 Response to antiviral treatment

The goal of antiviral treatment in chronic HCV infection is to render patients who are viraemic (PCR positive) clear of the virus (PCR negative) (Dillon, 2007:27). The decline of HCV RNA during therapy is highly associated with the likelihood of achieving an SVR. Viral kinetics on treatment are defined by several features of responses to HCV treatment and the careful monitoring of HCV RNA results is necessary to determine when treatment should be stopped

(Yee *et al*., 2012:4). Virological responses (when using peg-Interferon/ribavirin based therapy) are monitored during therapy and designated as follows:

– Rapid virological response (RVR): "HCV RNA negative at treatment week four by a sensitive PCR-based quantitative assay. RVR may allow shortening of therapy for HCV-G2 and HCV-G3 and possibly HCV-G1 when viral load is low" (Fried *et al.,* 2011:69);

– Early virological response (EVR): "EVR is categorised as a decrease in the HCV RNA level with ≥2 log reduction at week 12 of therapy. Failure to achieve an EVR remains the most accurate negative predictor of SVR in dual therapy with peg-INF and RBV and discontinuation of treatment should be considered in patients who are not responding after three months of therapy (detectable HCV RNA and abnormal ALT)" (Davis, 2002:S146);

– End-of-treatment response (ETR): "Negative HCV RNA (by a sensitive test) at the end of 24 or 48 weeks of treatment" (Ghany *et al.,* 2009:1341).

A complete virologic and biochemical response at the end of treatment, followed by the re-emergence of HCV RNA and/or the elevation of ALT levels during follow-up is categorised as treatment relapse. Relapsing responders initially treated for 24 weeks might be considered for retreatment for another 24 to 52 weeks, but relapsing responders who have already received treatment for 52 weeks have a very low probability of achieving SVR and retreatment is seldom recommended in these patients (Botha *et al*., 2010). A breakthrough response is "a temporary virological and biochemical response occurring during therapy followed by the reappearance of HCV RNA and/or abnormal ALT level before the end of treatment is known as". When a breakthrough response occurs, treatment should be discontinued (Ghany *et al.,* 2009:1341). When HCV RNA remains detectable and/or ALT levels fail to normalise throughout the treatment phase, it is considered a 'non-response or null response'. Patients who fail to achieve a virologic and/or biochemical response following six to 12 months of therapy are unlikely to respond to additional treatment regimens (Davis, 2002:S146).

Genotype is another determinant of the response to antiviral therapy, as different genotypes vary in their responsiveness to HCV combination therapy (Antaki *et al.*, 2009a:343). The existing South African hepatitis C management guidelines indicate that genotyping should be performed in all HCV-infected patients before initiating interferon-based therapy in order to plan the dose and treatment duration as well as to predict likely estimates of probability of a response (Botha *et al.,* 2010). The impact of genotype on treatment is so significant that the different genotypes should be considered as having entirely separate therapeutic regimes and separate response rates (Dillon, 2007:28). It is necessary that optimal treatment schedules be

determined for each HCV genotype; therefore, the less frequent genotypes deserve the same attention as the more common genotypes (Verbeeck *et al*., 2008:171).

2.4 Treatment of hepatitis C virus infection

The primary efficacy measure of HCV therapy is sustained response or sustained virologic response (SVR), defined as "*the clearance of HCV RNA from the blood and persistent normalisation of serum ALT levels observed 6-12 months after therapy has ended*" (Ghany *et al*., 2009:1341). Achievement of SVR is regarded as a virologic 'cure' and is associated with improved morbidity and mortality (Pearlman & Traub, 2010:889; Wendt & Bourlière, 2013:191). Successful treatment with antiviral drugs, *viz.* viral eradication, has been associated with prolonged patient survival and a reduced incidence of liver-related complications such as decompensated cirrhosis and HCC (Backus *et al*., 2011:515).

From 2000 until 2011, the SOC for patients with chronic HCV infection was a combination of peg-IFN alpha-2a or alpha-2b, and RBV (Alexopoulou & Papathiodoridis, 2012:6061). These drugs are administered for either 48 weeks (for HCV genotypes 1, 4, 5 and 6) or for 24 weeks (for HCV genotypes 2 and 3). The peg-INF/RBV combination typically produces SVR rates of 40 to 50% in patients with HCV-G1 and upwards of 75% in patients with HCV-G2 and HCV-G3 infections (Fried *et al*., 2001:975; Manns *et al.*, 2001:958). The response to combination treatment in HCV-G4 is intermediate between genotypes 1, 2 and 3 (43-70%), whereas SVR is achieved in >50% and 60 to 85% of cases in HCV-G5 and HCV-G6, respectively (Antaki *et al*., 2009b:384).

2.4.1 Ribavirin

Ribavirin (RBV) is a guanosine analogue that produces broad-spectrum activity against various RNA and DNA viruses (Sidwell *et al*., 1972:705). It was discovered in 1972 and originally only approved for the treatment of severe respiratory syncytial viruses in children (Krilov, 2001:243). In later years, RBV was also used in the treatment of Lassa fever virus infection, influenza A and B and other viruses (Andrei & De Clercq, 1993:45-50; Huggins, 1989:S750; Van Voris & Newell, 1992:61). RBV was only studied for the treatment of HCV in the early 1990s and despite observations of improvements in serum ALT levels and liver histology, RBV had no substantial effect on HCV RNA levels when used alone. Combining it with interferon alfa, however, demonstrated its value (Te *et al*., 2007:224). The mechanism responsible for RBV's increased efficacy during concomitant use with interferon has not been well established, but it could be attributable to the multivalent nature of RBV as a purine analogue and its involvement in multiple cellular pathways, including immunomodulation and inosine-5'-monophosphate dehydrogenase (IMPDH) inhibition (Te *et al*., 2007:224).

Its inability to directly or adequately inhibit viral replication in HCV patients as a single agent notwithstanding, RBV has been invaluable in the treatment of HCV for over a decade — first in combination with interferon and later peg-INF (Hoofnagle *et al*., 2003:66).

2.4.2 Pegylated interferon

Interferons are cytokines released by the host's immune- and other cells in the presence of pathogens. Cytokines are an assorted group of soluble polypeptides that operate as mediators between cells. They modulate viral replication; activate other immune cells (such as macrophages) and upregulate antigen presentation *via* major histocompatibility complex molecules (David *et al.,* 1995:1722; Lee *et al*., 2012:343). Interferons are therapeutically classified as 'biologic response modifiers' or immunotherapy. Immunotherapy mobilises the body's own immune system to combat, in particular, viral illnesses (Foster, 2010:147).

Peg-INF is interferon with polyethylene glycol (PEG) moiety attached to it. It was developed to enhance the half-life of interferon (Lee *et al*., 2012:343). There are currently two peg-INF molecules available for the treatment of CHC: peg-INF alpha-2a and peg-INF alpha-2b. Differences in the size and nature of the covalently attached polyethylene glycol moiety result in differences in pharmacokinetics and dosing regimens between the different peg-INFs. Both are administered with subcutaneous injections. Peg-INF alpha-2a can be administered once a week due to its restricted volume of distribution, long half-life and reduced clearance. Peg-INF-alpha-2b has a shorter half-life than peg-INF alpha-2a and requires weight-based dosing (Foster, 2010:147).

Peg-INF is associated with numerous, and often serious, side-effects, including flu-like symptoms; agitation/anxiety/severe depression; difficulty in sleeping; dry, itchy skin, hair loss, blurred vision, anaemia, thrombocytopenia and neutropenia (Wilkie, 2013:24).

Peg-INF has been part of the SOC for chronic HCV infection for more than a decade, but treatment with peg-INF-based therapy is lengthy, inconvenient and costly. Furthermore, even in patients who are eligible for treatment, not everybody responds to peg-INF (Gravitz, 2011:S4). The ideal is for a drug that can shorten the duration of treatment, increase efficacy and reduce its side-effects with the ultimate goal being interferon-free therapies (Au & Pockros, 2014:86).

2.4.3 Direct-acting antivirals

Two major advances in anti-HCV therapy recently resulted in changes in the treatment regimen of chronic HCV infection: i) the identification of several single-nucleotide polymorphisms associated with spontaneous and treatment-induced clearance of HCV infection; and ii) the

development of direct-acting antivirals (DAAs), which directly inhibit viral replication of HCV (Ghany *et al*., 2012:2).

A better understanding of HCV has facilitated efforts to improve efficacy and tolerability of HCV treatment. Multiple direct-acting antivirals or DAAs — medications targeted at specific processes within the HCV lifecycle — have been developed (Au & Pockros, 2014:78). DAAs target specific non-structural proteins within the HCV, which disrupts viral replication and infection. These molecules are defined by their mechanism of action and by their therapeutic target and there are currently four classes of DAAs, which include protease inhibitors (PIs) or NS3/4A inhibitors, NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs) and NS5A inhibitors (Poordad & Dieterich, 2012:450).

The launch of the first two protease inhibitors, boceprevir (BOC) and telaprevir (TLV), represented a new era of HCV therapy, as they were the first commercially available DAAs to be approved in late 2011 (Yee *et al*., 2012:2). Triple therapy, which included peg-INF/RBV and one of the DAAs, became the new SOC for patients with HCV-G1 after the approval of BOC and TLV. Adding BOC or TLV to peg-INF/RBV produces SVR rates between 63 and 75% and 69 and 88% in treatment-naïve and treatment-experienced HCV-G1 patients, respectively (Jacobson *et al.*, 2011:2405; Poordad *et al.*, 2011:1195; Sherman *et al.*, 2011:1014). However, clinical trials indicate that with the improved effectiveness and increased SVR rates achieved with BOC and TLV came increased rates of adverse effects, with some studies reporting so much as a two-fold increase in anaemia and with the use of protease inhibitors (Jacobson *et al.*, 2011:2405; Poordad *et al.*, 2011:1195; Sherman *et al.*, 2011:1014). Furthermore, BOC- and TLV-based regimens in combination with peg-INF/RBV are limited to HV-G1 (AASLD, 2015; EASL, 2015).

The approval of BOC and TLV paved the way for new generation DAAs and, since 2011, several more DAAs have been approved for the treatment of chronic HCV infection. The first of these was sofosbuvir, a pangenotypic nucleotide analogue inhibitor of HCV RNA-dependent RNA polymerase active against all six HCV genotypes. This was followed by simeprevir, a second-wave, second-generation NS3/4A protease inhibitor active against genotypes 1 and 4 and daclatasvir, a pangenotypic NS5A inhibitor (Au & Pockros, 2014:78). These three DAAs were licensed in the European Union in 2014 for use as part of combination therapies for HCV infection. Each of these three DAAs can be used as a component of a triple combination regimen with peg-IFN and RBV, yielding SVR rates of 60 to 100% according to the DAA used, the HCV genotype, the presence of detectable pre-existing amino acid substitutions conferring resistance to the DAA used and the severity of liver disease. Although these combinations are better tolerated than triple combination, including telaprevir or boceprevir, their side effect

profiles and management remain challenging because of the use of peg-IFN and of RBV (EASL, 2015:199).

These regimens can take up to a year to complete, place a high burden on patients by requiring weekly injections and complicated dosing schedules and are associated with significant side effects leading patients to discontinue treatment. The ideal treatment for HCV should be highly effective, easy to take, should have a low side effect profile, a low patient burden and should be affordable.

2.4.4 Sofosbuvir

Of the recently developed DAAs, sofosbuvir has drawn the most attention, because it is the first new DAA that the FDA approved for the treatment of genotypes 1 to 4 (Leof *et al*., 2014:1). With cure rates and side effect profiles better than previously seen for hepatitis C, sofosbuvir has been hailed as a 'miracle cure'. Not only was sofosbuvir the first new DAA to be approved as part of an interferon-free regimen (for HCV-G2 and HCV-G3), it was also the first DAA with proven efficacy for HCV-G5, the predominant genotype in South Africa and the target population of this study (Lawitz *et al*., 2013).

Sofosbuvir is an orally bioavailable, direct-acting NPI and a nucleotide analogue inhibitor of HCV NS5B — the key enzyme mediating HCV RNA (Bourliere *et al*., 2011:S88). Sofosbuvir actively competes with naturally occurring nucleotides at the highly conserved active site of the HCV NS5B polymerase, resulting in early RNA chain termination (Zeng *et al.*, 2013:3201). Sofosbuvir is a prodrug; after ingestion, it is rapidly converted to GS-331007, the predominant circulating drug that accounts for more than 90% of the systemically active drug. GS-331007 is efficiently taken up by hepatocytes and phosphorylated within the liver to a nucleotide triphosphate, GS-461203, the pharmacologically active uridine analogue 5'-triphosphate form of sofosbuvir (Poordad *et al*., 2013:48). This triphosphate compound mimics the natural cellular uridine nucleotide and is incorporated by the HCV RNA polymerase into the elongating RNA primer strand, resulting in chain termination. The active form GS-461203 targets the NS5B catalytic site and acts as a non-obligate chain terminator (Poordad *et al.,* 2013:48; Zeng *et al.*, 2013:3201).

The NEUTRINO clinical trial (NCT01641640) was a phase three, multicentre, open-label, single-group study that assessed the safety and efficacy of sofosbuvir used in combination with RBV and peg-INF alfa-2a in treatment-naïve patients with genotype 1, 4, 5 or 6 HCV infection (Lawitz *et al*., 2013:1881). In the NEUTRINO study, all enrolled patients received a 12 week course of sofosbuvir of 400 mg daily orally, plus weight-based RBV plus peg-INF. Most of the patients included in the NEUTRINO study had HCV-G1, 9% had HCV-G4 and 2% had genotype 5 or 6.

SVR rates 12 weeks after treatment has ended did not differ greatly according to the HCV genotype: 89% of patients with HCV-GT1 (92% for HCV-G1a and 82% for HCV-G1b) and 96% of patients with HCV-G4, respectively achieved SVR. The single patient with HCV-G5 and all six patients with HCV-G6 in the NEUTRINO trial achieved a sustained virologic response (Lawitz *et al*., 2013:1881).

The addition of sofosbuvir not only shortens treatment duration from 48 weeks to 12 weeks, but achieves SVR rates of close to 100% in patients with genotype 5 infection (Abergel *et al.*, 2015). Accordingly, sofosbuvir became the first DAA to be included in the EASL, AASLD and IDSA (Infectious Diseases Society of America) guidelines added to the current SOC for HCV-G5 in both the EASL and AASLD guidelines. In their latest updated guidelines, the EASL and AASLD cite the recommended treatment for patients with HCV-G5 infection, who are eligible to receive interferon, as the combination of sofosbuvir (400 mg once daily for 12 weeks) + RBV (1000 mg/day if <75 kg or 1200 mg/day if ≥75 kg for 12 weeks) + peginterferon alfa-2a (180 mcg subcutaneously once weekly for 12 weeks) or peginterferon alfa-2b 1.5 mcg/kg subcutaneously once weekly for 12 weeks (AASLD, 2015; EASL, 2015).

Shortly after the approval of sofosbuvir (marketed as *Sovaldi*® in the US), the FDA approved several more sofosbuvir-based combinations for CHC, including sofosbuvir + ledipasivr (*Harvoni®)* for HCV-G1, sofosbuvir + simeprevir (*Olysio*® + *Sovaldi*®) for HCV-G1 and sofosbuvir + daclatasvir (*Sovaldi*® + *Daklinza*®) for HCV-G3 (FDA, 2014).

Harvoni® (SOF/LDV) was the first once-daily single tablet regimen for the treatment of genotype 1 CHC. This fixed dose combination of sofosbuvir plus ledipasvir — an NS5A inhibitor — demonstrated high SVR rates, ranging from 93 to 99% in treatment-naïve and treatment-experienced HCV-GT1 patients (Afdhal *et al.*, 2014a:1483). SOF/LDV was initially only approved for patients with HCV-G1, but have recently been reported to also be effective in patients with other genotypes, including HCV-G5. In a small, open-label study conducted in France, investigators enrolled treatment-naive and treatment-experienced patients with HCV genotype 4 or 5 infection to receive a 12-week course of SOF/LDV. For the treatment-naïve patients with genotype 5 infection, 20 (95%) of 21 achieved an SVR12. The results for patients with genotype 5 infection were similar, regardless of cirrhosis presence (Abergel *et al*., 2015). It should be noted that effectiveness data of SOF/LDV in HCV-G5 is based on very small patient numbers in open label non-randomised studies. Nonetheless, based on the findings of the French study, the fixed-dose combination of sofosbuvir (400 mg) / ledipasvir (90 mg), one tablet once daily for 12 weeks was included in the 2015 EALS and AADSL guidelines for treatment of non-cirrhotic patients with HCV-G5. The EASL guidelines recommend that patients with compensated cirrhosis be treated with the same fixed-dose combination, and weighted based RBV, once a day for 12 weeks, or SOF/LDV monotherapy for 24 weeks (EASL, 2015).

2.4.5 Treatment of HCV-G5 in South Africa

Because the global genotype 5 population is relatively small, large single studies are challenging to perform. Since large clinical trials do not include a sufficient number of patients infected with genotype 5, data on response rates to antiviral therapy in patients infected with genotype 5 is limited and the optimal treatment schedule for HCV-G5 remains unclear (D'Heygere *et al.,* 2005:203). HCV-G5 is the predominant genotype in South Africa, but to date, no study has been published on the efficacy of peg-INF/RBV from this country. In other countries, HCV-G5 prevalence is extremely low and studies that have been published on the sensitivity of this genotype are based on small patient numbers (Bonny *et al*., 2006; Legrand-Abravanel *et al*., 2004). HCV-G5 is generally treated as HCV-G1 due to lack of evidence from clinical trials for these genotypes (Dillon, 2007:28). According to Bonny *et al*. (2006) and Legrand-Abravanel *et al.* (2004), however, the response of HCV-G5 to treatment is more similar to that of genotypes 2 and 3, as it has a better treatment response than HCV-G1. Table 2.10 shows the SVR rates achieved in patients with HCV-G5 infection, compared to SVR rates for genotypes 1, 2 and 3, treated with peg-INF/RBV as reported by various studies.

Table 2.10: Effectiveness of peg-INF/RBV in HCV-G5 *vs.* HCV genotypes 1, 2 and 3[I]

Reference	SVR HCV-G5	SVR HCV-G1	SVR HCV-G2/3
Antaki *et al.* (2009b)	54% (14/26)	-	-
Bonny *et al*. (2006)	60% (52/87)	37%	63%
Delwaide *et al*. (2005)	83% (5/6)	-	-
D'Heyegere *et al*. (2005)	55% (10/21)	38%	-
Legrand-Abravanel *et al.* (2004)	67% (8/12)	22.7%	66.6%
G = genotype; HCV = hepatitis C virus; SVR = sustained virologic response			

To date, there have been no randomised control trials or prospective follow-up studies that include data on the efficacy of the SOC in HCV-G5 infection in the South African setting. Despite the lack of data on the effectiveness of peg-INF/RBV in South African patients with HCV-G5, these patients are treated as patients with HCV-G1, with weight-based RBV and peg-INF for 48 weeks (Botha *et al*., 2010). As shown in Table 2.10, studies conducted on HCV-G5 infection in other countries have reported SVR rates of between 54 and 85% for this cohort of patients. Response rates of South African patients with HCV-G5 infection to the SOC are not exactly known, but it is estimated to be >50% (Sonderup, 2013). Because clinical trial data for HCV-5 patients in a South African setting is not available, response rates for SOC for our cost-effectiveness analysis were obtained from a meta-analysis for two large prospective trials performed in Belgium *viz.* the BERNAR-1 and BERNAR-2 trials (D'Heygere *et al*., 2011).

Results from the meta-analysis indicated RVR, EVR, EOT and SVR rates of 50%, 66.7%, 59.3% and 55.3%, respectively for HCV-G5 infection treated with SOC.

As far as the authors of this thesis are aware, this was the first comparative analysis of the response of genotype 5 to peg-INF therapy and the best available evidence of efficacy data on peg-INF/RBV to date. Based on these results, an SVR rate of 55.3% was assumed for the SOC-arm in the base case analysis.

2.5 Health-related quality-of-life in patients with chronic liver disease

The WHO defines quality-of-life (QoL) as "*an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns*". It is a broad ranging concept affected in a complex way by a person's physical health, psychological state, personal beliefs, social relationships and his/her relationship with prominent features of their environment (WHO, 1997). Because 'QoL' is so multidimensional and (theoretically) incorporates all aspects of an individual's life, 'health-related quality-of-life' (HRQoL) has become the preferred term for QoL in relation to health status. HRQoL is distinct from QoL as a whole, which includes factors such as adequacy of housing, income and perceptions of the immediate environment (Bowling, 1999). Patrick and Erickson (1993) define HRQoL as "*the value assigned to duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy*" (Patrick & Erickson as quoted by Feeny, 2000:II-152).

In general, there are four main uses of HRQoL assessments in healthcare: 1) treatment comparisons in clinical trials, 2) patient population studies to evaluate the burden of the disease in terms of HRQoL, 3) health economic evaluations to determine the best use of healthcare resources, and 4) treatment choices in individual patient care (McGee & Ring, 2010:332). HRQoL includes a physical, a social and a mental component, each of which consists of multiple subcomponents. The measurement of HRQoL is done by means of standardised, self-administered questionnaires. There are two basic types of HRQoL questionnaires: generic questionnaires and disease-specific questionnaires. A third type of HRQoL questionnaire — utility measures —measures HRQoL from a cost-effectiveness perspective (Gutteling *et al*., 2007:228).

2.5.1 Generic questionnaires

Generic questionnaires are by far the most well-known indirect method of utility measurement. The three most common instruments in use today are the EuroQol Five Dimension (EQ-5D), the Short Form Six Dimension (SF-6D) and the Health Utilities Index (HUI). Generic questionnaires have the advantage that patients' scores can be compared with the scores of other patient

populations and/or healthy control populations. A disadvantage is that generic instruments are not designed to identify disease-specific domains that may be important to establish clinical changes, i.e. they may lack sensitivity within specific disease contexts (Jenney & Campbell, 1997:348).

2.5.2 Disease-specific questionnaires

Disease-specific questionnaires are designed to be valid only for a specified condition and have the advantage of providing greater specificity and sensitivity. This approach emphasises the need to establish ranges of health-related changes that represent trivial, small but important, moderate and large changes in addition to mean differences (Guyatt *et al*., 1998:693).

2.5.3 HRQoL in health economics: utility measures

Utility measures originated in health economics and form an important subgroup of generic measures that are used in cost-effectiveness studies and medical decision-making. In most health economic evaluations, the summary measure of health outcome generally used is the quality-adjusted life-year (QALY) (Weinstein *et al*., 2009:S5). With utility measures, QALYs can be computed, which combines the HRQoL of a patient with his/her survival and provides an indication of the benefits gained from a variety of medical procedures in the terms of quality-of-life and survival of the patient (Scuffham *et al*., 2008:298; Whitehead & Ali, 2010:6).

Utility measurement consists of two main components, namely 1) the definition and description of a set of health states of interest, and 2) the valuation of those health states. These can be applied by either direct or indirect utility measurement. The three most frequently used direct utility measurement methods include the standard gamble (SG), time trade-off (TTO) and visual rating scales (VRS) (Tolley, 2009:3). Besides these sophisticated, yet labour-intensive methods, there are also generic 'off the shelf' quality-of-life instruments. Indirect utility measures most commonly used in cost-effectiveness studies are the HUI, SF-6D and the EQ-5D (Tolley, 2009:1).

The EQ-5D is preferred over the HUI and the SF-6D, as the SF-6D has shown a floor effect, especially in liver patients (Ferreira *et al.*, 2008:1037; Younossi *et al*., 2001:583). All of these generic instruments provide utility scores as an additional outcome (Tolley, 2009:1). Utility scores provide a single summary score of outcome (utilities values or health utilities) and are particularly important when there are both mortality and morbidity effects and some integration of them is needed (such as quality-adjusted survival). Utility values are useful as measures of outcome and 'inputs' in economic evaluations and have been used as the preference weights within the QALY model (Feeny, 2000:II-154).

In health economics, utilities are cardinal values that reflect an individual's preferences for a specific level of health status or different health outcomes. They are measured on an interval scale with zero reflecting states of health equivalent to death and one reflecting perfect health. Health utilities are then combined with survival estimates and aggregated across individuals to generate QALYs for use in cost-utility analyses of healthcare interventions (Torrance, 1986:2).

2.5.4 Health utilities for patients with chronic HCV infection

The increasing prevalence of chronic disease in developed countries has led to an increased focus on the emotional and social well-being of patients as well as their physical well-being, referred to as HRQoL (Gutteling *et al*., 2007:227). HRQoL has particularly become an important outcome measure in patients with chronic liver disease (CLD) (Van der Plas *et al.*, 2007:375).

Patients with CLD experience a variety of symptoms with profound negative effects on their HRQoL. Patients with hemochromatosis or viral hepatitis, especially hepatitis C, have a more impaired HRQoL than patients of other liver disease aetiological groups. Beside specific complications of cirrhosis; such as hepatic encephalopathy, ascites and variceal bleeds, symptoms such as abdominal pain, muscle cramps, fatigue, depression and anxiety have also been associated with reduced HRQoL in patients with CHC. Concerns about complications of the disease, decreased sexual interest, loneliness and hopelessness have also been implicated in decreased HRQoL (Gutteling *et al*., 2006:1629; Younossi *et al*., 1999:297). While investigators may choose from a variety of validated generic instruments for the measurement of HRQoL, these questionnaires fail to detect small but important improvements in HRQoL in patients with CLD. A liver-specific instrument is likely to be more responsive to changes in HRQoL, which, while small, are nevertheless important as studies have indicated that as liver disease becomes more severe, patients' HRQoL deteriorates (Younossi *et al.,* 1999:299).

Four liver disease-specific questionnaires have been developed and are used extensively. These include the Hepatitis Quality-of-life Questionnaire (HQL-Q), the Chronic Liver Disease Questionnaire (CLD-Q), the Liver Disease Quality of Life Questionnaire (LDQoL-Q) and the Liver Disease Symptom Index 2.0 (LDSI 2.0) (Gutteling *et al*., 2007:227). Table 2.11 lists these questionnaires with their most common strengths and weaknesses.

Table 2.11 Liver disease-specific questionnaires[m]

Questionnaire	Strength/Advantage	Weakness/Disadvantage	When to use
HQLQ	Consists of the widely validated SF-36 with five added disease-specific subscales	Excludes patients with other chronic liver disease than HCV. Fails to address hindrance.	Efficient instrument for healthcare professionals interested in HRQoL of patients with HCV. Comprises generic and disease-specific items simultaneously.
CLDQ	Short, and therefore feasible	Unable to discriminate between more advanced stages of liver disease. Fails to address hindrance.	Used when a short questionnaire is preferred.
LDQoLQ	Addresses a variety of domains and consists of 101 items	Very long, which may be a problem when completion time is limited, or multiple questionnaires are being administered. Fails to address hindrance.	Can be used when a lengthy questionnaire is not an issue and the aim is to obtain information on a wide range of liver disease-specific HRQoL domains.
LDSI 2.0	Short questionnaire that measures 9 possible liver disease-specific symptoms, as well as the hindrance that patients experience from having these symptoms		Recommended over the CLDQ when a short questionnaire is preferred, as it takes symptoms and hindrance into account.

HQLQ = Hepatitis Quality-of-Life Questionnaire; CLDQ = Chronic Liver Disease Questionnaire; LDQLQ = Liver Disease Quality-of-Life Questionnaire; LDSI 2.0 = Liver Disease Symptom Index 2.0

[m]Compiled from Gutteling et al. (2007:229)

Few estimates exist for utility measures for liver disease in the literature and, to date, health utilities for patients suffering from chronic HCV infection in South Africa have not been determined. In the absence of SA-specific utility data, systematic reviews were used as references for health state utility values used in our model (Chong *et al.,* 2003; Hsu *et al*., 2009; Longworth & Bryan, 2003; McLernon *et al*., 2008; Thein *et al*., 2005). Each health state in the model was assigned a utility score between 1 (perfect health) and 0 (death) to quantify patient utilities while residing in that health state. The impact of treatment on HRQoL is inexact, although it is known that there are definite decrements in HRQoL associated with the adverse and toxic effects of peg-INF treatment (Salomon *et al.,* 2003:229). A study conducted by Kerr *et al.* (2012) evaluated the impact of treatment attributes of peg-INF for HCV on HRQoL. Results from the study indicated that flu-like symptoms resulting from injected peg-INF as part of HCV treatment have a significant impact on patients' quality-of-life (Kerr *et al*., 2012:e153).

Another study, conducted to assess health utilities for sofosbuvir-containing therapy for CHC, found treatment with SOF + RBV minimally impacted patients' health utilities, as compared to interferon-based treatment (Stepanova *et al.,* 2014:684). The results showed that combining SOF with peg-INF caused a more severe impairment of the patient's HRQoL than an interferon-free regimen; although all treatment-related impairment were resolved within 12 weeks after the end of treatment (Stepanova *et al*., 2014:684). Younossi *et al*. (2015) assessed patient reported outcomes (PRO) in patients treated with SOF/LDV with and without RBV enrolled in the ION-1, -2, and -3 trials. Investigators administered four PRO questionnaires were administered at baseline, during, and post-treatment in patients treated with SOF/LDV ± RBV. Patients receiving LDV/SOF regimens showed significant improvement of PRO scores during treatment, whereas PRO scores declined during treatment with SOF/LDV+RBV. Results showed that receiving RBV was an independent predictor of PRO impairment. The study also calculated SF-6D utility scores for patients treated with SOF/LDV ± RBV, showing lower utility scores for patients who receive RBV in addition with SOF/LDV (Younossi *et al.*, 2015:1806). The utility values reported for patients while receiving treatment with SOC, sofosbuvir and SOF/LDV were taken from Kerr *et al*. (2012), Stepanova *et al*. (2014), and Younossi *et al.* (2015), respectively. The utility values assigned to patients in each health state of the model are presented in Table 2.12.

Table 2.12: Health state utilities of patients with chronic HCV infection

Health state	Utility	Range	Reference
Healthy	1		
CHC without cirrhosis (F2-F3 fibrosis)	0.790	(0.74-0.82)	Chong *et al.* (2003); Thein *et al*. (2005)
CHC (while on treatment with SOC)	0.430	(0.28-0.58)	Kerr *et al*. (2012)
CHC (while on treatment with SOF-TT*)	0.650	(0.43-0.86)	Stepanova *et al*. (2014)
CHC (while on treatment with SOF/LDV)	0.750	(0.59-0.91)	Younossi *et al.* (2015)
Compensated cirrhosis (≥F4 fibrosis)	0.748	(0.74-0.77)	Chong *et al.* (2003); McLernon *et al.* (2008)
Cirrhosis (while on treatment with SOC)	0.430	(0.28-0.58)	Kerr *et al*. (2012)
Cirrhosis (while on treatment SOF-TT*)	0.650	(0.43-0.86)	Stepanova *et al.* (2014)
Cirrhosis (while treated with SOF/LDV+RBV)	0.701	(0.55-0.85)	Younossi *et al.* (2015)
Decompensated cirrhosis	0.672	(0.60-0.69)	Chong *et al.* (2003); McLernon *et al.* (2008)
HCC	0.610	(0.20-0.67)	Hsu *et al.* (2009); Longworth and Bryan (2003); Thein *et al*. (2005)
SVR	0.89	(0.82-0.89)	Thein *et al*. (2005)

CHC = chronic hepatitis C; HCC = hepatocellular carcinoma; SOC = standard of care; SOF-TT = sofosbuvir triple therapy; SVR = sustained virologic response

**SOF-TT = sofosbuvir + peg-INF + RBV*

2.6 Chapter summary

In this chapter, the patient journey of an individual infected with the hepatitis C virus was characterised, focusing on defining HCV infection and researching all relevant aspects on the subject of the disease, including clinical features of the disease, routes of transmission, incubation period, risk factors, prevention, complications, diagnosis and testing, treatment and response. Herewith the objectives of the literature review were addressed.

The next chapter (Chapter 3) will focus on the results and discussions of the empirical investigation phase of the study. The results and discussion are presented in the form of three manuscripts.

CHAPTER 3: RESULTS AND DISCUSSION

This chapter focuses on the results and discussion of the empirical investigation of the study and is presented in article format. The results and discussion are presented in the form of three manuscripts addressing the main objectives of the empirical investigation.

3.1 Introduction

Manuscript one addressed the objectives: building a Markov model on TreeAge Pro Healthcare, 2014 software based on the natural history/disease states of chronic HCV infection identified in the literature review; populating the model with data, including annual transition probabilities, cost data, effectiveness data, health state utility values and background mortality rates; running the model through TreeAge Pro Healthcare, 2014 software to yield results based on cost-effectiveness and analysing these results; using the results to compare the alternative HCV treatment strategies based on cost-effectiveness and incremental cost-effectiveness ratios and determining if the modelled price of sofosbuvir and sofosbuvir-ledipasvir will be cost-effective for HCV infection in South Africa based on the willingness-to-pay (WTP) threshold of R200 000.00. Manuscript one was accepted for publication in PharmacoEconomics (refer to Annexure C). The author guidelines for PharmacoEconomics are included in Annexure B.1 (available at: http://www.springer.com/adis/journal/40273?print_view=true&detailsPage=pltci_2295304).

Manuscript two addressed the objective: quantifying the public health impact of the use of sofosbuvir-based regimens compared to current HCV treatments from a South African private sector third-party payer's perspective. Manuscript two was submitted to Public Health (refer to Annexure C). The author guidelines for Public Health are included in Annexure B.2 (available at:http://www.elsevier.com/wps/find/journaldescription.cws_home/645727?generatepdf=true).

Manuscript three addressed the objective: determining the budget impact of sofosbuvir-based regimens in South Africa as part of the total health budget. Manuscript three will be submitted to Medical Decision Making (refer to Annexure C). The author guidelines for Medical Decision Making is included in Annexure B.3 (available at: http://mdm.uic.edu/manuscript-requirements/)

3.2 Manuscript 1

Article title: Cost effectiveness modelling of sofosbuvir-containing regimens for chronic genotype 5 hepatitis C virus infection in South Africa

Running heading: Cost effectiveness of sofosbuvir-containing regimens for chronic HCV-5

Authors:

Fraser, Ilanca[1], Burger, Johanita[1], Lubbe, Martie[1], Dranitsaris, George[2], Sonderup, Mark[3] & Stander, Tienie[4]

Affiliation:

[1]Niche area: Medicine Usage in South Africa (MUSA), North-West University (Potchefstroom campus), Potchefstroom, South Africa

[2] Senior Specialist and Lecturer in Department of Medicine and Division of Hepatology, University of Cape Town and Groote Schuur Hospital

[3] Principal, Augmentium Pharma Consulting Inc., Toronto, Canada, M4K 1N2

[4]Researcher: HEXOR (Pty) Ltd, South Africa

Word count (Abstract):

256

Word count (Text):

4186

Title: Cost effectiveness modelling of sofosbuvir-containing regimens for chronic genotype 5 hepatitis C virus infection in South Africa

Running heading: Cost effectiveness of sofosbuvir-containing regimens for chronic HCV-5

Authors:

Fraser, Ilanca[1], Burger, Johanita[1], Lubbe, Martie[1], Dranitsaris, George[2], Sonderup, Mark[3] & Stander, Tienie[4]

Affiliation:

[1]Niche area: Medicine Usage in South Africa (MUSA), North-West University (Potchefstroom campus), Potchefstroom, South Africa

[2] Senior Specialist and Lecturer in Department of Medicine and Division of Hepatology, University of Cape Town and Groote Schuur Hospital

[3] Principal, Augmentium Pharma Consulting Inc. , Toronto, Canada, M4K 1N2

[4]Researcher: HEXOR (Pty) Ltd, South Africa

Corresponding Author:

Fraser, Ilanca

Mailing address: Medicine usage in South Africa (MUSA), Faculty of Health Sciences, North-West University, Potchefstroom Campus, Potchefstroom, South Africa, 2520

Degrees: BPharm, MPharm

Institution: North-West University, Potchefstroom Campus

Phone: +27 18 299 2285

Fax: +27 87 231 4105

E-mail address: ilancaroux@gmail.com

Acknowledgements The authors thank Margreet Bergh for assistance with model construction and –analysis in TreeAge Healthcare Pro **Funding** I Fraser received funding from HEXOR (Pty) Ltd and the North-West University. The views expressed in this manuscript are solely those of the authors and do not necessarily reflect the decisions or stated policy of HEXOR or the North-West University **Competing interests** None declared **Disclosure of potential conflicts of interest:** All of the authors declare they have no conflict of interest. **Compliance with ethical standards** No clinical study or patient data collection was performed for the preparation of this project. This study was approved by the North-West University Health Research Ethics Committee [NWU-00035-15-A1].

Abstract

Background The recently launched nucleotide polymerase inhibitor, sofosbuvir, represents a significant turn in the treatment paradigm of chronic hepatitis C. While effective, sofosbuvir is also associated with a considerable cost. *Objective* To evaluate the cost-effectiveness of sofosbuvir-containing regimens in treatment-naive patients with chronic hepatitis C virus genotype 5 (HCV-5) mono-infection in South Africa. *Design* We constructed a life-time horizon decision-analytic Markov model of the natural history of HCV infection to evaluate the cost effectiveness of sofosbuvir-ledipasvir monotherapy againts sofosbuvir triple therapy (sofosbuvir + pegylated-interferon and ribavirin (peg-INF/RBV)) and the current standard of care (peg-INF/RBV) for patients with chronic HCV-5 in the South African context. The model was populated with data from published literature, expert opinion and South African private sector cost data. The price modeled for sofosbuvir was the predicted South African private sector price of R82,129.32 (US$7,000) for 12 weeks. The analysis was conducted from a third-party payer perspective. *Outcome measures* Discounted and undiscounted costs (in 2015 ZAR and US$) and quality-adjusted-life years (QALYs); incremental cost-effectiveness ratios (ICERs). *Results* Outcomes from the cost-effectiveness model show that SOF/LDV yields the most favourable future health economic outcomes compared with SOF-TT and the current SOC in South Africa. Findings relating to the lifetime incremental cost per QALY gained for patients infected with HCV-5 indicate that SOF/LDV dominated both SOF-TT and SOC, i.e. SOF/LDV is less costly and more effective. *Conclusion* Outcomes from this analysis suggest that at a price of R123,190 ($US10,500) for 12 weeks SOF/LDV might be cost-effective for South African patients infected with HCV genotype 5.

Key points for decision makers

- At a price of R123,190 (US$10,500) for 12 weeks, SOF/LDV might be cost-effective for cirrhotic and non-cirrhotic South African patients infected with HCV genotype 5, dominating both SOF-TT and SOC with regard to the incremental cost per QALY gained.
- Compared to the current SOC, sofosbuvir might be cost-effective for South African patients infected with HCV genotype 5 at a price of R82,129 (US$7,000) for 12 weeks, when used in combination with peg-INF/RBV.
- Given the absence of prospective, long-term studies on sofosbuvir that include cost data in South Africa, further economic modelling of treatment strategies is needed to help policy makers in allocating scarce resources for optimal health benefits.

1 Introduction

Approximately 150 million people worldwide have chronic HCV infection [1]. The burden of HCV in South Africa (SA) is poorly defined, however, it is estimated to be low (0.1%–1.7%). The seroprevalence in blood donors, health care workers and HIV-positive patients ranges between 1.4–1.8% and 13-33%, respectively [2-6]. In Africa, genotypes 1, 4 and 5 dominate but regional variations occur [2-3]. Genotype 5 is prominent in SA, accounting for 36% of all confirmed HCV cases, followed by 1b (22%), 3a (11.7%) and 4 (8.91%). Genotype 2 accounts for less than 2% of HCV infections in SA [4]. Cirrhosis and hepatocellular carcinoma (HCC) complicates chronic infection and accounts for the rising incidence of HCC and chronic liver disease in several developed countries [7-8].

The existing standard of care (SOC) for all HCV genotypes in SA is the combination of pegylated interferon (peg-INF) and ribavirin (RBV). Treatment duration for HCV genotype 5 (HCV-G5) infection is 48 weeks [9]. Treatment response is assessed sustained virologic response (SVR), defined as the absence of detectable HCV RNA by sensitive PCR 24 weeks after the completion of therapy [10]. Treatment is expensive [around R195,000 (~US$16,620)[1] for 48 weeks] and requires specialist care [12]. Overall, peg-INF/RBV achieves SVR in approximately 50%-55% of patients, although differences do exist for different genotypes [13-14]. Regimens that include the nucleotide polymerase inhibitor, sofosbuvir (SOF), significantly increases treatment success, shortens treatment duration and causes less adverse events compared to SOC in patients with chronic HCV infection [15-16]. Overall SVR rates of 92% for non-cirrhotic and 80% for cirrhotic patients, 12 weeks after therapy has ended, have been reported for patients with genotypes 1, 4, 5 and 6 treated with a combination of SOF and peg-INF/RBV [16-18]. Less than a year after the approval of sofosbuvir, an all-oral, fixed-dose combination of SOF and ledipasvir (LDV) was approved by the FDA for HCV-G1 [19]. For patients ineligible, intolerant or unwilling to take interferon-based regimens, the SOF/LDV combination represents a significant advance. To date, there have been no large RCTs that include efficacy data for SOF/LDV in HCV-G5, however, a small open label study conducted in France found that SOF/LDV administered as monotherapy for 12 weeks in treatment-naïve and treatment-experienced patients infected with HCV-G5 yielded an SVR rate of 95%, irrespective of cirrhosis status [20]. Based on these results, both EASL [21] and AASLD [22] amended their guidelines to include SOF + peg-INF/RBV and SOF-LDV for HCV-G5 infection. While highly effective, these new drugs are very costly: in the United States SOF (Sovaldi®) is priced at US$84,000 (~R985,552) and SOF/LDV (Harvoni®) is priced at US$94,500 (~R1,108,746) for a treatment course for 12 weeks, eliciting a global debate on the pricing of new HCV drugs [23]. SOF is not yet registered in SA and its pricing has not yet been established. Our study was premised on the need to integrate evidence of clinical and economic outcomes in order to determine if SOF-containing regimens will be cost effective for the treatment of chronic HCV-G5 in SA.

[1] 1USD = 11.73276ZAR [11]

2 Methods

We constructed a decision-analytic Markov model of the natural history of HCV infection and progression toward advanced liver disease so as to evaluate the cost effectiveness (CE) of SOF-containing regimens versus the current SOC for treatment-naive patients with chronic HCV-G5 in the South African context. The natural history model simulates the journey of a hypothetical cohort of patients with chronic HCV-G5 infection through defined health states over a lifetime period until death. Given the slow progression of chronic HCV infection and that treatment benefits are expected in the long term, a life-time horizon model with an annual cycle length was constructed. In keeping with the South African Pharmacoeconomic guidelines [24], a third-party payer (i.e. funder) perspective was adopted and future costs and benefits were discounted at a baseline annual discount rate of 5% [24].

1.1 Model overview and assumptions

The model consisted of an initial decision tree, in which patients were eligible to receive treatment and a state-transition Markov model to simulate the natural history of CHC and project patients' outcomes. The model structure is described in more detail in **Online Resource A. Figure 1** shows the health-state transitions included in the model following the decision-tree. In brief, a cohort of patients with chronic HCV-G5 infection is entered into the model and followed as they age. The modelled cohort moves between defined health states on an annual basis according to annual transition probabilities, based on best available evidence **(Table 1)**. Health states included in the model were CHC without cirrhosis, compensated cirrhosis, decompensated cirrhosis, HCC, SVR without cirrhosis, SVR with cirrhosis, liver-related death and non-liver related death.

<<Insert Figure 1>>

Fig. 1 Model schematics. Transition to SVR is dependent on the treatment regime used and the presence or absence of cirrhosis. SVR rates used in the model are listed in Table 1. *CHC* chronic hepatitis C, *HCC* hepatocellular carcinoma, *SVR* sustained virological response

<<Insert Table 1>>

In our model, compensated cirrhosis is defined as METAVIR fibrosis score F4 and chronic HCV without cirrhosis is defined as METAVIR fibrosis scores[2] F2-3. Fibrosis ≤F1 was excluded from our model as the existing HCV management guidelines prioritises treatment for patients with ≥F2 fibrosis due to resource constraints [9]. Decompensated cirrhosis included those with ascites, oesophageal varices and hepatic encephalopathy. At the initiation of the model, patients started in one of two disease states: CHC without

[2] The Metavir scoring system is a scoring method used for measuring the degree of liver inflammation and staging of fibrosis in patients with hepatitis C. It uses a grading and a staging system where the grade indicates the amount of inflammation and the stage represents the amount of fibrosis or scarring. The grade is usually scored from 0-4 (0 = no activity and 3 or 4 = severe activity). The fibrosis score is also assigned a number from 0-4 (0 = no scarring; 1 = minimal scarring; 2 = scarring extending outside the areas in the liver that contains blood vessels; 3 = bridging fibrosis, spreading and connecting to other areas that contain fibrosis and 4 = cirrhosis or advanced scarring of the liver) [41].

cirrhosis, or compensated cirrhosis. Patients could follow one of three different paths in each one year cycle: a) continue in the same health state without suffering from any event; b) die of non-liver related causes; or c) progress to the next health state in the natural history model, based on their transition probabilities, irrespective of the treatment option chosen. Death from any cause not related to HCV could occur from any state and was estimated by applying age- and sex-specific rates of mortality, calculated as a multiple of the mortality in the general population of the same sex for a specific age **(Online Resource A)**. Liver-related death was only possible from decompensated cirrhosis and HCC states. The model allowed for antiviral treatment to be applied at two progressive states of the disease: CHC without cirrhosis and compensated cirrhosis. Patients initiated treatment as they entered the model and patients could only enter the model at the beginning. Treatment strategies for HCV-G5 infection included (1) SOC (peg-INF + RBV), (2) SOF triple therapy (SOF-TT) (SOF + peg-INF/RBV) and (3) SOF/LDV (fixed-dose, once a day tablet). To be consistent with current guidelines, we assumed a 48-week treatment duration for SOC and 12-week treatment durations for both SOF-containing regimens [9,21,22]. Patients were assumed to complete only one course of treatment before achieving SVR. Patients who achieved SVR were assumed to maintain SVR and experience no further disease progression until their death. Every patient who survived each one year cycle received one life year gained (LYG). TreeAge Pro Healthcare, 2014 software [42], was used for model creation and analysis. The model structure, inputs and assumptions were validated by independent clinical hepatologists.

1.2 Patient population

We considered a cohort of hypothetical treatment-naive HIV-negative patients with HCV-G5 infection. Baseline characteristics for the study population were based on the patient demographics of a South African HCV cohort [25]. The cohort was characterised by age, sex and according to the presence/absence of cirrhosis. The cohort was not stratified according to ethnicity or IL-28B genotype, as ethnicity and IL28B polymorphisms are seemingly not predictive of SVR rate in South African patients infected with HCV-G5 [25,43].

1.3 Data and Sources

1.3.1 Clinical data

Clinical inputs, including annual transition probabilities, treatment efficacy and treatment duration are shown in **Table 1.** The annual transition probabilities for progressing from one disease state to the next were derived from literature. Based on estimates of transition probabilities from CHC to cirrhosis [26] we assumed a transition probability of 20% over 20 years, converted to an annual probability (see **Online Resource A** for calculations). Probabilities for HCV-related death were taken from literature, whereas sex- and age-specific mortality rates from causes other than HCV were taken from the Actuarial Society of South Africa (ASSA) HIV demographic model: 2008 version [31].

Dosing and administration of SOF-TT and SOF-LDV were based on the treatment regimens as per the EASL and AASLD recommendations. Patients in the SOF-TT arm received 400 mg oral SOF daily together with oral, weight based RBV and 180 μg of peg-INF α-2a subcutaneously weekly for 12 weeks, irrespective of cirrhosis status [21-22]. Non-cirrhotic patients in the SOF/LDV arm received a combination of 400 mg SOF and 90 mg

LDV in a single tablet, once daily for 12 weeks. In the base case analysis, cirrhotic patients received the same fixed-dose combination for 12 weeks with weight based RBV daily [21,22]. The primary efficacy measure used in the model was SVR, 12 weeks and 24 weeks after completion of treatment for SOF-based therapy and SOC, respectively. SVR rates for patients who initiated treatment while in the "compensated cirrhosis" state were considered to be lower than for patients who initiated treatment while in the "CHC without cirrhosis" state. Response rates for SOF-TT were based on the results of the NEUTRINO trial [16]. A limitation is that the NEUTRINO trial only included one genotype 5 patient; however, to date most trials have unfortunately included very limited numbers of HCV-G5 patients, and at the time of this analysis, the NEUTRINO trial was the only major registration trial containing HCV-G5 patients. Response rates for SOF/LDV were based on the results of the open-label study conducted by Abergel *et al.* [20] in France. Treatment efficacy of SOC was based on pooled results from the BERNAR-1 and BERNAR-2 RCT's [32]. We applied the 12-week stopping rule to patients who received SOC. Patients who achieve EVR by week 12 completed the full 48 week treatment period and patients who did not achieve EVR stopped treatment after 12 weeks [44]. We assumed that 14% of patients without cirrhosis will fail to achieve EVR [45] and a 15% reduction in the probability to achieve EVR in patients with compensated cirrhosis.

1.3.2 Utility data

In the absence of SA-specific utility data, two systematic reviews and one original study [27,37,38] were used as references for health state utility values used in our model. The utility values assigned in the model are presented in **Table 1**. Serious adverse events associated with treatment were not considered, however, the model did take the disutility of treatment into account by considering lower utility values for those patients receiving treatment.

1.3.3 Cost data

The model accounted for three types of HCV-related cost: drug regimen, treatment monitoring and health state (downstream liver-disease complications). Costs of treatment cycles were expressed in South African Rand (ZAR) and United States Dollars (US$) at 2015 value. According to the South African third-party payer's perspective, only direct health care costs were considered — in particular, drug costs and the costs associated with disease management (diagnostic tests, routine blood tests, outpatient visits, hospitalisation etc.) **(Tables 2 and 3)**. Monitoring costs and recommended follow-up of patients were based on typical South African management of HCV and was confirmed by expert opinion (independent South African hepatologists). Costs of laboratory tests, radiological examination and consultations were based on the prices in the Referencing Price List (RPL), and were calculated according to specified monitoring resource use [46]. The latest RPL values (2009) were inflated using published annual medical inflation numbers from STATS SA and total monitoring costs over the treatment period were aggregated from calculated totals [47]. Drug costs included the costs of peg-INF, RBV, SOF, and SOF/LDV and drug regimen costs were based on unit drug costs, indicated drug dosing and therapy duration. Unit prices of peg-INF and RBV were taken from the Official Pharmaceutical

Bluebook [48]. The medicine price used to populate the model was a composite of single exit price (SEP)[3], value added tax (VAT) and the prescribed professional dispensing fee. A detailed description of the costs and calculations can be found in online resource.

<<Insert Tables 2 and 3>>

The FDA approved in SOF in December 2013 and SOF/LDV in October 2014 for the treatment of HCV. In the United States, SOF and SOF/LDV is priced at $84,000 (~R985,552) and $94,500 (~R1,108,746) for 12-weeks, respectively [50]. In September 2014, Gilead signed an agreement with seven India-based generic pharmaceutical manufacturers to develop SOF and SOF/LDV for distribution in 91 developing countries [51]. Under the licensing agreement, the generic manufacturers have the right to develop and market generic SOF and SOF/LDV in certain countries, including SA [52].

In 2015, generic manufacturers began selling SOF generics in India for about US$960 for a 12-week regimen [53]. In Pakistan and Brazil, governments opted for negotiating prices exclusively with Gilead and entered into agreements with the manufacturer to distribute Sovaldi® at subsidized rates of approximately US$1,500 and US$7,000, respectively [54,55]. In 2014, Gilead initiated a partnership with Egypt, agreeing to provide Sovaldi and Harvoni® to the country at a significantly reduced cost [56]. Sovaldi® is currently sold at a price of US$900 and Harvoni® at a price of US$1,200 for a 12-week treatment in Egypt, the lowest available prices in the world. Although SA might not be able to get these drugs at a price similar to Egypt, Egypt has demonstrated that with effective leadership and government support, price reductions are achievable. Because SA is included in the list of countries for distribution of the generic versions of SOF and SOF/LDV, it will almost certainly be able to have access to these drugs at a lower price. At the time of this analysis, SOF/LDV generics and information on their pricing were not yet available. Furthermore, neither SOF nor SOF/LDV is yet registered in SA and pricing have not been established. However, reliable indications are that SA will be benchmarked with the BRICS countries [57] and hence we assumed a cost of R82,129.32 (US$7,000) for a 12-week course of SOF and a cost of R123,194 (US$10,500) for a 12-week course of SOF/LDV in our base case scenario.

1.4 Model analysis

Comparisons of health and economic outcomes were made across treatment regimens for the modeled cohort. The long-term health economic outcomes included discounted and undiscounted life-time costs (in ZAR and US$), discounted and undiscounted life-years gained (LYG), discounted and undiscounted QALYs and incremental lifetime cost per QALY gained [incremental cost effectiveness ratios (ICERs)]. The primary outcome was QALYs, calculated by applying utility values to life years gained (LYG). The incremental lifetime cost per QALY gained for SOF-based therapy was compared against the willingness-to-pay (WTP) threshold of R200,000 (~US$17,046) per QALY[4].

[3] In South Africa, medicine prices are regulated (South Africa, 2014) and consists of a regulated SEP, VAT and a professional fee charged by the dispensing pharmacist, which makes discounting of any sort illegal [49].

[4] South Africa does not have a WTP threshold. We thus assumed an ICER of three times the GDP/capita as cost effective [58].

1.5 Sensitivity analysis

Deterministic and probabilistic sensitivity analyses were conducted. The one-way sensitivity analysis assessed the impact of individual changes to model inputs and assumptions on model results. Key parameters varied included SVR rates (±10% to a maximum of 99%), transition probabilities (95% CI), costs for health states (±20%) and utility values (range, minimum and maximum values taken from literature). We conducted the probabilistic sensitivity analysis by running 1,000 simulations, varying costs by gamma-distribution (±10%) and transition probabilities (±10%), SVR rates (±10%) and utility values (±20%) by beta-distribution.

3 Results

Table 4 presents the projected number of cases of advanced liver-disease complications and the number of cases of SVR over a life-time period for the modeled cohort in both treatment arms. SOF-containing treatments for HCV-G5 patients improve health outcomes and reduce HCV-related morbidity and mortality compared with current standard of care.

<<Insert Table 4>>

SOF-based regimens were associated with the lowest number of liver-related complications and mortality per 10,000 patients, yielding a 90% and 71% reduction when compared with SOC for SOF/LDV and SOF-TT, respectively. Compared to SOF-TT, treating patients with SOF/LDV reduced liver-related complications and deaths by 68%.

SOF/LDV yielded the highest overall SVR rate (93.8%) compared to the overall SVR rates of 88.5% for SOF-TT and 52.3% for SOC. In addition to a higher SVR rate, patients treated with SOF/LDV lived 0.15 and 0.64 years longer, and gained 0.25 and 1.9 more QALYs than those treated with SOF triple therapy and SOC, respectively. SOF/LDV was associated with the lowest discounted lifetime cost (R241,561 or ~US$20,589), followed by SOF-TT (R263,132 or ~US$22,472) **(Table 5)**. The total discounted lifetime cost of patients **(Table 5)** treated with SOC (R392,127) (~US$33,422) was almost 32% and 38% higher than those of patients treated with SOF-TT and SOF/LDV, respectively. Results from the cost effectiveness analysis (CEA) showed that SOF/LDV was the optimal strategy in treating patients with HCV-G5. In the base case analysis, SOF/LDV dominated (i.e. was less costly and more effective than) than both SOF-TT and SOC. Even though SOF-TT was not the optimal strategy, it still dominated SOC.

<<Insert Table 5>>

1.6 Sub-group analyses

In the first sub-group analysis, we evaluated the impact of the 12-week stopping rule on cost. In this analysis, the stopping rule was not considered in patients treated with SOC, and all patients who started treatment with SOC completed a 48 week course (overall SVR rate 55.3%). In this scenario, the total lifetime cost of patients treated with SOC was approximately 7% higher than when the stopping rule was applied, however, SOF/LDV was still the dominant strategy. In the second sub-group analysis, we considered treating patients with cirrhosis

in the SOF/LDV arm with 24 weeks of SOF/LDV monotherapy instead of 12 weeks with SOF/LDV+RBV[5]. In this scenario, SOF/LDV remained the preferred strategy, even though the total lifetime cost of SOF/LDV was more (R263,132 or US$22,427) than for SOF-TT, yielding and ICER of R7,992 (US$681).

1.7 Sensitivity analysis

Results from the deterministic sensitivity analysis (DSA) showed that SOF/LDV and SOF-TT continued to dominate SOC for all values of key parameters varied, and SOC was excluded as the least favourable option. **Figure 2** presents results of the DSA for SOF/LDV compared with SOF-TT. It displays the 11 parameters that most heavily influenced the ICER. The main input drivers of the ICER were SVR rates of SOF/LDV and SOF-TT, and utility values in the CHC state during treatment with SOF-TT. One-way sensitivity analysis showed that the net monetary benefit of SOF/LDV decreased with a decrease in the SVR rates for SOF/LDV, increased SVR rates of SOF-TT and increased utility in the CHC state during treatment with SOF-TT.

<<Insert Figure 2>>

Fig.2 ICER tornado diagram. *Decomp. cirrhosis* decompensated cirrhosis, *EV* expected value, *ICER* incremental cost-effectiveness ratio, *SOF/LDV* sofosbuvir-ledipasvir, *SOF-TT* sofosbuvir triple therapy, *SVR* sustained virologic response

Threshold analysis showed that SOF/LDV continued to be cost effective at a WTP-threshold of R200,000, even at the maximum and minimum values of the range set for each of these parameters. Only when SVR rates for SOF/LDV were <0.834, and the cost of SOF-TT and SOF/LDV were <R63,730 (US$5,432) or >R209,143 (US$17,826), respectively, did SOF-TT become the preferred strategy.

Figures 3.1 (ICE scatterplot graph) and **3.2** (CE acceptability curve) show results from the probabilistic sensitivity analysis (PSA). We conducted PSA on the ten parameters that most heavily influenced the ICER during the DSA, as well as on all treatment and monitoring costs to see how combined uncertainty affects the overall confidence in our base case conclusions.

According to the PSA, the probability of SOF/LDV being the optimal strategy was 83.5% at the WTP-threshold of R200,000 when key clinical and cost parameters were adjusted across wide but plausible ranges.

<<Insert Figure 3.1 and 3.2>>

Fig. 3.1 The ICE scatterplot graph Shows simulation iterations plotted for incremental cost and incremental effectiveness. The plots below and to the right of the WTP line confirm the base case analysis, i.e. where the ICER ≤ WTP-threshold when SOF/LDV is priced at R123,190 (US$10,500) for 12 weeks. *ICE* incremental cost-effectiveness, *WTP* willingness-to-pay

[5] Utility value for SOF/LDV for 24 weeks = 0.741 [37]

Fig. 3.2 The CE acceptability curve shows the percentage of simulation iterations that consider each strategy the most cost-effective over a range of WTP threshold values. *CE* cost-effectiveness, *peg-INF* pegylated interferon, *RBV* ribavirin, *WTP* willingness-to-pay

4 Discussion

This study comprises a health economic analysis of SOF-based treatments for the treatment of patients with HCV-G5. Our CE model demonstrates that in South Africa, the SOF/LDV combination yields the most favourable future health economic outcomes compared with the current SOC. Compared with SOC and SOF-TT, SOF/LDV was associated with the lowest incidence of liver disease complications and HCV-related deaths, due to increased efficacy in cirrhotic and non-cirrhotic patients. Findings from the base case analysis relating to the lifetime incremental cost per QALY gained for patients infected with HCV-G5, indicate that SOF/LDV dominates SOF-TT and SOC *viz.* SOF/LDV is less costly and more effective than both SOF-TT and SOC. Results from the sub-group analysis relating to the SOF/LDV arm showed that treating cirrhotic patients with 24 weeks monotherapy is less cost effective than 12 weeks SOF/LDV+RBV, but still more cost effective than SOF-TT and SOC overall. Results from the sensitivity analysis indicates that SOF/LDV continued to be a cost effective strategy even when key clinical and cost parameters were adjusted across wide, yet plausible, ranges.

Cost-effectiveness has been demonstrated for SOF-containing regimens across all genotypes, even at the current US price [59]. Recently published CEA's have revealed that HCV treatment regimens including SOF are generally cost effective when compared to existing treatment regimens [59-65]. A study comparing SOF/LDV with interferon-based therapies found that SOF/LDV was cost effective in over 80% of patients, depending on genotype and treatment-experience [60]. Another study found that SOF/LDV decreased the number of advanced liver disease cases by 0-93% compared with current regimens or no treatment in treatment-naïve patients and treatment-experienced patients, and with regard to lifetime incremental costs per QALY gained, SOF/LDV was either dominant or the most cost-effective treatment [61]. Data comparing SOF-based regimens to currently recommended treatments in a mixed cohort of mono-infected and co-infected CHC patients with GT1-4 in France, reported that SOF, at the early access program price, is a cost effective strategy in chronic HCV infection treatments at a commonly accepted threshold of €40,000 (~US$46,000) [62]. Another CEA compared SOF-based regimens and standard treatments in treatment-naïve patients with HCV genotype 1 (HVC-G1), reported that treatment with SOF is cost-effective in HCV-G1 patients with ≥F2 fibrosis [63]. A study comparing sofosbuvir, boceprevir, and telaprevir based therapies reported that SOF-based regimens were cost effective compared to boceprevir, except in cirrhotic and IL28B CC patients, and mostly cost-effective compared to telaprevir [64]. US data concluded that SOF-based treatment regimens generally dominate telaprevir or boceprevir-based regimens and compared to peg-INF/RBV had incremental costs per QALYs gained well below the US WTP-threshold of US$50,000 [65].

Overall, cost-effectiveness studies support SOF-based treatment as a cost-effective option for most HCV genotypes. When comparing QALYs gained, findings from our CEA support those from other recently published cost-effectiveness studies [61,62,65,66]; however, our CE-model found much lower incremental cost per QALY gained than the previous CEA. This is mainly because we modeled a discounted cost for SOF and

SOF/LDV, whereas studies conducted in Europe [62,66] and the US [65] modeled the current respective prices for SOF and SOF/LDV (ranging between $84,000 and 60,000euro) in their analyses. This highlights the fact that transferability of cost-effectiveness results between different countries is limited due to e.g. differences in epidemiology of the disease, clinical practice, consumer preferences and price levels. Hence, the cost effectiveness of SOF and SOF/LDV is dependent on its price and the CE threshold of the given country in which a CEA is performed.

Potential limitations of this model exist. First, it is largely populated with clinical trial data, which does not necessarily represent a real world environment. Real-world SVR rates and patient adherence associated with the modeled treatment regimens may be substantially lower and the frequency of side-effects may be higher than reported in clinical trial settings. Moreover, we obtained SVR rates for each treatment arm in our model from separate studies, as no head-to-head clinical trials including SOF and SOC were available at the time of this analysis. Also, as patients' demographical and clinical characteristics are different across clinical trials, SVR rates are influenced. Furthermore, our model only considers a treatment-naive cohort and does not demonstrate if there is a difference in the cost effectiveness of SOF-based therapy in treatment-experienced patients. We also assumed fibrosis progression in non-cirrhotic patients to be linear; however, studies have shown that fibrosis progression accelerates in the latter stages of the disease [67]. We compensated for accelerated fibrosis progression with increasing age by discriminating cohorts according to age. Our model also disregards the effect of risk factors such as increased alcohol consumption on fibrosis progression, since we did not model for comorbidities or associated risk factors. This might also underestimate our all-cause mortality, as studies have indicated increased all-cause mortality in HCV populations due to increased co-morbidities [68]. We also did not take HIV is into account as a potential confounder of treatment efficacy. This might be important for South Africa, as an estimated 12.2% of the South African population (6.4 million persons) are HIV positive [69]. Studies have also indicated a significantly higher prevalence of HCV among HIV infected patients as compared to HIV negative patients (13.4% vs. 1.73%) [70]. Evidence on improved efficacy of SOF in HIV-infected cohorts over the current SOC notwithstanding [71-72], efficacy data of sofosbuvir in HIV-positive HCV-G5 are unavailable. However, HIV-infection is an important confounding factor when considering the cost-effectiveness of SOF-based therapy in the South African population. Other sofosbuvir combinations are currently being tested in on-going trials e.g. GS-9669 (NS5B non-nucleoside inhibitor) [73] and GS-5816 (second-generation NS5A inhibitor) [74], and further guideline adaptations may follow. These drugs remain unregistered and unavailable in South Africa; however, with recent findings on the efficacy of drugs like SOF and SOF/LDV in HCV-G5, future research is warranted on the cost-effectiveness of new HCV drugs in SA.

5 Conclusion

Outcomes from this analysis suggest that, at a price of R123,193 (US$10,500) for 12 weeks, the fixed-dose combination of sofosbuvir and ledipasivr might be cost-effective for South African patients infected with HCV genotype 5. Considering the rapid progress in HCV therapies and the recent approval of all-oral, interferon-free regimens, it is essential to motivate for improved access to these drugs. The burden of hepatitis C in South Africa may not be substantial, but the principles learnt from our struggle with HIV should be applied in this instance — the issues are intrinsically the same and warrant no different a response.

References

1. WHO (World Health Organization). Hepatitis C fact sheet N˚164. 2013. Available at: http://www.who.int/mediacentre/factsheets/fs164/en/ Accessed: 9 Dec. 2013.
2. Abuelhasssan W. Review: hepatitis C virus infection in 2012 and beyond. South Afr J Epidemiol Infect. 2012;27(3):93-7.
3. Karoney MJ, Siika AM. Hepatitis C virus (HCV) infection in Africa: a review. Pan Afr Med J. 2013;14:44.
4. Prabdial-Sing N, Puren A, Schoub B. The status of hepatitis C – the silent "volcano" in South Africa. Communicable Diseases Surveillance Bulletin. 2013;11(1):22-5.
5. Tucker TJ, Voight M, Bird A, Robson S, Gibbs B, Kannemeyer J, Galloway M, Kirsch RE, Smuts H. Hepatits C virus infection rate in volunteer blood donors from the Western Cape — comparison of screening tests and PCR. S Afr Med J. 1997;87(5):603-5.
6. Vardas E, Ross MH, Sharp G, McAnerney J, Sim J. Viral hepatitis in South African healthcare workers at increased risk of occupational exposure to blood-borne viruses. J Hosp Infect. 2002;50(1):6-12.
7. Lavanchy D. Evolving epidemiology of hepatitis C virus. Clin Microbiol Infect. 2011;17(2):107–15.
8. Massard J, Ratziu V, Thabut D, Moussalli J, Lebray P, Benhamou Y, Poynard T. Natural history and predictors of disease severity in chronic hepatitis C. J Hepatology. 2007;44:S19–S24.
9. Botha JF, Kassianides C, Schneider HR, Song E, Spearman W, van der Merwe SW. South African hepatitis C management guidelines 2010. South Afr Gastroenterol. 2010;8(1). Available at: http://www.sages.co.za/images/hcvjfb.pdf. Accessed: 12 Dec 2014.
10. Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. Clin Infect Dis. 2011;52(7):889-900.
11. OANDA currency converter. Average exchange rate for the first quarter of 2015. 2015. Available at: http://www.oanda.com/currency/converter/ Accessed on: 3 May 2015.
12. Ford N, Singh K. Cooke GS, Mills EJ, Von Schoen-Angerer T, Kamarulzaman A, Du Cross P. Expanding access to treatment for hepatitis C in resource-limited settings: lessons From HIV/AIDS. Clin Inf Dis. 2012;Mar:1-8.
13. Dillon J. Management of hepatitis C. Primary Health Care. 2007;17(5):25-9.
14. Gravitz L. A smouldering public-health crisis. Nature. 2011;474:S2-4.
15. Gilead Sciences, Inc. Sovaldi®. Highlights of prescribing information. 2015. Available at: http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf Accessed: 10 April 2015.
16. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Schultz M, Davis MN, ZeidKayali Z, Reddy KR et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. The New Engl J Med. 2013;368(1):33-44.
17. ClincalTrials.gov. Sofosbuvir with Peginterferonalfa 2a and ribavirin for 12 weeks in treatment-naive subjects with chronic genotype 1, 4, 5, or 6 HCV infection (NEUTRINO). 2013. Available at: https://clinicaltrials.gov/ct2/show/NCT01641640 Accessed: 24 Feb 2014.
18. Leof A, Gerrity M, Thielke A, King V. Sofosbuvir for the treatment of hepatitis C and evaluation of the 2014 American Association for the Study of Liver Diseases treatment guidelines. Portland.

19. FDA (US Food and Drug Administration). FDA approves first combination pill to treat hepatitis C. 2014. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm418365.htm Accessed: 13 Nov. 2014.
20. Abergel A, Loustaud-Ratti V, Metivier S, Jiang D, Kersey K, Knox SJ, Svarovskaia E, Pang PS, Samuel D, Asselah T. Ledipasvir/Sofosbuvir for the treatment of patients with chronic genotype 4 or 5 HCV infection. Paper presented at The International Liver Congress 2015: 50th annual meeting of the European association for the Study of the Liver (EASL), Vienna, Austria; April 22-26. Available at: http://natap.org/2015/EASL/EASL_80.htm Accessed: 21 Aug. 2015.
21. European Association for the Study of the Liver (EASL). EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatology. 2015;63:199–236.
22. American Association for the Study of Liver Diseases (AASLD). Summary of recommendations for patients who are initiating therapy for HCV infection by HCV genotype. 2015. Available at: http://www.hcvguidelines.org/printpdf/full-report/initial-treatment-box-summary-recommendations-patients-who-are-initiating-therapy-hcv Accessed: 28 Aug. 2015.
23. Jack A. Indian health activists move to prevent Gilead's drug patent. 2013. Financial Times, 24 Nov. Available at: http://www.ft.com/intl/cms/s/0/7dd38ee4-551a-11e3-86bc-00144feabdc0.html?siteedition=intl#axzz2ldUq9CwB Accessed: 25 Nov. 2014.
24. South Africa. Medicines and Related Substances Act (Act no. 101 of 1965): regulations relating to a transparent pricing system for medicines and schedules substances. 2013. (Government notice no. R68). Government gazette, 36118, 1 Feb.
25. Sonderup MW, Abuelhassan W, Spearman W. IL28B polymorphisms are not predictive in hepatitis C genotype 5 infected South African patients. Paper presented at 63rd Annual Meeting of the American Association for the Study of Liver Diseases, Boston, MA, USA November 9 – 13. 2012. Available at: http: http://onlinelibrary.wiley.com/doi/10.1002/hep.26040/epdf Accessed: 17 Fe. 2015.
26. Alberti A, Chemello L, Benvegnhù L. Natural history of hepatitis C. J Hepatology. 1999;31(Suppl. 1):11-24.
27. Alawazi W, Cunningham M, Dearden J, Foster GR. Systematic review: outcome of compensated cirrhosis due to chronic hepatitis C infection. Alim Pharmacol Ther. 2013;32:344-55.
28. Sweeting M, De Angelis D, Neal KR, ME, Irving W, Wright M, Brant L, et al. Estimated progression rates in three United Kingdom hepatitis C cohorts differed according to method of recruitment. J Clin Epidemiol. 2006;59:144–52.
29. Saab S, Hunt D, Stone M, McClune A, Tong M. Timing of hepatitis C antiviral therapy in patients with advanced liver disease: a decision analysis model. Liver Transplant. 2010;16:748–59.
30. Hutchinson S, Bird S, Goldberg D. Modeling the current and future disease burden of hepatitis C among injection drug users in Scotland. Hepatology. 2005;42:711–23.
31. Actuarial Society of South Africa. Actuarial Society of South Africa HIV demographic model 2008 version. 2008. Available at: http://aids.actuarialsociety.org.za/Models-3145.htm Accessed: 1 Feb 2015.
32. D'Heygere F, George C, Van Vlierberghe H, Decaestecker J, Nakad A, Adler M, Delwaide J, Laureys A, Nevens F. Efficacy of interferon-based antiviral therapy in patients with chronic hepatitis C infected with genotype 5: a meta-analysis of two large prospective clinical trials. J Viral Hepat. 2011;83:815-9.

33. Thein HH, Krahn M, Kaldor JM, Dore GJ. Estimation of utilities for chronic hepatitis C from SF-36 scores. Am J Gastroenterol. 2005;100(3):643-51.
34. Chong CA, Gulamhussein A, Heathcote EJ, Lilly L, Sherman M, Naglie G, Krahn M. Health-state utilities and quality of life in hepatitis C patients. Am J Gastroenterol. 2003;98(3):630-38.
35. Kerr C, Lloyd A, Ali S, Goreb C, Tyas DA. Impact of treatment attributes of peginterferon for hepatitis C on quality of life and treatment preference. Health Outcomes Res Med. 2012;3(3):e153-67.
36. Stepanova M, Nader F, Cure S, Bourhis F, Hunt, Younossi M. Patients' preferences and health utility assessment with SF-6D and EQ-5D in patients with chronic hepatitis C treated with sofosbuvir regimens. Alim Pharmacol Ther. 2014;40:676-85.
37. Younossi ZM, Stepanova M, Marcellin P, Afdhal N, Kowdley KV, Zeuzem S, Hunt SL. Treatment with ledipasvir and sofosbuvir improves patient-reported outcomes: Results from the ION-1, -2, and -3 clinical trials. Hepatology. 2015 Jun;61(6):1798-808.
38. McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. Med Decis Making. 2008;8:582-92.
39. Hsu PC, Krajden M, Yoshida EM, Anderson FH, Tomlinson GA, Krahn MD. Does cirrhosis affect quality of life in hepatitis C virus-infected patients? Liver Int. 2009;449-58.
40. Longworth L, Bryan S. An empirical comparison of EQ-5D and SF-6D in liver transplant patients. Health Economics Letters. 2003;7(2):16-22.
41. Franciscus A. HCV Diagnostic Tools: grading & staging a liver biopsy. Available at: http://hcvadvocate.org/hepatitis/factsheets_pdf/grade_stage.pdf Accessed: 2 Mar. 2015.
42. TreeAge Pro 2014, R1.2.TreeAge Software, Williamstown, MA; software available at http://www.treeage.com.
43. Sonderup, M. Treating hepatitis B and C (in South Africa). World Hepatitis Day Presentation. 2013. Available at: http://hcvadvocate.org/hepatitis/factsheets_pdf/grade_stage.pdf Accessed: 17 Feb. 2015.
44. Ghany MG, Strader DB, Thomas DL, Seeff LB. American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009;49:1335-74.
45. Ferenci P, Lafer H, Scherzer TM, Maieron A, Hofer H, Stauber R, Gschwantler M, Brunner H, Wenisch C, Bischof M, Strasser M, Datz C, Vogel W, Löschenberger K, Steindl-Munda P; Austrian Hepatitis Study Group. Peginterferon alfa-2a/ribavirin for 48 or 72 weeks in hepatitis C genotypes 1 and 4 patients with slow virologic response. Gastroenterol. 2010;138(2):503-12.
46. Council for Medical Schemes. Reference Price List (RPL). National reference price list for services by medical practitioners, effective from 1 January 2009. 2009. Available at: http://wcawca.co.za/files/bhf_2009_medical_practitioners.pdf Accessed: 10 Oct. 2014.
47. Statistics South Africa (STATS SA). Statistical Release P0141: Consumer Price Index (CPI). 2015. Available at: http://www.statssa.gov.za Accessed: 20 Mar. 2015.
48. The Official Pharmaceutical Bluebook. 2015. Available at: http://www.pbb.co.za/ Accessed: 3 Feb. 2015.
49. South Africa. Medicines and Related Substances Act (Act no. 101 of 1965): regulations relating to a transparent pricing system for medicines and schedules substances. 2014. (Government notice no. R264). Government gazette, 37527, 3 Apr.

50. Pollack A. FDA Approves pill to treat hepatitis C. NY Times, 7 Dec. 2013. Available at: http://www.nytimes.com/2013/12/07/business/fda-approves-pill-to-treat-hepatitis-c.html?ref=health Accessed: 9 Dec. 2013.
51. Gilead Sciences, Inc. Gilead announces generic licensing agreements to increase access to hepatitis C treatments in developing countries. 2014. Available at: http://www.gilead.com/news/press-releases/2014/9/gilead-announces-generic-licensing-agreements-to-increase-access-to-hepatitis-c-treatments-in-developing-countries Accessed: 25 May2015.
52. Gilead Sciences, Inc. Chronic hepatitis C treatment expansion: generic manufacturing for developing countries. 2014. Available at: http://www.gilead.com/~/media/Files/pdfs/other/HCVGenericAgreementFactSheet.pdf Accessed: 6 Nov. 2014.
53. NATCO Pharma Ltd. NATCO receives generic sofosbuvir (Sovaldi®) approval for India. News and announcements: 11 March 2015. Available at: http://natcopharma.co.in/about/news/#news1 Accessed: 20 Aug. 2015.
54. FEROZSONS Laboratories Ltd. 2014. Ferozsons Lab, Gilead Sciences sign agreement. News center: 20 Jun. 2014. Available at: http://www.ferozsons-labs.com/index.php?option=com_news&view=news&news_id=78# Accessed: 20 Aug. 2015.
55. GTPI (The Working Group on Intellectual Property of the Brazilian Network for the Integration of Peoples). Brazil is excluded from license authorizing production of generic medicine for hepatitis C. 2014. Available at: http://www.deolhonaspatentes.org.br/media/file/GTPI_statement_Gilead_license_sofosbuvir.pdf Accessed: 20 Aug. 2015.
56. Fick M, Hirschler B. 2014. Gilead offers Egypt new hepatitis C drug at 99 percent discount. *Reuters*, 21 Mar. Available at: http://www.reuters.com/article/2014/03/21/us-hepatitis-egypt-gilead-sciences-idUSBREA2K1VF20140321 Accessed: 20 Aug. 2015.
57. Government of South Africa. BRICS (Brazil, Russia, India, China, South Africa). 2015. Available at: http://www.gov.za/about-government/brics-brazil-russia-india-china-south-africa Accessed: 4 Jul. 2015.
58. WHO (World Health Organization). Cost effectiveness and strategic planning: cost-effectiveness thresholds. 2015. Available at: http://www.who.int/choice/costs/CER_thresholds/en/ Accessed: 19 May 2015.
59. De Groote K, Michielsen P, Delwaide J. Cost-effectiveness model for sofosbuvir in chronic hepatitis C. Paper presented at the 17th Annual European ISPOR Congress, Amsterdam, The Netherlands; November 8-12, 2014. Available at: http://orbi.ulg.ac.be/bitstream/2268/174731/1/ISPOR%20poster_BE_FINALversie(b)%20(voorkeur).pdf Accessed: 20 Aug. 2015.
60. Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. Ann Intern Med. 2015;162(6):397-406.
61. Younossi ZM, Park H, Saab S, Ahmed A, Dieterich D, Gordon SC. Cost-effectiveness of all-oral sofosbuvir/ledipasvir regimens in patients with chronic hepatitis C genotype 1 infection. Aliment Pharmacol Ther. 2015;41(6):544-63.

62. Leleu H, Blachier M, Rosa I. Cost-effectiveness of sofosbuvir in the treatment of patients with hepatitis C. J Viral Hep. 2015;22:376-83.
63. Deuffic-Burban S, Schwarzinger M, Obach D, Mallet V, Pol S, Pageaux GP, Canva V, Deltenre P, Roudot-Thoraval F, Larrey D, et al. Should we await IFN-free regimens to treat HCV genotype 1 treatment-naive patients? A cost-effectiveness analysis (ANRS 95141). J Hepatol. 2014;61(1):7–14.
64. Petta S, Cabibbo G, Enea M, Macaluso FS, Plaia A, Bruno R, Gasbarrini A, Crax A, Camm C. Cost-effectiveness of sofosbuvir-based triple therapy for untreated patients with genotype 1 chronic hepatitis C. Hepatology. 2014;59:1692–1705.
65. Saab S, Gordon SC, Park H, Sulkowski M, Ahmed A, Younossi Z. Cost-effectiveness analysis of sofosbuvir plus peginterferon/ribavirin in the treatment of chronic hepatitis C virus genotype 1 infection. Aliment Pharmacol Ther. 2014;40(6):657-75.
66. Pfeil AM, Reich O, Guerra IM, Cure , Negro F, Müllhaupt B, Lavanchy D, Schwenkglenks M. Cost-effectiveness analysis of sofosbuvir compared to current standard treatment in Swiss patients with chronic hepatitis C. PLOS ONE. 2015. DOI:10.1371/journal.pone.0126984
67. Zarski J, Hutchison JM, Bronowicki J, Sturm N, Garcia-Kennedy R, Hodaj E, Trusta B, Wright T, Gish R. Rate of natural disease progression in patients with chronic hepatitis C. J Hepatology. 2003;38:307-14.
68. El-Kamary SS, Jhaveri R, Shardell MD. All-Cause, Liver-Related, and Non–Liver-Related Mortality Among HCV-Infected Individuals in the General US Population. CID. 2011;53:150-7.
69. Shisana, O, Rehle, T, Simbayi LC, Zuma, K, Jooste, S, Zungu N, Labadarios, D, Onoya, D Ramlagan, S, Mbelle N, et al. South African National HIV Prevalence, Incidence and Behaviour Survey, 2012. Cape Town, HSRC Press. 2014. Available at: http://www.hsrc.ac.za/uploads/pageContent/4565/SABSSM%20IV%20LEO%20final.pdf Accessed: 15 Jun. 2015.
70. Parboosing R. Clinical and epidemiological aspects of HIV and hepatitis C virus co-infection in KwaZulu-Natal Province of South Africa. 2008. Durban: UKZN. (Thesis — MMed).
71. Molina JM, Orkin C, Iser DM, Zamora FX, Nelson M, Stephan C, Massetto B, Gaggar A, Ni L, Svarovskaia E, et al. Sofosbuvir plus ribavirin for treatment of hepatitis C virus in patients co-infected with HIV (PHOTON-2): a multicentre, open-label, non-randomised, phase 3 study. The Lancet. 2015;385(9973):1098-1106.
72. ClinicalTrials.gov. Efficacy and safety of sofosbuvir plus ribavirin in chronic genotype 1, 2 and 3 hepatitis C Virus (HCV) and human immunodeficiency virus (HIV) co-infected adults. 2014. Available at: https://clinicaltrials.gov/show/NCT01667731 Accessed: 24 Aug. 2015.
73. ClinicalTrials.gov. Ledipasvir/Sofosbuvir fixed-dose combination with ribavirin or GS-9669 in subjects with chronic genotype 1 HCV infection. 2015. Available at: https://clinicaltrials.gov/ct2/show/NCT01984294 Accessed: 7 Jun. 2015.
74. Gilead Sciences, Inc. Gilead announces phase 2 data for investigational all-oral regimen of sofosbuvir plus GS-5816 for the treatment of chronic hepatitis C. 2014. Available at: http://www.gilead.com/news/press-releases/2014/11/gilead-announces-phase-2-data-for-investigational-alloral-regimen-of-sofosbuvir-plus-gs5816-for-the-treatment-of-chronic-hepatitis-c Accessed: 15 Feb. 2015.

Table 1. Model parameter values and ranges

Variable	Base Case		Reference
Model assumptions			
Perspective	Third-party payer		[24]
Discount rate	5% per annum		[24]
Time horizon	Lifetime		
Cycle length	12 months		
Cohort characteristics			
Start age	52 years		[25]
Weight (males)	80kg		[25]
Weight (females)	60kg		[25]
Gender distribution	55% male; 45% female		[25]
Disease stage distribution	80% non-cirrhotic; 20% cirrhotic		[25]
HCV natural history	**Annual probability**	**Range**	
CHC → cirrhosis[1]	0.011	(0.005 – 0.018)	[26]
Cirrhosis → decompensated cirrhosis	0.064	(0.030 – 0.070)	[27]
Cirrhosis → HCC	0.036	(0.015 – 0.040)	[27]
Decompensated cirrhosis → HCC	0.068	(0.041 – 0.099)	[28,29]
Decomp. cirrhosis → liver-related death	0.168	(0.120 – 0.400)	[30]
HCC → liver-related death	0.605	(0.300 – 0.800)	[30]
Mortality unrelated to HCV			[31]
Effectiveness of treatment (Probability of SVR)			
Standard of care (peg-INF/RBV)			
CHC, no cirrhosis	55%	(0.45 – 0.65)	[32]
Compensated cirrhosis[2]	40%	(0.30 – 0.50)	[32]
Sofosbuvir + peg-INF/RBV			
CHC, no cirrhosis	92%	(0.89 – 0.99)	[16]
Compensated cirrhosis	80%	(0.67 – 0.89)	[16]
Sofosbuvir-ledipasvir			
CHC, no cirrhosis	95%	(0.90 – 0.99)	[20]
Compensated cirrhosis	95%	(0.90 – 0.99)	[20]
Utility values			
SVR (without cirrhosis)	1		
CHC (without cirrhosis)	0.790	(0.74 – 0.82)	[23,34]
CHC *(while on treatment with SOC)*	*0.430*	*(0.28 – 0.58)*	[35]
CHC *(while on treatment with SOF+peg-INF/RBV)*	*0.650*	*(0.43 – 0.86)*	[36]
CHC *(while on treatment with SOF/LDV)*	*0.750*	*(0.59 – 0.91)*	[37]
Compensated cirrhosis	*0.748*	*(0.74 – 0.77)*	[34,38]
Cirrhosis *(while on treatment with SOC)*	*0.430*	*(0.28 – 0.58)*	[35]
Cirrhosis *(while on treatment with SOF+peg-INF/RBV)*	*0.650*	*(0.43 – 0.86)*	[36]
Cirrhosis *(while on treatment with SOF/LDV+RBV)*	*0.701*	*(0.55 – 0.85)*	[37]
Decompensated cirrhosis	0.672	(0.60 – 0.69)	[34,38]
HCC	0.610	(0.20 – 0.67)	[33,39,40]
SVR	0.87	(0.82 – 0.89)	[33]

CHC chronic hepatitis C, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *peg-INF* pegylated-interferon, *RBV ribavirin, SOC* standard of care, *SOF* sofosbuvir, *SOF/LDV* sofosbuvir-ledipasivr, *SVR* sustained virologic response

[1]Annual probability of CHC to cirrhosis was calculated from assumed probability of 20% over 20 years (Appendix A). Sensitivity analyses were performed to account for lower and higher (10% *vs.* 30% over 10 years) rates of progression.

Table 2. Assumptions regarding resource use and unit costs associated with HCV management in each health state

Cost component	Unit cost (ZAR)	Unit cost (US$)	Interval	
Baseline / Diagnosis				
Consultation with hepatologist	344.87	29.39	Baseline	
HCV antibody	198.74	16.94	Baseline	
HCV PCR & viral load	2,850.60	242.96	Baseline	
HCV genotyping	1,606.90	136.96	Baseline	
HBV serology[1]	596.22	50.82	Baseline	
HIV-test	1,164.55	99.26	Baseline	
HAV-immunity (HAV IgG)	113.63	9.68	Baseline	
TFT	508.68	43.36	Baseline	
LFT	517.22	44.08	Baseline	
FBC	174.80	14.90	Baseline	
U&E	49.72	4.24	Baseline	
INR	82.36	7.02	Baseline	
Alpha fetoprotein	170.37	14.52	Baseline	
Iron studies	423.41	36.09	Baseline	
Liver biopsy	86,653.00	7,385.56	Initial staging	
Abdominal ultrasound	678.75	57.85	Initial staging	
Chronic hepatitis C				
During treatment				
Hepatologist consultation	344.87	29.39	**SOC:**	@ weeks 1, 2, 4, 8, 12, 16, 20, 24 and 48
			SOF:	@ weeks 1, 2, 4, 8 and 12
			SOF/LDV:	@ weeks 1, 2, 4 and 12
LFT	517.22	44.08	**SOC:**	@ weeks 2, 4, 8, 12, 16, 20, 24, 32, 40 and 48
FBC	174.80	14.90	**SOF:**	@ weeks 2, 4, 8 and 12
U&E	49.72	4.24	**SOF/LDV:**	@ weeks 2, 4 and 12
INR	174.94	14.91		
Viral load[2]	1,579.50	134.62	**SOC:**	@ weeks 4, 12, 48 and 24 weeks post Rx
			SOF and SOF/LDV:	@ weeks 4 and 12; and 12 weeks post Rx
Treatment failed				
LFT, FBC, U&E, INR & AFP	1,087.07	92.65	6 monthly	

Liver biopsy	86,653.00	7,385.56	Every five years	
Compensated Cirrhosis				
During treatment				
Hepatologist consultation	344.87	29.39	**SOC:**	@ weeks 1, 2, 4, 8, 12, 16, 20, 24 and 48
			SOF:	@ weeks 1, 2, 4, 8 and 12
			SOF/LDV:	@ weeks 1, 2, 4 and 12
LFT	517.22	44.08	**SOC:**	@ weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48
FBC and Diff count	174.80	14.90	**SOF:**	@ weeks 2, 4, 8, 12 and 12 weeks after Rx
U&E	49.72	4.24	**SOF/LDV:**	@ weeks 1, 2, 4 and 12
INR	174.94	14.91		
Viral load	1,579.50	134.62	**SOC:**	@ weeks 4, 12, 48
			SOF and SOF/LDV:	@ weeks 4 and 12; and 12 weeks after Rx
Treatment failed				
LFT, FBC, U&E, INR & AFP	1,087.07	92.65	4 – 6 monthly	
Liver biopsy	86,653.00	7,385.56	Every three years	
Abdominal ultrasound	678.75	57.85	6 monthly	
Drug treatment				
RBV (*Copegus 200mg)*	425.37 per 42 tabs	36.25/42 tabs	**≤75kg:** 1000 mg/day x 48 weeks (SOC); x 12 weeks SOF and SOF/LDV in cirrhotic patients	
			>75kg: 1200 mg/day x 48 weeks (SOC); x 12 weeks SOF and SOF/LDV in cirrhotic patients	
Peg-INF*(Pegasus 180µg)*	3,668.69 per injection	312.69/injection	**SOC:** 180 µg/week x 48 weeks **; SOF:** 180 µg/week x 12 weeks	
Sofosbuvir	82,129.32 per 84 tablets	7,000/84 tablets	400mg/day x 12 weeks	
Sofosbuvir-ledipasvir	123,193.98 per 84 tablets	10,500/84 tablets	400mg/90mg x 12 weeks	
Decompensated cirrhosis				
Esophageal varices	102,572.22	8,742.38	Average annual cost. Includes six monthly screening for HCC using AFP and liver US	
Ascites	69,625.00	5,934.24		
Encephalopathy	226,825.00	19,332.62		
Hepatocellular carcinoma	60,833.00	5,184.88	Average cost per patient for 12 months post index; index being first claim with ICD-10 code “C22.0”.	

[1]HCV serology included HBV sAg, HBV sAb and HBV core antibody (total)

[2]Viral load: at week 4 = rapid virologic response; at week 12 = early virologic response; at week 48 = end of treatment; 24 weeks post treatment (SOC) and 12 weeks post treatment (SOF, SOF/LDV) = sustained virologic response

AFP alpha fetoprotein, *CT* computerized (or computed) tomography, *Diff count* differential count, *FBC* full blood count, *HAV* hepatitis A virus, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *INR* international normalised ratio, *LFT* liver function tests, *Peg-INF* pegylated interferon, *RBV* ribavirin, *Rx* treatment, *U&E* urea & electrolytes, *US* ultrasound

Table 3. Total annual cost of HCV management during each modeled health state

Variable	Cost (ZAR)	Cost (US$)
Diagnosis / Baseline	96,493.35	8,224.27
Chronic hepatitis C without cirrhosis		
During treatment with SOC (48 weeks completed)	213,572.25	18,203.07
During treatment with SOC (12 week stopping rule applied)[a]	61,138.35	5,210.91
During treatment with SOF (12 weeks)	141,004.82	12,018.04
During treatment with SOF/LDV (12 weeks)	123,193.98	10,500
Annual follow-up after treatment failed	2,174.13	185.30
Compensated cirrhosis		
During treatment with SOC (48 weeks)	216,322.32	18,437.46
During treatment with SOC (12 week stopping rule applied)[a]	62,971.74	5,367.17
During treatment with SOF (12 weeks)	141,004.82	12,018.04
During treatment with SOF/LDV+RBV (12 weeks)	136,782.29	11,658.15
Annual follow-up after treatment failed	4,618.69	393.66
Decompensated cirrhosis[b]		
Ascites	69,625.00	5,934.24
Esophageal varices[c]	102,572.22	8,742.38
Hepatic encephalopathy	226,825.00	19,332.62
HCC	227,694.08	19,429.71
Liver biopsy[d]	86,653.00	7,385.56
SVR (with cirrhosis)[e]	849.12 – 1,698.24	72.37 – 144.74

[a]The 12 week stopping rule was applied to patients who failed to achieve EVR. Costs applied to patients who discontinued treatment after 12 weeks was calculated as 12 weeks' drug cots and two-thirds of monitoring costs associated with SOC, for both cirrhotic and non-cirrhotic patients

[b]The total annual cost of decompensated cirrhosis is a weighted average between the average annual cost of ascites, variceal bleed and hepatic encephalopathy; calculated by multiplying the average annual cost for each sequale by fix proportions derived from literature: ascites, 62%; variceal hemorrhage, 28% and hepatic encephalopathy, 10%.

[c]The cost for esophageal varices is a weighted average between the average annual cost of bleeding (R362,309.00) and non-bleeding (R32,083.00) varices, assuming that, on average, varices has a 30% chance of bleeding.

[d]Patients without cirrhosis who did not achieve SVR get a liver biopsy every five years after treatment failure; whereas patients with compensated cirrhosis get a liver biopsy every three years after treatment failure

[e]For patients with cirrhosis who achieve SVR, the cost of HCC screening (using AFP and liver ultrasound) every six to twelve months was included

AFP alpha fetoprotein, *HCC* hepatocellular carcinoma, *SOC* standard of care, *SOF* sofosbuvir

Table 4. Long-term health outcomes

Complication	Number of cases per treated cohort of 10,000 patients		
	Standard of care	*Sofosbuvir + peg-INF/RBV*	*Sofosbuvir-ledipasvir*
Decompensated cirrhosis	891	260	83
HCC	720	210	67
HCC Death	680	200	63
Liver related death	1230	350	113
SVR with cirrhosis	790	1580	1876
SVR without cirrhosis	4440	7270	7506

HCC hepatocellular carcinoma, *peg-INF* pegylated interferon, *RBV* ribavirin, *SVR* sustained virologic response

Table 5. Long-term health-economic outcomes

	Life-years	QALY	Total cost	Incremental life-years	Incremental QALY	Incremental cost / QALY gained
BASE CASE: discounted						
SOF/LEDIPASVIR	12.82	12.32	**R241,560.54** ($20,588.55)	-	-	-
SOF+PEG-INF/RBV	12.67	12.07	**R263,132.38** ($22,427.15)	-0.15	-0.25	**DOMINATED**
PEG-INF/RBV	12.18	10.40	**R392,126.64** ($33,421.52)	-0.49	-1.92	**DOMINATED**
BASE CASE: undiscounted						
SOF/LEDIPASVIR	22.26	21.44	**R252,139.66** ($23,497.25)	-	-	-
SOF+PEG-INF/RBV	21.89	20.94	**R282,539.53** ($24,081.25)	-0.37	-0.50	**DOMINATED**
PEG-INF/RBV	20.66	18.02	**R476,964.81** ($40,652.40)	-1.60	-3.42	**DOMINATED**
SUB-GROUP ANALYSIS A: 12 week stopping rule not applied						
SOF/LEDIPASVIR	12.82	12.32	**R241,560.54** ($20,588.55)	-	-	-
SOF+PEG-INF/RBV	12.67	12.07	**R263,132.38** ($22,427.15)	-0.15	-0.25	**DOMINATED**
PEG-INF/RBV	12.18	10.38	**R419,372.12** ($35,743.69)	-0.64	-1.94	**DOMINATED**
SUB-GROUP ANALYSIS B: SOF/LDV for 24 weeks in cirrhotic patients						
SOF+PEG-INF/RBV	12.67	12.07	**R263,132.38** ($22,427.15)	-	-	-
SOF/LEDIPASVIR	12.82	12.31	**R265,108.46** ($22,595.58	+0.15	+0.25	**R7,991.67**
PEG-INF/RBV	12.18	10.40	**R392,126.64** ($33,421.52)	-0.49	-1.67	**DOMINATED**

peg-INF pegylated-interferon, *QALY* quality-adjusted life-years, *RBV* ribavirin, *SOF* sofosbuvir

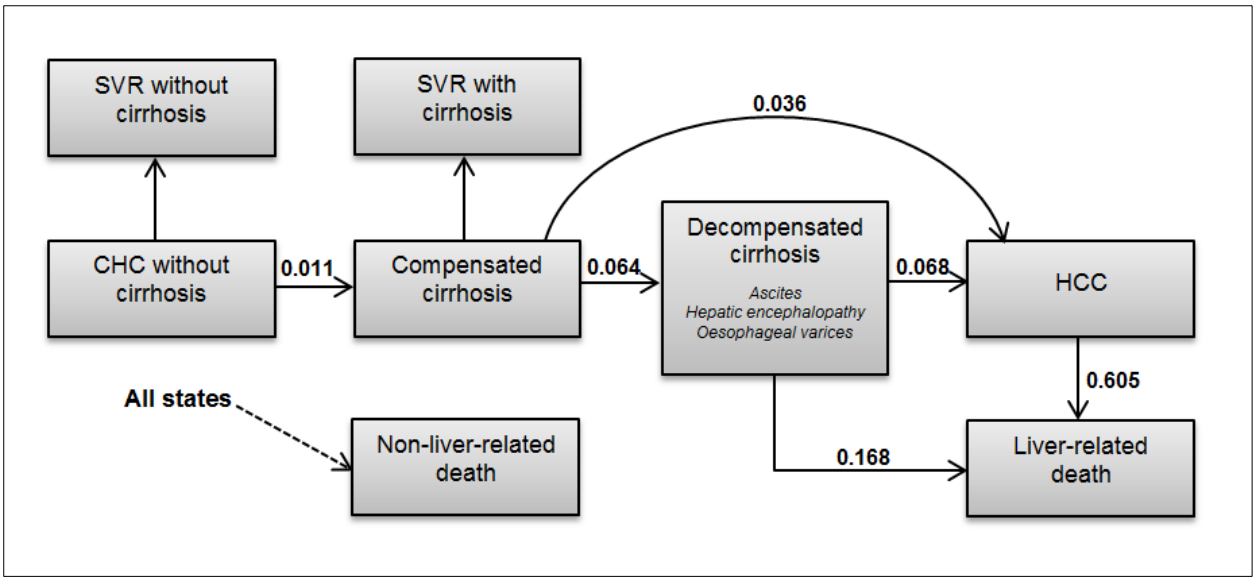


Fig. 1 Model schematics. Transition to SVR is dependent on the treatment regime used and the presence or absence of cirrhosis. SVR rates used in the model are listed in Table 1. *CHC* chronic hepatitis C, *HCC* hepatocellular carcinoma, *SVR* sustained virological response

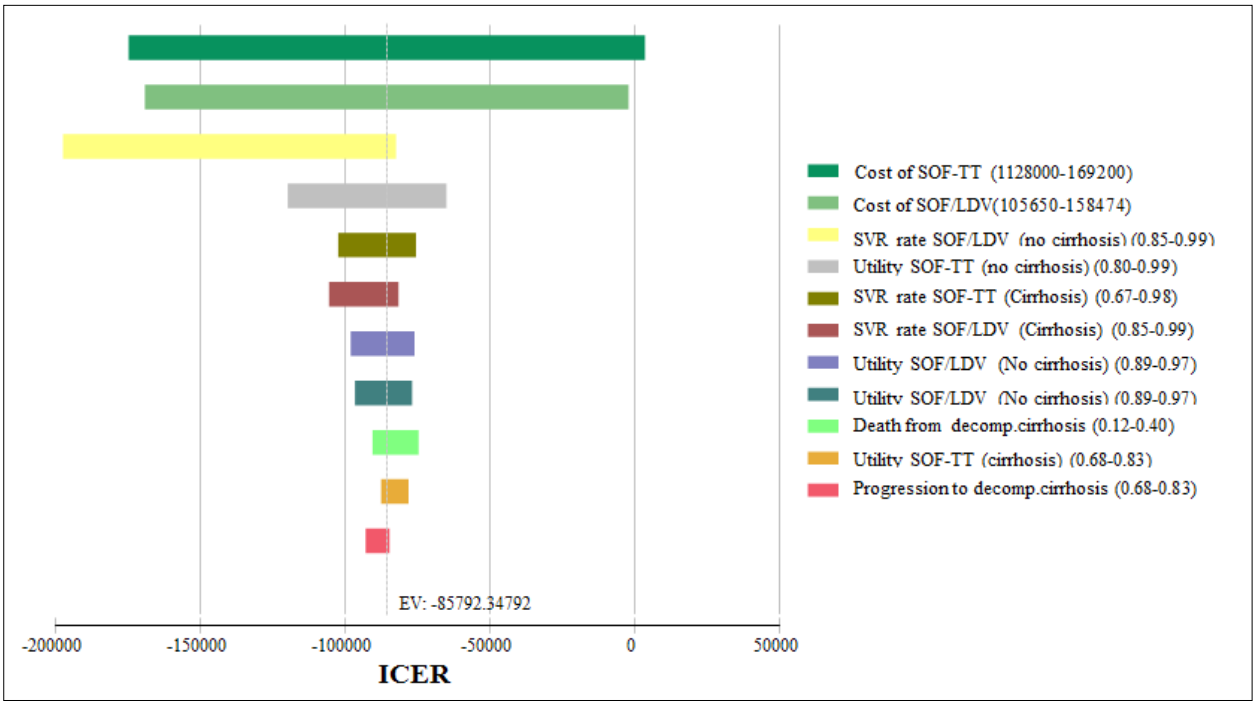


Fig.2 ICER tornado diagram. *Decomp. cirrhosis* decompensated cirrhosis, *EV* expected value, *ICER* incremental cost-effectiveness ratio, *SOF/LDV* sofosbuvir-ledipasvir, *SOF-TT* sofosbuvir triple therapy, *SVR* sustained virologic response

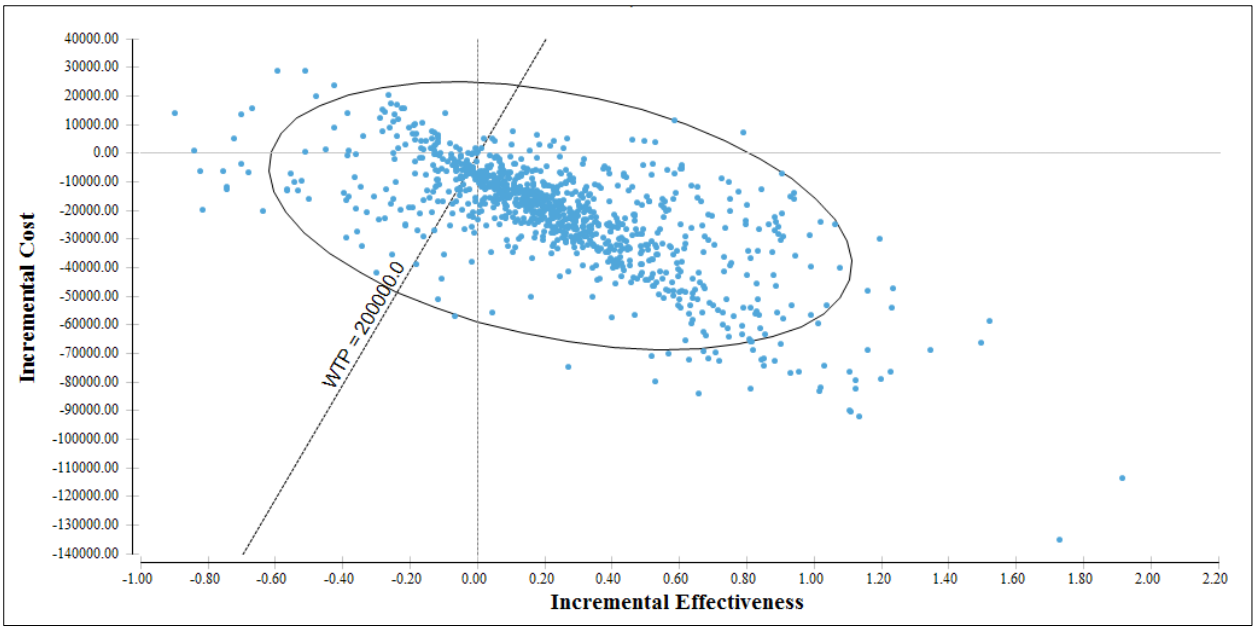


Fig. 3.1 The ICE scatterplot graph Shows simulation iterations plotted for incremental cost and incremental effectiveness. The plots below and to the right of the WTP line confirm the base case analysis, i.e. where the ICER ≤ WTP-threshold when SOF/LDV is priced at R123,190 (US$10,500) for 12 weeks. *ICE* incremental cost-effectiveness, *WTP* willingness-to-pay

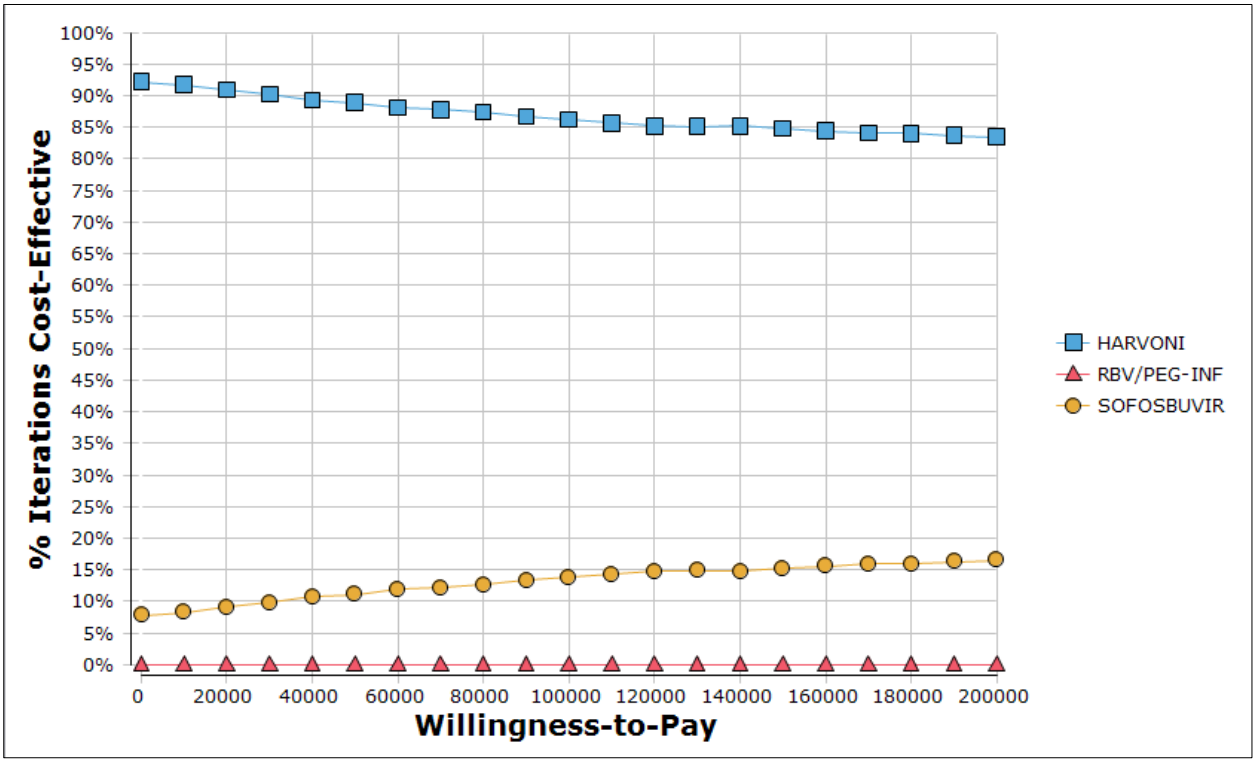


Fig. 3.2 The CE acceptability curve shows the percentage of simulation iterations that consider each strategy the most cost-effective over a range of WTP threshold values. *CE* cost-effectiveness, *peg-INF* pegylated interferon, *RBV* ribavirin, *WTP* willingness-to-pay

ONLINE RESOURCE A:

Cost-effectiveness modeling of sofosbuvir-containing regimens for chronic genotype 5 hepatitis C virus infection in South Africa

Journal: PharmacoEconomics

Running heading: Cost-effectiveness of sofosbuvir-containing regimens for chronic HCV-5

Authors:

Fraser, Ilanca[1], Burger, Johanita[1], Lubbe, Martie[1], Dranitsaris, George[2], Sonderup, Mark[3] & Stander, Tienie[4]

Affiliation:

[1]Medicine Usage in South Africa (MUSA), North-West University (Potchefstroom campus), Potchefstroom, South Africa

[2]Senior Specialist and Lecturer in Department of Medicine and Division of Hepatology, University of Cape Town and Groote Schuur Hospital

[3]Principal, Augmentium Pharma Consulting Inc., Toronto, Canada

[4]Researcher: HEXOR (Pty) Ltd, South Africa

Corresponding Author:

Fraser, Ilanca

Mailing address: Medicine usage in South Africa (MUSA), Faculty of Health Sciences, North-West University, Potchefstroom Campus, Potchefstroom, South Africa, 2520

Degrees: BPharm, MPharm

Institution: North-West University, Potchefstroom Campus

Phone: +27 18 299 2285

Fax: +27 87 231 4105

E-mail address: ilancaroux@gmail.com

CONTENTS

Introduction

The purpose of this online resource is to provide supplementary information to the manuscript Cost-effectiveness modeling of sofosbuvir-containing regimens for chronic genotype 5 hepatitis C virus infection in South Africa

Supplementary Data is supporting material that cannot be included in the printed version for reasons of space, and that is not essential for inclusion in the full text of the manuscript but would nevertheless benefit the reader. It should not be essential to understanding the conclusions of the paper but should contain data that is additional or complementary and directly relevant to the article content.

Supplementary data will be made available by the publisher as online-only content linked to the online manuscript. Such information includes more detailed methods, extended data sets/data analysis, tables, or additional figures. In addition, other material, including video clips and sound files, that enhance or extend the context of the paper beyond that which can appear in print are welcome

1 Description of model structure

To determine the expected health-economic outcomes in patients with chronic hepatitis C (CHC), we developed a decision analytic model to simulate the disease progression of chronic hepatitis C virus (HCV) infection and compared three treatment strategies: current standard of care (SOC) *vs.* sofosbuvir tripe therapy (SOF-TT) and sofosbuvir-ledipasiv monotherapy (SOF/LDV).

The model consisted of an initial decision tree, followed by a state-transition Markov model **(Figure S1)**. In the decision tree, patients were eligible to receive treatment. Treatment strategies included: i) SOC [pegylated-interferon (peg-INF) + ribavirin (RBV)] and ii) SOF-triple therapy (sofosbuvir + peg-INF + RBV) and iii) SOF/LDV. The state-transition model simulated the natural history of CHC. We used a cohort simulation model because it allows for tracking infected cohorts over time and also permits simulation of events in a population as they occur [1]. Through a Markov simulation, a hypothetical cohort of male and female patients with chronic HCV infection moved through defined health states in the model. Main health states included were: CHC without cirrhosis (treatment naive *vs.* treatment failed); compensated cirrhosis (treatment naive *vs.* treatment failed); decompensated cirrhosis; hepatocellular carcinoma (HCC); sustained virologic response (SVR) without cirrhosis; SVR with cirrhosis; liver-related death and non-liver related death. Time was represented by annual cycles, i.e. one cycle was 12 months, during which patients could remain in the same histologic or clinical state; progress to another histologic or clinical state; die of liver-related causes; or die of other causes (non-liver related).

All patients in the cohort entered the model with a confirmed diagnosis of CHC and initiated treatment upon entering the model. We developed a three-armed study — patients in the first arm of the model received

SOF/LDV, while patients in the second arm received SOF-TT and patients in the third arm received SOF/LDV. For all three treatment strategies, the aim of treatment was SVR and, based on the efficacy rates of each treatment option modeled, treatment could either be successful (achieved SVR) or unsuccessful (failed to achieve SVR). Patients only received treatment during the first model cycle and patients were assumed to complete only one course of treatment before achieving SVR. Patients who achieved SVR were assumed to maintain SVR and not experience further disease progression until they died, thus, we assumed that SVR eliminates the risk of progressive liver disease. Patients who did not achieve SVR, on the other hand, were assumed to be at risk of progressive liver disease. No response after 12 weeks (SOF-containing regimens) or 48 weeks (SOC) was considered as treatment failure and patients progressed to the next health state. Retreatment, relapse or recurrence was not considered.

For each treatment arm, the cohort was divided according to the presence or absence of cirrhosis and at the start of the state-transition model patients were placed in one of two disease states: "CHC without cirrhosis" or "compensated cirrhosis". The initial distribution of patients without cirrhosis (80%) and those with cirrhosis (20%) is representative of the South African HCV population. Based on this initial distribution assumed, 80% of the cohort in each treatment arm started in the "CHC without cirrhosis (treatment naive)" state for the first cycle of the Markov model. In our model, patients without cirrhosis were assumed to have advanced fibrosis (METAVIR score ≥F2).

The current South African hepatitis C management guidelines state that "treatment should be considered in all adults with confirmed chronic hepatitis C and particularly in those who are at increased risk of developing cirrhosis. For patients in whom liver histology is available, treatment is indicated if advanced fibrosis (F2 or F3 according to the METAVIR scoring system) is present" [2]. Even though fibrosis is not a prerequisite for treatment, we excluded ≤F1 because as it stands, these patients do not automatically qualify for treatment in the peg-INF/RBV era. Furthermore, funders in South Africa only pay for >F1 fibrosis. We accept that in the era or direct acting antivirals, all patients qualify for treatment — even so, treatment prioritization must occur and in both EASL and AASLD guidelines, patients with ≤F1 fibrosis are not prioritized unless another indication for treatment exists e.g. cryoglobulinemia, extreme fatigue etc. [3,4]. However, it difficult to model for this scenario as clear data does not exist to include such estimates.

We further assumed that spontaneous clearance of HCV is only possible from F0 and therefore not a possibility in our model. CHC patients without cirrhosis who achieved SVR (treatment successful) moved to the "SVR without cirrhosis" state at the end of the first cycle and remained there until death (non-liver related). Patients without cirrhosis who failed treatment, moved to the "CHC without cirrhosis (treatment failed)" state at the end of the first cycle. During the subsequent cycles, patients in the "CHC treatment failed" state could either remain in that state or progress to the "compensated cirrhosis (treatment failed)" state according to the annual transition probabilities. The remaining 20% of the modeled cohort started in the "compensated cirrhosis (treatment naive)" state. Those who achieved SVR moved to the "SVR with cirrhosis" state — a state for patients who are cured of HCV, but who have a lower utility than full health because of the advanced stage of fibrosis. Patients with cirrhosis who failed treatment moved to the "compensated cirrhosis treatment failed" state at the end of the

first cycle. During subsequent cycles, all patients in the "compensated cirrhosis treatment failed" state, including those who transitioned from "CHC without cirrhosis treatment failed", could either remain in that state, progress to "decompensated cirrhosis" or progress to "HCC", based on annual transition probabilities.

"Decompensated cirrhosis" included ascites, esophageal varices and hepatic encephalopathy as serious hepatic manifestations. From the "decompensated cirrhosis" state, patients could progress to "HCC", die from liver-related causes, or remain in the decompensated state, depending on the transition probabilities. Recovery from decompensation to compensated cirrhosis is only possible from a liver transplant. Since we did not consider liver transplants in our model, recovery from decompensated cirrhosis to a recovered health state was not possible. Patients who have progressed to HCC could either remain in the "HCC" state at the end of a 12 month cycle or die a liver-related death. Death from any cause was possible from all health states and background mortality for all patients in the model was assumed to be the same mortality rate as for the general population. The simulation was carried out until the cohort reached an age of approximately 100 years (cycle length, 50 years). The model structure, inputs and assumptions were validated by a panel of clinical hepatologists.

2 Data sources

2.1 Clinical data

Clinical data/inputs included annual transition probabilities, treatment efficacy and treatment duration. No clinical study or patient data collection was performed for the preparation of this project. This study was approved by the North-West University Health Research Ethics Committee [NWU-00035-15-A1].

2.1.1 Transition probabilities

In the context of modelling, the annual transition probability is *"the probability of progressing from a given health/disease state to the next health/disease state in a Markov process"* [5]. The natural history of chronic HCV infection has been described many times in literature and the transition probabilities of disease progression have been documented and published [6-12]. Available literature served as the data source for the transition probabilities used in this model. Studies indicate that 10% - 30% of patients with CHC will develop cirrhosis over a period of 20 years [7,8]. A meta-analysis conducted by Thein *et al.* predicted the cumulative probability of cirrhosis at 20 and 30 years after the infection at 16% and 41% respectively but noted that the 20-year predicted estimates of cirrhosis vary by study design, setting, and population, and by different age at HCV infection and duration of infection [12]. For our model, we assumed a transition probability of 20% over 20 years [7]. To calculate the annual probability for progression from CHC to cirrhosis, we assumed time to cirrhosis (in years) has an exponential distribution:

$$P[cirrhosis\ in\ 20\ years] = 1 - exp[-Beta * (20 * 12)/12]$$

To calculate Beta for an annual probability of 0.2:

$$1 - exp(-Beta * 20) = 0.2$$
$$1 - 0.2 = exp(-Beta * 20)$$
$$-ln(0.8) = Beta * 20$$
$$\boldsymbol{Beta = 0.011157178}$$

$$[P\ cirrhosis\ in\ 12\ months] = 1 - exp\left(-Beta * \frac{12}{12}\right) =$$
$$1 - exp(-0.011157178 * 1) =$$
$$\mathbf{0.011095167}$$

Annual transition probabilities for other health state transitions; i.e. compensated cirrhosis to decompensated cirrhosis and HCC, decompensated cirrhosis to HCC and liver-related death and HCC to liver-related death were based on best available evidence [6,7,9-11]. We accounted for uncertainty around progression rates by using a range of natural history parameters during sensitivity analyses.

2.1.2 Background mortality data

Death from any cause (non-liver related death) was possible from all modelled health states. Sex- and age-specific mortality rates from causes other than HCV were taken from the Actuarial Society of South Africa (ASSA) HIV demographic model: 2008 version [13], run for 2014. We assumed background mortality to only be dependent on sex and age, irrespective of the patients' disease status. For our model, background mortality rates were weighted for HIV-negative males and females, based on the assumption that 55% of the cohort was male and 45% was female.

2.1.3 Clinical efficacy

Treatment success is determined by achievement of SVR. Clinical inputs for treatment efficacy and duration for SOF triple therapy were derived from the phase III NEUTRINO clinical trial [14]. Response rates for sofosbuvir-ledipasvir (SOF/LDV) were based on the results of the open-label study conducted by Abergel *et al*. [15] in France. SVR rates SOC were derived from a meta-analysis of two large Belgium phase III/IV prospective RCTs, i.e. the BERNAR-1 and BERNAR-2 trials [16]. The NEUTRINO clinical trial (NCT01641640) was a phase three, multicenter, open-label, single-group study that assessed the safety and efficacy of sofosbuvir used in combination with RBV and pegylated-interferon alfa-2a (peg-INF α-2a). In the NEUTRINO study, patients infected with HCV genotypes 1, 4, 5, or 6 received SOF, RBV, and peg-INF α-2a for 12 weeks.

Most of the patients included in the NEUTRINO study had hepatitis C genotype 1, 9% had genotype 4 and 2% had genotype 5 or 6. To date, there have been no large RCTs that include efficacy data for SOF/LDV in HCV-G5, however, a small open label study conducted in France found that SOF/LDV administered as monotherapy

for 12 weeks in treatment-naïve and treatment-experienced patients infected with HCV-G5 yielded an SVR rate of 95%, irrespective of cirrhosis status [15].

Response rates for peg-INF/RBV of patients with HCV genotype-5 infection are poorly documented. A recent meta-analysis attempted to compare the efficacy of antiviral treatment in patients infected with genotype-5 to those infected with other genotypes [16]. The study included response rates of patients with HCV genotype 5 treated with peg-INF/RBV and compared baseline characteristics, early virologic response (EVR), response at 24 weeks and 48 weeks, end of treatment response and SVR [16]. As this meta-analysis is the only comparative analysis of HCV-5 response to peg-INF/RBV derived from two large prospective RCTs, it was used as reference for efficacy rates for the standard of care.

We applied the 12 week stopping rule to patients receiving SOC in our model. Given the high cost and significant potential toxicity associated with peg-INF/RBV, it is important to identify early predictors of nonresponse that accurately determine which patients should stop therapy because of lack of efficacy. For dual therapy with peg-INF/RBV, experts recommend stopping therapy if there is a lack of EVR at week 12 [17]. EVR is categorized as a decrease in the HCV RNA level by at least 2 log10 at week 12 of therapy. Failure to achieve an EVR remains the most accurate negative predictor of SVR in dual therapy [18] as only about 1% of patients who do not achieve an EVR will achieve an SVR [18]. A negative EVR has proved highly valuable in making a decision to stop therapy in those patients considered highly unlikely to achieve SVR. For our model, we assumed that 14% of patients without cirrhosis will fail to achieve EVR [19]. We further assumed a 15% reduction in the probability to achieve EVR in patients with compensated cirrhosis. Patients receiving SOC who failed to achieve EVR discontinued treatment after 12 weeks.

2.2 Utility values

Health-related quality-of-life (HRQoL) of patients with chronic liver disease has been shown to be impaired, especially in those patients with hepatitis C [20]. Beside specific complications of cirrhosis, such as hepatic encephalopathy, ascites and variceal bleeds, symptoms such as abdominal pain, muscle cramps, fatigue, depression and anxiety have also been associated with reduced HRQoL in patients with CHC. Concerns about complications of the disease, decreased sexual interest, loneliness and hopelessness have also been implicated in decreased HRQoL [20].

There is paucity for utility measures for liver disease in the literature, and to date, health utilities for patients suffering from chronic HCV infection in South Africa (SA) have not been determined. A systematic review of health state utilities in liver disease [21] showed no significant difference between the utility of compensated cirrhosis in HCV compared with moderate HCV, but showed a decreased utility for decompensated cirrhosis.

This study did not, however, include utility values for HCC. Another systematic review [12] reported very similar results to the review [21] but also, included a utility value for HCC. For our model, we employed health utility values taken from literature as efficacy measures [12,21-23].

In health economic evaluations, the summary measure of health outcome generally used is the quality-adjusted life-year (QALY) [24]. The QALY combines the HRQoL of a patient with his/her survival and provides an indication of the benefits gained from a health intervention — in the terms of both quality-of-life and life years gained [25]. In order to generate QALYs, health utilities are needed [26]. Utility measures originated in health economics, and form an important subgroup of generic measures of HRQoL that are used in cost-effectiveness studies and medical decision-making [27].

The impact of treatment on HRQoL is inexact, although it is known that there are definite decrements in HRQoL associated with the adverse and toxic effects of peg-INF treatment [28]. Kerr *et al*. (2012) [22] evaluated the impact of treatment attributes of peg-INF for HCV on HRQoL. Results from the study indicated that flu-like symptoms resulting from injected peg-INF as part of HCV treatment have a significant impact on patients' quality-of-life. Another study [23] conducted to assess health utilities for sofosbuvir-containing therapy for CHC, found treatment with SOF + RBV minimally impacted patients' health utilities, as compared to interferon-based treatment. The results furthermore showed that combining SOF with peg-INF caused a more severe impairment of the patient's HRQoL than an interferon-free regimen; although all treatment-related impairment resolved within twelve weeks after the end of treatment. Younossi *et al*. (2015) assessed patient reported outcomes (PRO) in patients treated with SOF/LDV with and without RBV enrolled in the ION-1, -2, and -3 trials. Investigators administered four PRO questionnaires were administered at baseline, during, and post-treatment in patients treated with LDV/RBV±RBV. Patients receiving LDV/SOF regimens showed significant improvement of PRO scores during treatment, whereas PRO scores declined during treatment with SOF/LDV+RBV. Results showed that receiving RBV was an independent predictor of PRO impairment. The study also calculated SF-6D utility scores for patients treated with SOF/LDV±RBV, showing lower utility scores for patients who receive RBV in addition with SOF/LDV [29].

We used annual transitions and yearly cycle-time in the model. Since the duration of treatment of SOF-based therapy is 12 weeks, we adjusted the utilities for patients receiving SOF-based treatment by calculating a weighted average for utilities for patients in the either of the SOF arms of the model for the first cycle by applying the following formula: (using SOF-TT as an example) we applied the utility value during treatment (0.65) to all patients for three months and the relevant utility for SVR (1 for no-cirrhotic vs. 0.87 for cirrhotic patients) to patients who achieved SVR, and the utility of the relevant disease state (0.79 for CHC and 0.784 for cirrhosis) to patients who failed to achieve SVR for the remaining 9 months of the year.

$$Weighted\ utility\ = \left(\frac{3}{12} x\ a\ x\ b\right) + \left(\frac{9}{12} x\ c\ x\ d\right) + \left(\frac{9}{12} x\ e\ x\ f\right)$$

Where:

a = percentage of patients receiving treatment; b = utility value during treatment with SOF; c = percentage of patients who achieved SVR; d = utility value during SVR; e =percentage of patients who failed to achieve SVR; f = utility value during relevant disease state (CHC without cirrhosis vs. cirrhosis)

2.3 Cost data

The model accounted for three types of HCV-related cost, i.e. drug regimen, treatment monitoring and health state (downstream liver-disease complications). Costs of treatment cycles were expressed in South African Rand (ZAR) and United States Dollars (US$) at 2015 value. According to the South African third-party payer's perspective, only direct costs were considered — in particular, the drug costs (peg-INF, RBV, SOF) and the costs associated with disease management (i.e. diagnostic tests, routine blood tests, outpatient visits, hospitalisation etc.) Patients initiated treatment at the start of the model. In addition to receiving drug-treatment, all patients underwent baseline testing and diagnosis upon entering the model. Patients in both arms of the model acquired a once-off cost for pathology (including HCV antibody, HCV PCR & viral load, HCV genotyping, HBV sAg, HBV sAb, HBV core antibody (total), HIV-test (rapid and Western Blot technique), HAV-immunity (HAV IgG), TFT, LFT, FBC, U&E, INR, AFP and iron studies, abdominal ultrasound), the cost of a liver biopsy and the cost of a consultation with a specialist (hepatologist), irrespective of the treatment option chosen (Table S2). A detailed description of drug and monitoring costs are shown in Table S1.

Patients only received treatment during the first model cycle, as no response after 48 weeks (SOC) or 12 weeks (SOF) was considered as treatment failure. After treatment failure patients progressed to the next health state in the model during the following cycle, as no retreatment was offered. During the first model cycle, patients received either SOF/LDV for 12 weeks (arm 1), SOF-TT for 12 weeks (arm 2) or SOC for 48 weeks (arm 3). The same treatment was offered to patients with and without cirrhosis in each arm respectively. During treatment, patients are subjected to routine monitoring and screening. Therefore, in addition to the cost of drugs, patients in both treatment arms also acquired treatment and monitoring costs. The frequency of these test were dependant on the treatment regime and the disease state the patient is in when he/she receives treatment. Treatment management and monitoring of patients during treatment was based on the typical South African management of HCV, confirmed by South African hepatologists. The total cost of drug treatment and total monitoring costs were added to calculate a total treatment cost for cirrhotic and non-cirrhotic patients in each treatment arm.

Costs for the first cycle were calculated as cost per patient per year. For the SOF/LDV arm, costs included baseline costs, the cost of SOF/LDV monotherapy for 12 weeks for patients with no cirrhosis, or the cost of SOF/LDV + the cost of daily weighted based RBV for 12 weeks for patients with compensated cirrhosis, and monitoring costs for 12 weeks. For the SOF-TT arm, costs included baseline costs, the cost of SOF for 12 weeks treatment, cost of peg-INF/RBV for 12 weeks and monitoring costs for 12 weeks. For both SOF-based therapy arms, patients who achieved SVR after 12 weeks would not acquire any more costs for the remainder of the year, and was therefore only awarded the total cost of drugs and monitoring for the first year. Patients who failed treatment would require follow-up tests six months after treatment has ended. We therefore awarded an additional cost of R1,087 (US$93) to non-cirrhotic and R2853 (US$243) to cirrhotic patients who failed treatment.

Costs of RBV (Copegus®) and peg-INF (Pegasus®) were taken from the Official Pharmaceutical Bluebook [30], updated 16 April 2015, accessed 17 April 2015. The modelled price represents retail value including dispensing fee and VAT. Monitoring costs, including costs of pathology tests and doctors consultations were derived from the Referencing Price List (RPL) [31]. The RPL is a schedule of health service procedure codes administered by the South Afrcian Department of Health (DoH) and linked to reference prices. The RPL was designed by the Council for Medical Schemes on behalf of the Department of Health, and was first published in 2004. This list does not contain negotiated prices and is compiled by gathering submissions from all disciplines of health service with suggestions regarding the actual cost of running a practice.

2.3.1 Base case analysis

During the base case analysis, non-cirrhotic patients in the SOF/LDV arm received a combination of 400 mg SOF and 90 mg LDV in a single tablet, once daily for 12 weeks. In the base case analysis, cirrhotic patients received the same fixed-dose combination for 12 weeks with weight based RBV daily. Patients in arm two received SOF-TT: 400mg SOF once a day, RBV once a day and 180 ug peg-INF once a week for 12 weeks. In all arms of the study, the dose of RBV was related to patient weight (≤75 kg, 1000 mg per day; >75 kg, 1200 mg per day). The cost of RBV was calculated as a weighted average for males and females (given the proportion of males *vs.* females is 55% and 45%) based on the assumption that males weighed >75 kg and weighed females ≤75 kg. We assumed that LFT, FBC, U&E and INR tests were performed in patients who received SOF-TT treatment (those with- and without cirrhosis) at weeks 2, 4, 8 and 12; and for SOF/LDV at weeks 2, 4 and 12. Viral load testing was performed at weeks 4 (RVR), 12 (EOT) and 12 weeks post treatment (SVR) (refer to **Tables S3(a) and S3(b)**).

Patients in the SOC arm received oral RBV (Copegus®) once a day and one 180 ug injection of peg-INF (Pegasus®) subcutaneously once a week for 48 weeks (based on South African management guidelines) [2]. Patients who started in the "CHC (treatment naive)" state, underwent blood tests (including LFT, FBC, U&E and INR) at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40 and 48 and HCV viral load testing at weeks 4 (RVR), 12 (EVR), 48 (EOT) and 24 weeks post-treatment. Patients also consulted a hepatologist at weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 40 and 48 (see **Table S3(a)**). Patients who started in the "Compensated cirrhosis (treatment naive)" state, received the same drug therapy as patients without cirrhosis, however, blood tests were performed at weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48. Intervals of viral load testing and hepatologist consultations were the same for cirrhotic and non-cirrhotic patients (refer to **Table S3(b)**). Patients who achieved EVR completed the full 48 week treatment period, i.e. peg-INF + RBV for 48 weeks plus monitoring costs for 48 weeks. Patients who failed to achieve EVR, discontinued drug treatment after 12 weeks. Costs associated with early termination was calculated as 12 weeks drug costs plus two thirds of the monitoring costs associated with the disease state during which the patient received treatment (refer to **Table S3(c)**). Costs applied to these patients were calculated as 12 weeks drug costs (peg-INF + RBV: R48,746 or ~US$4,155) and two thirds of the monitoring costs associated with SOC (R12,392 or ~US$1,056 for patients without cirrhosis and R14,226 or ~US$1,213 for patients with compensated cirrhosis). Patients who achieved EVR completed the full 48 weeks of treatment. Of those patients without cirrhosis who did achieve EVR, 65% achieved SVR

(overall SVR rate of 55.3%) and 56% of patients with compensated cirrhosis achieved SVR after achieving EVR (overall SVR rate of 40%).

The total cost for patients in each arm of the model, for the first 12 month cycle, thus consisted of both drug costs and monitoring costs for the treatment period. Drug and monitoring costs were calculated and added to derive a "total treatment cost" for each treatment option/disease state combination, i.e. i) CHC without cirrhosis receiving SOC, ii) CHC without cirrhosis receiving SOF-based therapy, iii) Cirrhotic patients receiving SOC, and iv) Cirrhotic patients receiving SOF-based therapy. No other costs were considered during the first cycle **(Tables S3(a) – S3(c))**.

In both treatment arms, patients in the "CHC without cirrhosis treatment naive" state who achieved SVR moved to the "SVR without cirrhosis" state at the end of the first cycle. No costs were incurred in this state and patients continued in this state until death. CHC patients who failed to achieve SVR moved to the "CHC without cirrhosis treatment failed" state at the end of the first cycle. The current management guidelines in South Africa recommend that CHC patients without cirrhosis who have failed treatment, receive follow-up blood tests every six months and a liver biopsy every five years. Patients in both arms in the "CHC without cirrhosis treatment failed" state therefore incurred costs for LFT, FBC, U&E, INR and AFP twice a year and the cost of a liver biopsy once every five years **(Table S4(a))**.

Patients who started the model in the "Compensated cirrhosis treatment naive" state who achieved SVR moved to the "SVR with cirrhosis" state. Patients in this state were considered cured of HCV (or HCV negative), but were assumed to have a lower health-related quality-of-life (or utility) because of the advance stage of liver fibrosis. Current clinical practice recommends on-going HCC screening in cirrhotic patients who have achieved SVR. Therefore, CHC patients with cirrhosis in both arms incurred the cost for a liver ultrasound, every year they remained in the "SVR with cirrhosis" state **(Table S5)**. Cirrhotic patients who failed treatment moved to the "Compensated cirrhosis treatment failed" state at the end of the first cycle. Current clinical guidelines recommend close monitoring of cirrhotic patients who are not on treatment. This includes blood tests (LFT, FBC, U&E, INR and AFP) every four months, HCC screening every six months and a liver biopsy every three years. The costs of these tests were applied to patients in the "Compensated cirrhosis treatment failed" state in both arms of the model **(Table S4(b))**.

The total annual cost of decompensated cirrhosis was calculated as a weighted average between the average annual cost of ascites, esophageal varices and hepatic encephalopathy; calculated by multiplying the average annual cost for each sequale by fixed proportions derived from literature: ascites, 62%; esophageal varices, 28% and hepatic encephalopathy, 10%. The cost for esophageal varices is a weighted average between the average annual cost of bleeding (R362,309.00 or ~US$30,880) and non-bleeding (R32,083.00 or ~US$2,802) varices, assuming that, on average, varices has a 30% chance of bleeding.

Costs for ascites, esophageal varices and hepatic encephalopathy and HCC were derived from South African private sector cost data. Costs used for these three complications were taken to be the average annual cost per

event and we used RPL, CPT and ICD-10 codes to identify these events. The cost for oesophageal varices was calculated using RPL code(s) 1552 and/or 1553. For patients who had an in-hospital event where this RPL code(s) was claimed, the sum of all relevant costs were divided by the number of cases/events during one year to calculate the average cost per event. Cases were sub-divided into two groups: one group including ICU claims and another, excluding ICU claims. The average annual event cost was calculated for both subgroups. Where a patient had ICU claims, we assumed it to be a case of bleeding varices (or oesophageal haemorrhaging). Where there were no ICU claims, we assumed it to be a case of varices without bleeding.

The sum of all related in-hospital costs, associated with the ICD-10 code "R18" was divided by the number of cases to calculate an average annual event cost for ascites. Cases where the ICD-10 code R18 (ascites) was claimed, together with a claim for theatre, was removed from the final calculation. Using the same methodology, an average total event cost for encephalopathy was calculated for patients with in-hospital events claimed using the ICD120 code G93.4, including theatre cases.

The cost of a liver biopsy was also calculated as an average annual event cost and we used CPT codes for identification of events. Events were categorised as: 76942 = ultrasound guidance for needle placement; 77002 = fluoroscopic guidance for needle placement; 77012 = CT guidance for needle placement and 77021 = MR guidance for needle placement. Patients who had claims with these CPT codes, who also had claims in theatre, were removed from the final calculation. The sum of all claims (where these relevant CPT codes were used) for in-hospital cases was divided by the number of cases to calculate an average annual event cost for a liver biopsy.

The cost of HCC was the average annual cost per patient with HCC and included all claims made by a patient with ICD-10 code "C22.0". Patients were identified when they had their first claim with ICD-10 code C22.0 (index date) and followed for 12 months post index date. All costs in- and out-of-hospital were extracted and divided by the number of patients identified, resulting in the annual average cost per patient with HCC.

3 Model validity and uncertainty

3.1 Methodological uncertainty

The Panel on Cost-Effectiveness in Health and Medicine recommends the societal perspective for cost-effectiveness studies, as it includes all significant health outcomes and costs, irrespective of who experiences these costs or whether the costs are matched by budgetary outlays [32]. However, there is a question as to whether the societal approach should be used in countries without a nationalised health service (NHS). Because South Africa does not have National Health Insurance (NHI) as yet, and the Pricing Committee of South Africa will generally only accept pharmacoeconomic submissions that adopt a third party payer (i.e. a funder) perspective [33], we adopted a third-party payer perspective for our study. Because other (indirect) costs are not considered in our model, costs associated with CHC may be underestimated.

3.2 Structural uncertainty

Different Markov models developed for HCV have utilised different health states, with different probabilities for progressing to more advanced liver disease [5]. In order to estimate the long-term impact of health and economic outcomes in a clinical trial setting, the model predicted the course of liver disease for each individual over their remaining lifetime and mortality based on literature estimates of natural disease progression data. It is possible that disease progression may vary depending on a patient's gender, race, other comorbidities (e.g. co-infection with hepatitis B virus or HIV) or alcohol consumption, which was not accounted for in this model. The model is also limited in that it does not account for the potential risk of HCC to develop in patients who achieve SVR (specifically if treated at F4 cirrhosis stage). However, according to Gellad *et al*. (2012:1195) in contrast to models attempting to predict future economic and health burdens from chronic HCV, it is unlikely that imperfections in the modeling of the natural history of chronic hepatitis C will be of sufficient magnitude to affect the interpretation of the results [34].

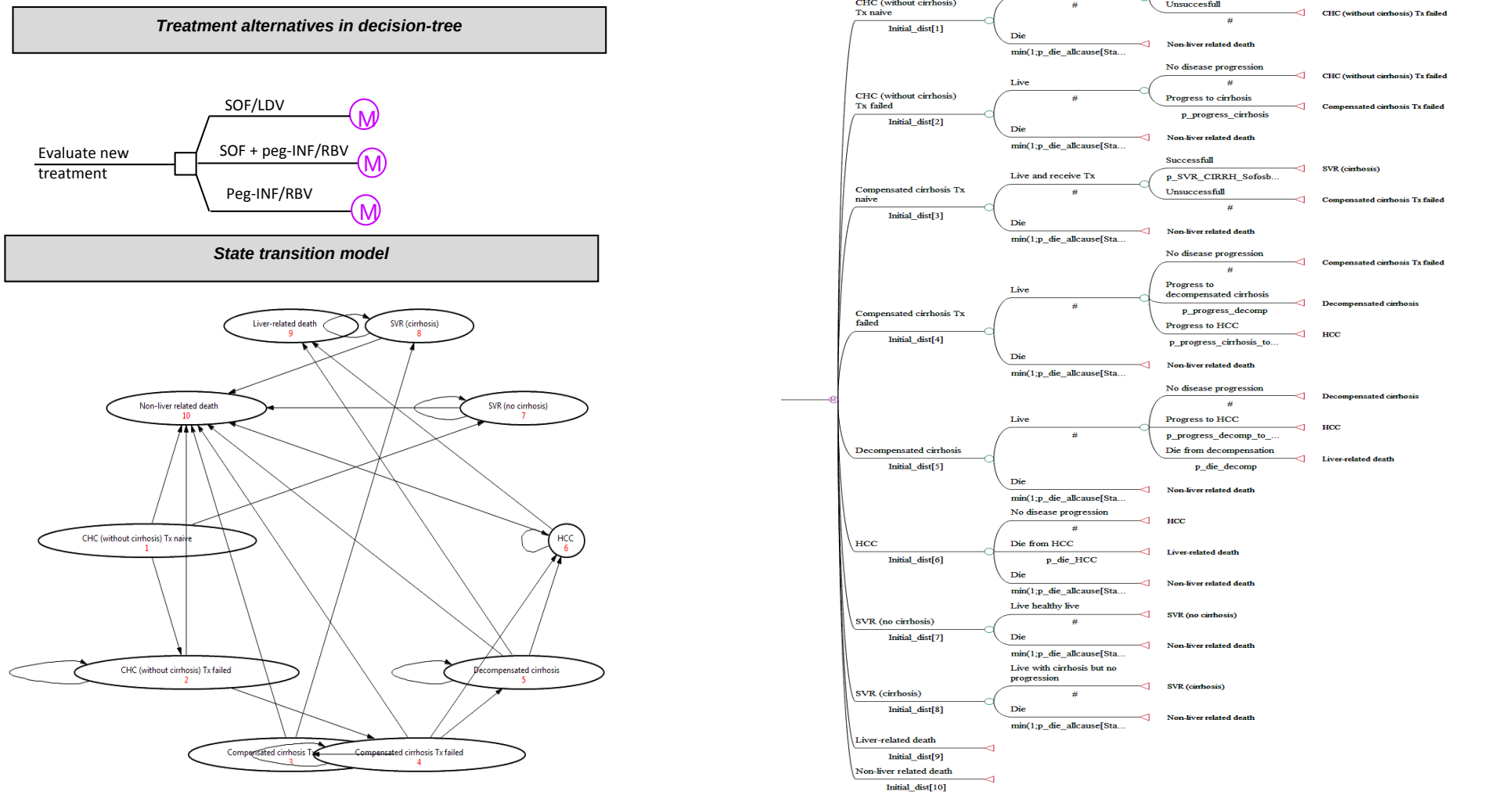
References

1. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making. 1993;13:322-39.
2. Botha JF, Kassianides C, Schneider HR, Song E, Spearman W, van der Merwe SW. South African hepatitis C management guidelines 2010. S Afr Gastroenterol. 2010;8(1). Available at: http://www.sages.co.za/images/hcvjfb.pdf. Accessed: 12 Dec 2014.
3. European Association for the Study of the Liver (EASL). EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatology. 2015;63:199–236.
4. American Association for the Study of Liver Diseases (AASLD). When and in whom to initiate HCV therapy. 2015. Available at: http://www.hcvguidelines.org/printpdf/91 Accessed: 20 Aug. 2015.
5. Ademi Z, Kim H, Zomer E, Reid CM, Hollingsworth B, Liew D. Overview of pharmacoeconomic modelling methods. Br J Clin Pharmacol. 2012;75(4):944-50.
6. Alawazi W, Cunningham M, Dearden J, Foster GR. Systematic review: outcome of compensated cirrhosis due to chronic hepatitis C infection. Alim Pharmacol Ther. 2013;32:344-55.
7. Alberti A, Chemello L, Benvegnhù L. Natural history of hepatitis C. J Hepatology. 1999;31(Suppl. 1):11-24.
8. Chen SL, Morgan TR. The Natural History of Hepatitis C Virus (HCV) Infection. Int J Med Sci. 2006;3(2):47–52.
9. Hutchinson S, Bird S, Goldberg D. Modeling the current and future disease burden of hepatitis C among injection drug users in Scotland. Hepatology. 2005;42:711–23.
10. Saab S, Hunt D, Stone M, McClune A, Tong M. Timing of hepatitis C antiviral therapy in patients with advanced liver disease: a decision analysis model. Liver Transplant. 2010;16:748–59.
11. Sweeting M, De Angelis D, Neal KR, ME, Irving W, Wright M, Brant L, et al. Estimated progression rates in three United Kingdom hepatitis C cohorts differed according to method of recruitment. J Clin Epidemiol. 2006;59:144–52.
12. Thein HH, Krahn M, Kaldor JM, Dore GJ. Estimation of utilities for chronic hepatitis C from SF-36 scores. Am J Gastroenterol. 2005;100(3):643-51.
13. Actuarial Society of South Africa. Actuarial Society of South Africa HIV demographic model 2008 version, 2008. Available at: http://aids.actuarialsociety.org.za/Models-3145.htm. Accessed: 1 Feb 2015.
14. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Schultz M, Davis MN, ZeidKayali Z, Reddy KR, Jacobson IM, Kowdley KV, Nyberg L, Subramanian GM, Hyland RH, Arterburn S, Jiang D, McNally J, Brainard D, Symonds WT, McHutchison JG, Sheikh AM, Younossi Z, Gane EJ. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med. 2013;368(1):33-44.
15. Abergel A, Loustaud-Ratti V, Metivier S, Jiang D, Kersey K, Knox SJ, Svarovskaia E, Pang PS, Samuel D, Asselah T. Ledipasvir/Sofosbuvir for the treatment of patients with chronic genotype 4 or 5 HCV infection. Paper presented at The International Liver Congress 2015: 50th annual meeting of the European association for the Study of the Liver (EASL), Vienna, Austria; April 22-26. Available at: http://natap.org/2015/EASL/EASL_80.htm Accessed: 21 Aug. 2015.

16. D'Heygere F, George C, Van Vlierberghe H, Decaestecker J, Nakad A, Adler M, Delwaide J, Laureys A, Nevens F. Efficacy of interferon-based antiviral therapy in patients with chronic hepatitis C infected with genotype 5: A meta-analysis of two large prospective clinical trials. J Viral Hepat. 2011;83:815-9.
17. Ghany MG, Strader DB, Thomas DL, Seeff LB. American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009;9:1335-74.
18. Davis GL. Monitoring of viral levels during therapy of hepatitis C. Hepatology. 2002;36(5):S145-51.
19. Ferenci P, Lafer H, Scherzer TM, Maieron A, Hofer H, Stauber R, Gschwantler M, Brunner H, Wenisch C, Bischof M, Strasser M, Datz C, Vogel W, Löschenberger K, Steindl-Munda P; Austrian Hepatitis Study Group. Peginterferon alfa-2a/ribavirin for 48 or 72 weeks in hepatitis C genotypes 1 and 4 patients with slow virologic response. Gastroenterol. 2010;138(2):503-12.
20. Gutteling J, De Man RA, van der Plas SM, Schalm SW, Busschbach JJV, Darlington ASE. Determinants of quality of life in chronic liver patients. Alim Pharmacol Ther. 2006;23:1629-35.
21. McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. Med Decis Making. 2008;8:582-92.
22. Kerr C, Lloyd A, Ali S, Goreb C, Tyas DA. Impact of treatment attributes of peginterferon for hepatitis C on quality of life and treatment preference. Health Outcomes Res Med. 2012;3(3):e153-67.
23. Stepanova M, Nader F, Cure S, Bourhis F, Hunt S, Younossi M. Patients' preferences and health utility assessment with SF-6D and EQ-5D in patients with chronic hepatitis C treated with sofosbuvir regimens. Alim Pharmacol Ther. 2014;40:676-85.
24. Weinstein MC, Torrance G, McGuire A. QALYs: The Basics. Value in health. 2009;12(1):S5-9.
25. Scuffham PA, Whitty JA, Mitchell A, Viney R. The use of QALY weights for QALY calculations: a review of industry submissions requesting listing on the Australian Pharmaceutical Benefits Scheme 2002-2004. Pharmacoeconomics. 2008;26(4):297-310.
26. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. Br Med Bulletin. 2010;96:5-21.
27. Tolley K. What are health utilities? 2009. Available at: http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/Health-util.pdf Accessed: 11 Nov. 2014.
28. Salomon JA, Weinstein MA, Hammitt JK, Goldie SJ. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. J Am Med Ass. 2003;290(2):228-37.
29. Younossi ZM, Stepanova M, Marcellin P, Afdhal N, Kowdley KV, Zeuzem S, Hunt SL. Treatment with ledipasvir and sofosbuvir improves patient-reported outcomes: Results from the ION-1, -2, and -3 clinical trials. Hepatology. 2015 Jun;61(6):1798-808.
30. The Official Pharmaceutical Bluebook. 2015. Available at: http://www.pbb.co.za/ Accessed: 3 Feb. 2015.
31. Council for Medical Schemes. Reference Price List (RPL). National reference price list for services by medical practitioners, effective from 1 January 2009. 2009. Available at: http://wcawca.co.za/files/bhf_2009_medical_practitioners.pdf Accessed: 10 Oct. 2014.
32. Gold MR, Siegel JE, Russell LB, Weinstein MC, editors. New York, NY: Oxford University Press; 1996. Cost-Effectiveness in Health and Medicine: Report of the Panel on Cost-Effectiveness in Health and Medicine.

33. South Africa. Medicines and Related Substances Act (Act no. 101 of 1965): regulations relating to a transparent pricing system for medicines and schedules substances. 2013. (Government notice no. R68). Government gazette, 36118, 1 Feb.
34. Gellad ZF, Reed SD, Muir AJ. Economic evaluation of direct-antiviral therapy in chronic hepatitis C. Antiviral Ther. 2012;17:1189-99.
35. Statistics South Africa (STATS SA). Statistical Release P0141: Consumer Price Index (CPI). 2015. Available at: http://www.statssa.gov.za Accessed: 20 Mar. 2015
36. OANDA currency converter. Average exchange rate for the first quarter of 2015. 2015. Available at: http://www.oanda.com/currency/converter/ Accessed on: 3 May 2015.

Figure S1. Model schematics



The small square in the decision tree represents the decision to treat a patient with SOC or SOF-based therapy. The small circle with inset "M" indicates the Markov model. Persons begin the model receiving treatment, and if treatment is successful (the patient achieves sustained virologic response), the patient transitions to a SVR state. If treatment is not successful, the person continues progressing through the natural history of HCV. Death can occur from any health state in the Markov model. Health state transitions in the cost-effectiveness model. Values represent annual transition probabilities.

Table S1. Detailed description of RPL codes and associated costs

Pathology				
Unit	*RPL code*	*Cost* (2009 values)*	*Description*	*Inflated price** (2015 values)*
Consultation	0192	R226.10		R344.87
HCV antibody	4531	R130.30	Hepatitis: Per antigen or antibody	R198.74
HCV PCR				R1271.10
HCV viral load				R1579.50
HCV genotyping				R1606.90
HBV sAg	4531	R130.30	Hepatitis: Per antigen or antibody	R198.74
HBV sAb	4531	R130.30	Hepatitis: Per antigen or antibody	R198.74
HBV core antibody (total)	4531	R130.30	Hepatitis: Per antigen or antibody	R198.74
HIV-test (rapid)	4614	R107.90	HIV Ab - Rapid Test	R164.58
Western Blot	3969	R655.60	Western blot technique	R999.97
HAV-immunity (HAV IgG)	4182	R74.50	Quantitative protein estimation: Nephelometer or Turbidometeric method	R113.63
TFT	4484	R333.50	Thyrotropin (TSH) + Free Thyroxine (FT4)	R508.68
LFT	4009	R42.90	Bilirubin: Total	R65.43
	4010	R32.60	Bilirubin: Conjugated	R49.72
	4001	R46.60	Alkaline phosphatase	R71.08
	4143	R48.6	Serum/plasma enzymes	R74.13
	4117	R28.00	Protein: Total	R42.71
	4131	R48.60	Alanine aminotransferase (ALT)	R74.13
	3999	R43.20	Albumin	R65.89
	4130	R48.60	Aspartate aminotransferase (AST)	R74.13
FBC	3755	R94.40	Full blood count (including items 3739, 3762, 3783, 3785, 3791) (3739: erythrocyte count; 3762: haemoglobin estimation; 3783: leucocyte	R143.99

			differential count; 3785: leucocytes; 3791: packed cell volume (haematocrit)	
	3797	R20.20	Platelet count	R30.81
U&E	4423	R32.60	Urea	R49.72
INR	3805	R54.00	Prothrombin index	R82.36
AFP	4522	R111.70	Alpha-feto protein	R170.37
Iron studies	4071	R60.70	Iron	R92.58
	4528	R111.70	Ferritin	R170.37
	4144	R105.20	Transferrin	R160.46
Liver biopsy	1743	R235.70	Needle biopsy of liver	R359.51
Abdominal ultrasound	3627	R445.00	Ultrasound examination includes whole abdomen and pelvic organs, where pelvic organs are clinically indicated (including liver, gall bladder, spleen, pancreas, abdominal vascular anatomy, para-aortic area, renal tract, pelvic organs)	R678.75

Drugs

Active ingredient	*Trade Name & Strenght*	*Cost per pack*	*Cost per unit*	*Dose*
Ribavirin	Copegus® 200 mg	R425.37 per 42 tablets	R10.13 per 200 mg tablet	≤75 kg: 1000 mg / day >75kg: 1200 mg / day
Pegylated-interferon α-2a	Pegasus® 180 µg	R3668.60 per pre-filled syringe	R3668.60 per pre-filled syringe	180 µg / day
Sofosbuvir	Sovaldi® (USA) 400 mg	R82,129.32 per 84 tablets	R977.73 per 400 mg tablet	400 mg / day
Sofosbuvir/ledipasvir	Harvoni® (USA) 400 mg/90 mg	R123,190.48 per 84 tablets	R1466.55 per fixed-dose tablet	400/90 mg / day

AFP alpha fetoprotein, *FBC* full blood count, *HAV* hepatitis A virus, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *IgG* immunoglobulin G, *INR* international normalized ratio, *LFT* liver function test, *PCR* polymerase chain reaction , *sAb* serum antibody, *sAg* serum antigen, *TFT* thyroid function test, *U&E* urea and electrolytes

*The latest issue of the RPL was published in 2009.

**Current cost values were calculated by multiplying values taken from the 2009 RPL with the inflation factor of 1.525276881. The inflation factor was calculated by using year-on-year medical inflation rates published by STATS SA from 2009 to 2015 [35]

♠1US$ = 11.73276 ZAR [36]

Table S2. Baseline costs

Unit	RPL code	Price (2015) in ZAR
Consultation	0192	344.87
HCV antibody	4531	198.74
HCV viral load	-	1579.50
HCV PCR	-	1271.10
HCV genotyping	-	1606.90
HBV sAg	4531	198.74
HBV sAb	4531	198.74
HBV core antibody (total)	4531	198.74
HIV-test (rapid)	4614	164.58
Western Blot	3969	999.97
HAV-immunity (HAV IgG)	4182	113.63
Thyroid function test	4484	508.68
Liver function test	4009	65.43
	4010	49.72
	4001	71.08
	4143	74.13
	4117	42.71
	4131	74.13
	3999	65.89
	4130	74.13
FBC (incl. 3739, 3762, 3783, 3785, 3791)	3755	143.99
	3797	30.81
Urea and electrolytes	4423	49.72
International normalized ratio	3805	82.36
Alpha fetoprotein	4522	170.37
Iron studies	4071	92.58
	4528	170.37
	4144	160.46
Liver biopsy (event)	1743	86653.00
Ultrasound liver	3627	678.75
Total for baseline		**96133.85**

FBC full blood count, *IgG* immunoglobulin G, *HAV* hepatitis A virus, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *PCR* polymerase chain reaction , *sAb* serum antibody, *sAg* serum antigen

♣1US$ = 11.73276 ZAR [36]

Table S3(a). Costs associated with CHC (without cirrhosis) during treatment

Standard of care: First cycle					Sofosbuvir-based regimens: First cycle				
Unit	*RPL code*	*Price (ZAR)*	*Interval*	*Total cost (ZAR)*	*Unit*	*RPL code*	*Price (ZAR)*	*Interval*	*Total cost (ZAR)*
Consultation	0190	344.87	9 times	3103.79	**Consultation**	0190	344.87	5 times	1724.35
LFT	4009	65.43	10 times	654.34	**LFT**	4009	65.43	4 times	261.74
	4010	49.72		497.24		4010	49.72		198.90
	4001	71.08		710.78		4001	71.08		284.31
	4143	74.13		741.28		4143	74.13		296.51
	4117	42.71		427.08		4117	42.71		170.83
	4131	74.13		741.28		4131	74.13		296.51
	3999	65.89		658.92		3999	65.89		263.57
	4130	74.13		741.28		4130	74.13		296.51
FBC	3755	143.99	10 times	1439.86	**FBC**	3755	143.99	4 times	575.94
	3797	30.81		308.11		3797	30.81		123.24
U&E	4423	49.72	10 times	497.24	**U&E**	4423	49.72	4 times	198.90
INR	4071	92.58	10 times	925.84	**INR**	4071	92.58	4 times	370.34
	3805	82.36		823.65		3805	82.36		329.46
Viral load		1579.50	4 times	6318.00	**Viral load**		1579.5	3 times	4738.50
Total monitoring cost (SOC)				18588.70	**Total monitoring cost (SOF-TT)**				10129.62
					Total monitoring cost (SOF/LDV) ***(LFT, FBC, U&E and INR only 3 times, only 4 consultations)***				8868.05
Drug treatment: Female (≤75kg)					**Drug treatment: Female (≤75kg)**				
					Sofosbuvir 400 mg	SOF	82129.32	84 tabs	82129.32
					Sofosbuvir/ledipasvir 400/90	SOF/LDV	123190.48	84 tabs	123190.48
Copegus 200mg	RBV	425.37/42	1680 tabs	17014.80	Copegus 200 mg	RBV	425.37/42	420 tabs	4253.70
Pegasus 180ug	PEG-INF	3668.69	48 inj	176097.12	Pegasus 180 ug	PEG-INF	3668.69	12 inj	44024.28
Total cost of drug treatment: SOC (females)				193111.92	**Total cost of drug treatment: SOF-TT (females)**				130407.30
					Total cost of drug treatment: SOF/LDV (females)				123190.48

Drug treatment: Males (>75kg)					**Drug treatment: Males (>75kg)**				
					Sofosbuvir 400 mg	SOF	82129.32	84 tabs	82129.32
					Sofosbuvir/ledipasvir 400/90	SOF/LDV	123190.48	84 tabs	123190.48
Copegus 200mg	RBV	425.37/42	2016 tabs	20417.76	Copegus 200mg	RBV	425.37/42	504 tabs	5104.44
Pegasus 180ug	PEG-INF	3668.69	48 inj	176097.12	Pegasus 180ug	PEG-INF	3668.69	12 inj	44024.28
Total cost for drug treatment: SOC (males)				196514.88	**Total cost for drug treatment: SOF-TT (males)**				131258.04
					Total cost for drug treatment: SOF/LDV (males)				123190.48
Weighted average drug cost for males and females				194983.55	**Weighted average drug cost for males and females (SOF-TT)**				130875.21
TOTAL ANNUAL TREATMENT COST (SOC):				213572.25	**TOTAL ANNUAL TREATMENT COST (SOF-TT):**				141004.82
					TOTAL ANNUAL TREATMENT COST (SOF/LDV):				132062.03

LFT, FBC, U&E, INR: SOC @ weeks 2,4,8,12,16,20,24,32,40,48; SOF@ weeks 2,4,8,12. Viral load: SOC @ weeks 4 (RVR), 12 (EVR), 48 (EOT) and 24 weeks post treatment (SVR); SOF @ weeks 4, 12 and 12 weeks after treatment (SVR). Hepatologist consultations: SOC: 1,2,4,8,12,16,20,24,48; SOF @ weeks 1,2,4,8,12.

FBC full blood count, *LFT* liver function test, INR = international normalized ratio; PEG-INF = pegylated-interferon; RBV = ribavirin; SOC = standard of care; SOF = sofosbuvir; U&E = urea & electrolytes. RVR = rapid virologic response; EVR = early virologic response; EOT = end of treatment; SVR = sustained virologic response

*1US$ = 11.73276 ZAR [36]

Table S3(b). Costs associated with compensated cirrhosis during treatment

Standard of care: First cycle					Sofosbuvir-based regimes: First cycle				
Unit	*Code*	*Price (ZAR)*	*Interval*	*Total (ZAR)*	*Unit*	*Code*	*Price (ZAR)*	*Interval*	*Total (ZAR)*
Consultation	0190	344.87	9 times	3103.79	**Consultation**	0190	344.87	5 times	1724.35
LFT	4009	65.43	13 times	850.65	**LFT**	4009	65.43	4 times	261.74
	4010	49.72		646.41		4010	49.72		198.90
	4001	71.08		924.01		4001	71.08		284.31
	4117	42.71		555.20		4117	42.71		170.83
	4143	74.13		963.67		4143	74.13		296.51
	4131	74.13		963.67		4131	74.13		296.51
	4130	74.13		963.67		4130	74.13		296.51
	3999	65.89		856.60		3999	65.89		263.57
FBC & Diff count	3755	143.99	13 times	1871.82	**FBC & Diff count**	3755	143.99	4 times	575.94
	3797	30.81		400.54		3797	30.81		123.24
U&E	4423	49.72	13 times	646.41	**U&E**	4423	49.72	4 times	198.90
INR	4071	92.58		1203.60	**INR**	4071	92.58	4 times	370.34
	3805	82.36		1070.74		3805	82.36		329.46
Viral load		1579.50	4 times	6318.00	**Viral load**		1579.50	3 times	4738.50
Total monitoring cost (SOC)				21338.77	**Total monitoring cost (SOF-TT)**				10129.62
					Total monitoring cost (SOF/LDV) ***(LFT, FBC, U&E and INR only 3 times, only 4 consultations)***				8868.05
Drug treatment: Female (≤75kg)					**Drug treatment: Female (≤75kg)**				
					Sofosbuvir 400 mg	SOF	82129.32	84 tabs	82129.32
					Sofosbuvir/ledipasvir 400/90	SOF/LDV	123190.48	84 tabs	123190.48
Copegus 200mg	RBV	425.37/42	1680 tabs	17014.80	Copegus 200 mg	RBV	425.37/42	420 tabs	4253.70
Pegasus 180ug	peg-INF	3668.69/inj	48 inj	176097.12	Pegasus 180 ug	peg-INF	3668.69/inj.	12 inj	44024.28
Total cost of drug treatment: SOC (females)				193111.92	**Total cost of drug treatment : SOF-TT (females)**				130407.30
					Total cost of drug treatment: SOF/LDV (females)				127444.68

Drug treatment: Males (>75kg)					**Drug treatment: Males (>75kg)**				
					Sofosbuvir 400 mg	SOF	82129.32	84 tabs	82129.32
					Sofosbuvir/ledipasvir 400/90	SOF/LDV	123190.48	84 tabs	123190.48
Copegus 200mg	RBV	425.37/42	2016 tablets	20417.76	Copegus 200 mg	RBV	425.37/42	504 tabs	5104.44
Pegasus 180ug	PEG-INF	3668.69/inj.	48 injections	176097.12	Pegasus 180 ug	PEG-INF	3668.69/inj.	12 inj	44024.28
Total cost of drug treatment: SOC (males)				196514.88	**Total cost of drug treatment: SOF-TT (males)**				131258.04
					Total cost of drug treatment: SOF/LDV (males)				128298.42
Weighted average drug cost for males and females				194983.55	**Weighted average drug cost for males and females (SOF-TT)**				130875.21
					Weighted average drug cost for males and females (SOF/LDV)				127914.24
TOTAL ANNUAL TREATMENT COST: SOC				216322.32	**TOTAL ANNUAL TREATMENT COST: SOF-TT**				141004.82
					TOTAL ANNUAL TREATMENT COST: SOF/LDV				136782.29

LFT, FBC, U&E, INR: SOC @ weeks 2,4,8,12,16,20,24,28,32,36,40,44,48; SOF@ weeks 2,4,8,12. Viral load: SOC @ weeks 4 (RVR), 12 (EVR), 48 (EOT) and 24 weeks post treatment (SVR); SOF @ weeks 4, 12 & 12 weeks after treatment (SVR). Hepatologist consultations: SOC: 1,2,4,8,12,16,20,24,48; SOF @ weeks 1,2,4,8,12. *FBC* full blood count, *LFT* liver function test, *INR* international normalized ratio, *PEG-INF* pegylated-interferon, *RBV* ribavirin, *SOC* standard of care, *SOF* sofosbuvir, *U&E* urea & electrolytes, *RVR* rapid virologic response, *EVR* early virologic response, *EOT* end of treatment, *SVR* sustained virologic response

Table S3(c). Costs associated with early termination of SOC

Chronic hepatitis C without cirrhosis				**Compensated cirrhosis**			
Drug costs	*Unit cost*[♣] *(ZAR)*	*Number of units*	*Total (ZAR)*	**Drug costs**	*Unit cost (ZAR)*	*Number of units*	*Total (ZAR)*
RBV (≤75 kg, males)	10.13 / tab	504	5104.44	RBV (≤75 kg, males)	10.13 / tab	504	5104.44
RBV (>75kg, females)	10.13 / tab	420	4253.70	RBV (>75kg, females)	10.13 / tab	420	4253.70
peg-INF	3668.69 / inj	12	44024.28	peg-INF	3668.69 / inj	12	44024.28
Total drug cost (males)			49128.72	*Total drug cost (males)*			49128.72
Total drug cost (females)			48277.98	*Total drug cost (females)*			48277.98
Weighted average cost of drugs			48745.89	**Weighted average cost of drugs**			48745.89
Monitoring costs	**Cost for 48 weeks**		**12 weeks**	**Monitoring costs**	**Cost for 48 weeks**		**12 weeks**
	18588.70		12392.47		21338.77		14225.85
Total treatment cost			61138.35	**Total treatment cost**			62971.74

[♣]Unit price of RBV was calculated as the price of a single 200mg tablet, based on the pack price of Copegus® 200mg @ R425.37 per 42 tablets. Unit price of peg-INF was taken as the price of a single 180ug injection @ R3668.69 per pre-filled syringe. Number of units of RBV for 12 week period was calculated based on patient weight: ≤75 kg, 1000mg per day; >75 kg, 1200 mg per day

Table S4(a). Monitoring costs of CHC (without cirrhosis) after treatment failed

Standard of care: Subsequent cycles					**Sofosbuvir-based regimens: Subsequent cycles**				
Unit	*RPL code*	*Interval*	*Price (ZAR)*	*Total (ZAR)*	*Unit*	*RPL code*	*Interval*	*Price (ZAR)*	*Total (ZAR)*
LFT,FBC, U&E, INR	-	6 monthly	916.69	1833.38	**LFT, FBC, U&E, INR**	-	6 monthly	916.69	1833.38
AFP	4522	6 monthly	170.37	340.75	**AFP**	4522	6 monthly	170.37	340.75
Annual cost of CHC *(No treatment)*				2174.13	**Annual cost of CHC** *(No treatment)*				2174.13

AFP alpha fetoprotein, *FBC* full blood count, *LFT* liver function test, *INR* international normalized ratio, *U&E* urea & electrolytes

Table S4(b). Monitoring costs of compensated cirrhosis after treatment failed

Standard of care: Subsequent cycles					**Sofosbuvir-based regimens: Subsequent cycles**				
Unit	*RPL code*	*Interval*	*Price (ZAR)*	*Total (ZAR)*	*Unit*	*RPL code*	*Interval*	*Price (ZAR)*	*Total (ZAR)*
LFT, FBC, U&E, INR	-	4 monthly	916.69	2750.07	**LFT, FBC, U&E, INR**	-	4 monthly	916.69	2750.07
AFP	4522	4 monthly	170.37	511.12	**AFP**	4522	4 monthly	170.37	511.12
Abdominal US	3627	6 monthly	678.75	1357.50	**Abdominal US**	3627	6 monthly	678.75	1357.50
Annual cost of compensated cirrhosis *(No treatment)*				4618.69	**Annual cost of compensated cirrhosis** *(No treatment)*				4618.69

AFP alpha fetoprotein, *FBC* full blood count, *LFT* liver function test, *INR* international normalized ratio, *U&E* urea & electrolytes, *US* ultrasound

Table S5. Costs associated with SVR with cirrhosis: HCC screening using abdominal ultrasound and alpha fetoprotein

Unit	RPL code	Interval	Annual cost (ZAR) *(twelve monthly screening)*	Annual cost (ZAR) *(six monthly screening)*
Abdominal ultrasound	3627	6-12 monthly	678.75	1357.50
Alpha fetoprotein	4522	6-12 monthly	170.37	340.74
Total cost per annum			849.12	1698.24

Table S6. Cost of decompensated cirrhosis

	Average annual cost per event	Proportion of decompensated patients	Average annual cost *x* proportion
Ascites	69625.00	0.62	43168.00
Variceal bleed	131151.00	0.28	36722.00
Hepatic encephalopathy	226825.00	0.1	22683.00
Total cost of decompensated cirrhosis			102572.22

3.3 Manuscript 2

Article title: Public health impact of sofosbuvir-based regimens for chronic hepatitis C virus infection in South Africa

Running heading: Public health impact of sofosbuvir in South Africa

Authors:

I Fraser[1] *BPharm, MPharm*, JR Burger[1] *MPharm, PhD*, MS Lubbe[1] *MPharm, PhD*, MW Sonderup[2] *MBChB, FCP(SA), MMed* & MP Stander[3] *MBChB, MBA*

Affiliation:

[1]Medicine Usage in South Africa (MUSA), North-West University (Potchefstroom campus), Potchefstroom, South Africa

[2]Senior Specialist and Lecturer in Department of Medicine and Division of Hepatology, University of Cape Town and Groote Schuur Hospital

[3]Researcher: HEXOR (Pty) Ltd, Midrand, Johannesburg, South Africa

Word count (Abstract):

259

Word count (Text):

3107

Title: Public health impact of sofosbuvir-based regimens for chronic hepatitis C virus infection in South Africa

Running heading: Public health impact of sofosbuvir-based regimens in South Africa

Authors:

I Fraser[1] *BPharm, MPharm*, JR Burger[1] *MPharm, PhD*, MS Lubbe[1] *MPharm, PhD*, MW Sonderup[2] *MBChB, FCP(SA), MMed* & MP Stander[3] *MBChB, MBA*

Affiliation:

[1]Niche area: Medicine Usage in South Africa (MUSA), North-West University (Potchefstroom campus), Potchefstroom, South Africa

[2]Senior Specialist and Lecturer in Department of Medicine and Division of Hepatology, University of Cape Town and Groote Schuur Hospital

[3]Researcher: HEXOR (Pty) Ltd, Midrand, Johannesburg, South Africa

Corresponding Author:

Burger, Johanita

Mailing address: Private Bag x6001, North-West University, Potchefstroom Campus, Potchefstroom, South Africa, 2520

Degrees: BPharm, MPharm (Pharmacy Practice), PhD (Pharmacy Practice)

Phone: +27 18 299 2285

Fax: +27 87 231 4105

E-mail address: Johanita.Burger@nwu.ac.za

Abstract

Objective: The future public health burden of chronic hepatitis C viral (HCV) infection could be mitigated by antiviral therapy, especially when taking into the account the recent revolution in antiviral drugs for the treatment of HCV. The aim of this study was to project the impact of the use of sofosbuvir-based regimens in South African patients with chronic hepatitis C (CHC) on the size of the HCV-infected population, as well as on the number of cases of HCV-related mortality. *Study design:* Decision-analytic Markov model. *Methods:* A dynamic population Markov model of CHC patients in South Africa was constructed to assess the impact of sofosbuvir-based regimens on the future burden of CHC. Data was derived from published literature. *Results:* If South African patients with CHC were treated with sofosbuvir-based regimen instead of the current standard of care, and policy-makers and physicians were to scale up active treatment of CHC to at least 10% of all diagnosed non-cirrhotic CHC patients annually, a total of 203 cases of decompensated cirrhosis, 145 cases of hepatocellular carcinoma and 188 liver-related deaths in could be avoided over the next two decades. *Conclusions:* The current treatment paradigm in South Africa is inadequate to control the HCV disease burden. Increased treatment and/or more efficient therapies are necessary to keep the number of HCV infected patients with advanced liver diseases and liver-related deaths from growing. With cure rates of >90%, sofosbuvir-based regimens have to potential to significantly reduce risks for HCV-related morbidity and mortality in the long term, provided that we treat enough patients early in the disease.

Keywords

Sofosbuvir, hepatitis C virus (HCV), public health impact

Introduction

Chronic hepatitis C (CHC) is a highly prevalent infectious disease, affecting approximately 150 million people worldwide.[1] As many as 350,000 hepatitis C-related deaths occur annually due to hepatic decompensation and/or the development of hepatocellular carcinoma (HCC).[2-4] Once dominated by the human immunodeficiency virus (HIV), the hepatitis C virus (HCV) has come to be recognised as a global epidemic which poses major public health challenges with long-term economic and social consequences, especially in low-and middle income countries.[5,6]

CHC is, amongst other viral hepatitides, an often neglected problem in many parts of Africa. Unawareness, together with issues relating to poverty, socio-economic depravation and access to medical care, contribute to reduced opportunity for patients to receive a clinical assessment and treatment for CHC.[7] Efficacy of treatments for HCV is rapidly improving and new treatments have demonstrated efficacy rates >90%,[8] though, from a public health perspective, these treatment advances are unlikely to have a major impact — particularly in developing countries where recognition of infection and rates of treatment uptake among diagnosed patients are insufficient to control the HCV disease burden. [9]

In South Africa (SA), public awareness, political drive and access to preventative services are far too low.[10] Diagnosis and treatment for CHC remain largely inaccessible to many patients, as the current standard of care (SOC) — a combination of pegylated interferon (peg-INF) injected weekly and ribavarin (RBV) taken orally daily; both for a period of 48 weeks[11] — is lengthy and prohibitively expensive [around R195 000 (~US$16 620)[a] for 48 weeks of treatment].[13] CHC is also not a prescribed minimum benefit in SA,[14] meaning that most private health insurers do not pay for treatment, and those that do, only partially cover costs, leaving many private sector patients having to pay large amounts out of pocket to receive treatment.[15] Over and above the high cost of treatment, the peg-INF/RBV combination cures approximately only 50% of patients.[6,16] The oral direct-acting antiviral (DAA), sofosbuvir (SOF), significantly increases treatment success in CHC patients.[17] One of the most advanced DAAs to date, SOF has been proven to not only cure more patients with CHC than current treatments, but does so in a shorter period of time.[18] SOF in combination with peg-INF and daily weight based RBV (SOF triple therapy / SOF-TT) for 12 weeks is the only HCV treatment regimen that has been included in the EASL (European Association for the Study of the Liver) and AASLD (American Association for the Study of Liver Disease) guidelines for all six HCV genotypes,[19,20]whereas the fixed-dose combination of SOF and ledipasvir (LPV) in a single tablet for 12 weeks is the preferred interferon-free regimen for genotypes 1 and 4-6.[19] SOF and SOF/LDV is yet to be registered in SA, however, considering the potential for near universal curability with SOF-based regimens and the human and societal costs associated with untreated CHC, a pre-emptive and strategic response to public health is necessary to eradicate HCV-related morbidity and mortality.[21] We believe that the public health impact of the current treatment paradigm of antiviral therapy for CHC in SA may be limited, as much by under-utilisation as by the inherent limitations in the current SOC. Failure of third-party payers in SA (both in the public and private healthcare sectors) to control CHC may have significant implications for the future public health burden of HCV infection, not to mention for imminent costs to health and welfare budgets.

[a]1USD = 11.73276ZAR.[12]

The aim of this study was to project the impact of the use of sofosbuvir-based regimens in South African patients with chronic HCV infection on the size of the HCV-infected population, as well as on the number of cases of advanced liver-disease and liver-related deaths, compared to the current SOC.

Methods

We constructed a dynamic population Markov model of patients with CHC in SA to estimate the impact of sofosbuvir-based regimens on the future burden of HCV. The model was based on a previously developed decision-analytic Markov model of the natural history of HCV infection and progression toward advanced liver disease.[22] We adapted the previous model to represent the HCV-infected population in SA. Health states included in the disease-progression model were: i) new infections; ii) undiagnosed viremic infections; iii) diagnosed CHC (treatment naïve); iv) diagnosed CHC (treatment failed); v) compensated cirrhosis; vi) decompensated cirrhosis; vii) HCC; viii) SVR; ix) liver-related death, and x) non liver-related death. The model started with the annual number of new infections that progressed to chronic HCV infection. The progression of new cases along with all cases of current chronic HCV infections was followed for twenty annual cycles. During this time the population could change in size due to new infections, or due to patients being removed from the cohort because of death from liver disease or other causes, as shown in **Figure 1.**

<<Insert Figure 1>>

Fig. 1 — Simplified structure of Markov model representing HCV-infected population in South Africa

We simulated two treatment scenarios in our model: i) treatment with SOC; and ii) treatment with sofosbuvir-based regimens. For the purpose of this study, only patients who have been positively diagnosed with CHC and who have a METAVIR[b] score of ≥F1 were eligible to receive treatment. Fibrosis ≤F1 was excluded from our model as the existing HCV management guidelines prioritises treatment for patients with ≥F2 fibrosis due to resource constraints[11]. The primary efficacy measure used in the model was sustained virologic response[c] (SVR)[24]. The most prevalent genotype in SA is genotype 5, accounting for 36% of all confirmed HCV cases, followed by 1b (22%), 3a (11.7%) and 4 (8.91%). Genotype 2 accounts for less than 2% of HCV infections in SA.[25] The EASL guidelines recommend SOF-TT as the first treatment option for genotypes 1 and 3-6, and SOF/LDV as an interferon-free option for genotypes 1 and 4-6.[19] The overall SVR rate of SOF + peg-INF/RBV is 89% in patients with genotypes 1, 4, 5 and 6.[17] The overall SVR rate for SOF/LDV for patients with genotypes 1 and 4-6 is 95%.[26-31] Because not all patients with HCV in SA will be eligible for treatment with SOF-TT or SOF/LDV, respectively, patients who received SOF-based regimens were assumed to be treated with either daily SOF/LDV (400 mg/90 mg); or daily sofosbuvir (400 mg) and weight-based RBV with 180 μg peg-INF weekly, each for 12 weeks[19,20]. We assumed an average SVR rate of 92% (across all genotypes) for patients in the SOF arm of our model. Patients in the SOC arm received weekly peg-INF and daily weight-

[b] The Metavir scoring system is a scoring method used for measuring the degree of liver inflammation and staging of fibrosis in patients with hepatitis C. It uses a grading and a staging system where the grade indicates the amount of inflammation and the stage represents the amount of fibrosis or scarring[23]

[c] Sustained virologic response (SVR); defined as the clearance of HCV RNA from the blood and persistent normalisation of serum alanine transaminase (ALT) levels, 12 weeks and 24 weeks after completion of treatment with SOF and SOC respectively[24]

based RBV for a period of 48 weeks[11]. Patients were assumed to complete only one course of treatment before achieving SVR and patients who achieved SVR were assumed to maintain SVR and experience no further disease progression until their death. Patients who failed to achieve SVR returned to the diagnosed CHC (treatment failed) state where they could follow one of three different paths in each cycle, based on their transition probabilities: a) continue in the same health state without suffering from any event; b) progress to the next health state in the natural history model, or c) die of non-liver related causes. Death from other causes (non liver-related) was possible from all health states, whereas liver-related mortality was only possible from decompensated and HCC states. Every patient who survived each one year cycle received one life year gained (LYG). The primary endpoint of the model was the number of cases of advance liver-disease and number of liver-related deaths projected to be prevented by SOF-based regimens *vs.* SOC over the next two decades. The model cycle length was one year, and discounting was performed at a rate of 5%. TreeAge Pro Healthcare (2014 software)[32] was used for model creation and analysis. The model structure, inputs and assumptions were validated by independent South African clinical hepatologists.

Input data and model assumptions

Table 1 lists all model parameters.

<<Insert Table 1>>

Prevalence and incidence

Our baseline prevalence and incidence were based on the results of a recent study reporting on the current and future disease burden of HCV in SA.[33] We assumed a baseline viremic prevalence of 0.77%, and a baseline incidence of 6 940 new infections per year. Approximately 55 500 patients in SA currently have diagnosed CHC and the annual diagnosis rate is 0.7%. For our model, we assumed that the annual number of new infections and newly diagnosed cases remained unchanged from the last reported year.[33]

Number of patients treated for hepatitis C

Reports indicate that 100 patients were treated for CHC in SA in 2011.[41] Assuming that only patients who have been diagnosed can receive treatment, and that the number of treated patients remained constant after the last reported year; we calculated the annual treatment rate for CHC in SA as 0.18%.[33]

Treatment efficacy

Clinical inputs, including treatment efficacy and treatment duration were based on published results of randomized controlled trials (RCTs). SVR rates and dosing and administration data of SOF-TT were based on the results of the NEUTRINO clinical trial and the 2015 EASL guidelines.[17,19] SVR rates for SOF/LDV were based on ION-1, ION-2, ION-3, and SYNERGY trials, as well as the open-label study conducted by Abergel *et al*.[26-31] Treatment efficacy of SOC was based on pooled results from the BERNAR-1 and BERNAR-2 RCTs.[40] To be consistent with current guidelines, we applied the 12 week stopping rule to patients who received SOC *viz.* patients who achieved EVR by week 12 completed the full 48 week treatment period and patients who did not achieve EVR stopped treatment after 12 weeks.[42]

Transition probabilities and background mortality

The annual transition probabilities for progressing from one disease state to the next as well as the probabilities for HCV-related death were derived from literature and are shown in **Table 1.** Sex- and age-specific mortality rates from causes other than HCV were taken from the Actuarial Society of South Africa (ASSA) HIV demographic model: 2008 version.[39]

Results

Results from the base case analysis are presented in **Table 2.** It shows the estimated burden of HCV in SA after two decades, assuming that we continue to treat only 0.18% of diagnosed CHC patients every year either with SOC or SOF-based regimens, respectively, compared to the current estimated burden of HCV (as reported by Hatzakis *et al*. in 2015).[33]

<<Insert Table 2>>

An often referenced concept about efforts to address the HIV/AIDS burden is the "treatment cascade". The development of the HIV treatment cascade has been a valuable tool to help clinicians, public health officials and advocates visualise the state of HIV testing, and active linkage in care to initiation of treatment. Based on available data, we developed a treatment cascade of the current HCV situation in SA[33] **(Figure 2).**

<<Insert Figure 2>>

Fig. 2 — Current and future treatment cascade of HCV in South Africa based on current treatment protocol

Based on current estimates, only 1% of all diagnosed HCV-patients, or 0.025% of the total population with chronic HCV infection in SA are currently receiving treatment. From the results of the base case analysis it is evident that, assuming we continue to treat only 0.18% of all diagnosed patients every year for the next 20 years, the South African HCV treatment cascade will not look much different by 2035, irrespective of the treatment option chosen. These results show that, even though the total number of viremic infections is estimated to decrease over the next two decades, cases of advanced liver disease will continue to rise over the next two decades, with a ~32% increase in the number of HCC cases and a ~39% increase in decompensated cirrhosis cases, irrespective of the treatment option chosen. Results also show an increase of 58.5% in the number of liver-related deaths from 1 550 in 2015 to ~2 458 in 2035. These estimates highlight the noticeable gaps in HCV awareness, screening and treatment.

Impact of sofosbuvir on future burden of disease

The total number of cases of HCV-related complications and deaths over the next two decades are shown in **Table 3.**

<<Insert Table 3>>

From these results it is clear that treating 0.18% of all diagnosed patients per year is not sufficient to show any benefit of using sofosbuvir over the current SOC. However, if policy-makers and physicians were to aim to scale up active treatment of HCV to at least 10% of all diagnosed non-cirrhotic CHC patients annually — assuming that newly diagnosed patients are also eligible for treatment — the impact of antiviral therapy on chronic HCV-infections and the added benefit of treating patients with sofosbuvir instead of the current SOC becomes visible **(Table 3).** By treating at least 10% of all diagnosed non-cirrhotic CHC patients annually for the next 20 years with SOF-based regimens, the number of cases of decompensated cirrhosis, HCC and liver-related deaths saved will increase twelve-fold over SOC. Furthermore, as shown in **Figure 3**, the incidence of new cases will start to decline faster, reducing the increase in liver-related morbidity and mortality with 5%.

<<Insert Figure 3>>

Fig. 3 — Incidence of new cases of decompensated cirrhosis, HCC and liver-related death

As demonstrated by **Figure 4**, the annual treatment rate will increase from 0.025% to 0.65% over the next two decades if policy-makers were to actively scale up HCV treatment. Furthermore, opting to treat patients with SOF-based regimens instead of SOC, will almost double the annual percentage of patients who achieve SVR; curing 0.60% of the total HCV infected population compared to 0.36% if practitioners continue to treat patients with SOC.

<<Insert Figure 4>>

Fig. 4 — Future HCV-treatment cascade assuming proposed treatment protocol: standard of care (SOC) *vs.* sofosbuvir-based regimens (SOF)

Discussion

Liver-related morbidity and mortality in South Africa is estimated to rise over the next two decades. According to a panel of experts, an estimated 100 patients were treated for HCV in 2011.[41] In this analysis, we assumed that the future treatment paradigm will remain the same as in the last reported year. If this assumption is correct, the public health impact of anti-HCV drugs in South Africa is limited. Treating approximately 100 patients a year, or 0.18% of all diagnosed CHC patients, is not enough to adequately control the HCV population and prevent complications and deaths due to chronic HCV infection. Our results also show that a cohort of ~100 treated patients per year is too small to demonstrate any meaningful benefit of using SOF-based regimens over the current SOC. However, if policy-makers and physicians were to aim to scale up active treatment of HCV to at least 10% of all diagnosed non-cirrhotic CHC patients annually, i.e. ~1,000 – 1,500 patients per year, the impact of antiviral therapy on chronic HCV-infections is more demonstrable. Furthermore, if policy-makers were to decide to treat patients with SOF-based regimens instead of SOC, a total of 203 cases of decompensated cirrhosis, 145 cases of HCC and 188 liver-related deaths could be avoided over the next two decades. These numbers seem low, but considering the considerable costs associated with treating decompensated cirrhosis and HCC, this could have a significant impact on health-care budgets in the long term.

This is further compounded when taking into account that liver-transplant, which could cost up to a total of R6.8 million (~US$580 000), may be necessary.[43] A recent study modelling the cost-effectiveness of SOF-based regimens for HCV patients in South Africa showed that the use of SOF/LDV or SOF-TT in a hypothetical cohort of 10 000 patients infected with HCV genotype-5 resulted in a reduction of 71% and 93% respectively in the number of cases of decompensated cirrhosis, HCC and liver-related death compared to the current standard of care, given that all 10 000 patients receive treatment.[22] This reduction in HCV-related morbidity and mortality in patients treated with SOF-based regimens is the result of an increased SVR rate in these patients; treating patients with SOF/LDV produced an overall SVR rate of 93.8%, and SOF-TT produced an overall SVR rate of 88.5%, compared to an overall SVR rate of 52.3% in patients treated with SOC. Results from our current model and our previous study unequivocally demonstrate that the use of SOF-based regimens for patients chronically infected with HCV improves health outcomes and reduces HCV-related morbidity and mortality compared with current standard of care.

There are certain limitations that could influence the outcomes from this study. In the absence of South African-specific data, our model was largely populated with data from international published literature. We focused on systematic reviews for clinical inputs such as annual transition probabilities, however, it is possible that disease progression may vary depending on factors such as genotype, a patient's gender, race, other comorbidities or alcohol consumption[34]; which we did not accounted for in this model. Treatment efficacy was furthermore based on clinical trial data, which does not necessarily represent a real-world environment. Real-world SVR rates and patient adherence associated with the modelled treatment regimens may be substantially lower, or the frequency and severity of side-effects may be higher than reported in clinical trial settings. Since sufficient real-world data to fully populate the model is unavailable, we could not account for concerns relating to variances between clinical trial and real-world safety and efficacy. Because neither SOF nor SOF/LDV is registered in SA yet, we can't say for certain which drug (if either) will be the preferred regimen in SA for each genotype. Therefore, we assumed an average SVR rate for the sofosbuvir-based treatment arm in our model, based on the average SVR rates of SOF-TT and SOF/LDV for the most prevalent genotypes in SA. We also did not take HIV status into account as a potential confounder of treatment efficacy although data to date suggests that HIV co-infected patients respond in a similar fashion to HCV mono-infected patients with the new HCV therapies. Other limitations to this study are the assumptions that the number of new of HCV will remain constant over the next 20 years and that there will be enough diagnosed patients to receive treatment. While higher numbers of annual new infections could result in a higher total number of infections in the future, insufficient numbers of diagnosed patients could limit the county's ability to treat, and consequently control our HCV population.

In conclusion, even though the total number of HCV infections in South Africa is expected to decline, HCV-related morbidity and mortality is expected to increase as the population ages and patients with chronic infection progress to more advanced liver-disease. The current treatment paradigm in South Africa is insufficient to control the HCV disease burden and this failure of policy-makers to control hepatitis disease could have great significance for future costs to health and welfare budgets. Increased treatment and/or higher efficacy therapies are needed to keep the number of HCV infected patients with advanced liver diseases and liver related deaths from increasing. Our results have shown that sofosbuvir-based regimens not only has to potential to cure almost

twice as many patients with chronic HCV infection, but also significantly reduce risks for HCV-related morbidity and mortality in the long term, provided that we treat enough patients early in the disease. However, unless policy makers in South Africa adopt proven public health strategies to actively identify those infected, ensure appropriate diagnosis and treatment, and provide comprehensive follow-up and support, the individual and public health benefits of curative therapies such as sofosbuvir will fail to materialize.

Acknowledgements

The authors thank Margreet Bergh for assistance with model construction and analysis.

Ethical approval

North-West University Health Research Ethics Committee [NWU-00035-15-A1].

Funding

I Fraser received funding from HEXOR (Pty) Ltd and the North-West University. The views expressed in this manuscript are solely those of the authors and do not necessarily reflect the decisions or stated policy of HEXOR or the North-West University.

Competing interests

None declared.

Disclosure of potential conflicts of interest

Dr Sonderup has declared that he has received speaker fees from Gilead Pty (Ltd). As an employer of HEXOR (Pty) Ltd, Dr Stander has received consultation fees from Gilead Pty (Ltd). HEXOR (Pty) Ltd also received funding from Gilead Pty (Ltd) for this study. All other authors declare they have no conflict of interest.

References

1 Lavanchy D. Evolving epidemiology of hepatitis C virus. *Clin Microbiol Infect* 2011;**17**:107–15.

2 WHO (World Health Organization). Hepatitis C fact sheet N˚164. 2013. Available at: http://www.who.int/mediacentre/factsheets/fs164/en/ Accessed: 9 Dec. 2013.

3 Khayrihhay MH, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 2013;**57**:1333-42.

4 Maasoumy B, Wedemeyer H. Natural history of acute and chronic hepatitis C. *Best Pract Res Clin Gastroenterol* 2012;**26**:401-12.

5 Dinner K, Donaldson T, Potts J, Sirna J, Wong T. Hepatitis C: a public health perspective and related implications for physicians. *Royal College Outlook* 2005;**2**:20-2.

6 Gravitz L. A smouldering public-health crisis. *Nature* 2011;**474**:S2-4.

7 Cooper CL, Mills E, Wabwire BO, Ford N, Olupot-Olupot, P. Chronic viral hepatitis may diminish the gains of HIV antiretroviral therapy in sub-Saharan Africa. *Int J Infect Dis* 2009;**13**:302-6.

8 National Center for Pharmacoeconomics (NCPE Ireland). Cost effectiveness of sofosbuvir (in combination with either ribavirin or pegylated interferon + ribavirin) (Sovaldi®) for the treatment of hepatitis C infection. 2014. Available at: http://www.ncpe.ie/wp-content/uploads/2014/03/Summary-Report-for-Sofosbuvir-Sovaldi-For-website1.pdf Accessed: 18 Jun. 2015.

9 Thomas DL. Global control of hepatitis C: where challenge meets opportunity. *Nat Med* 2013;**19**:8508.

10 Open Society Institute (OSI). War on drugs: report of the Global Commission on Drug Policy. 2011. Available at: http://www.refworld.org/docid/4e3250d32.html Accessed: 23 Jul. 2015.

11 Botha JF, Kassianides C, Schneider HR, Song E, Spearman W, van der Merwe SW. South African hepatitis C management guidelines 2010. Available at: http://www.sages.co.za/images/hcvjfb.pdf. Accessed: 12 Dec 2014.

12 OANDA currency converter. Average exchange rate for the first quarter of 2015. 2015. Available at: http://www.oanda.com/currency/converter/ Accessed: 3 May 2015.

13 Ford N, Singh K, Cooke GS, Mills EJ, Von Schoen-Angerer T, Kamarulzaman A, et al. Expanding access to treatment for hepatitis C in resource-limited settings: lessons From HIV/AIDS. *Clin Inf Dis* 2012;**Mar**:1-8.

14 South Africa. 1998. Medical Schemes Act 131 of 1998.

15 Sonderup M, Spearman W, Geffen N. 2011. When the private health sector falls short: Discovery Health and its failure to adequately cover hepatitis B and C. Available at: http://www.quackdown.info/article/when-private-health-sector-falls-short/ Accessed: 29 Aug. 2014.

16 Dillon J. Management of hepatitis C. *Prim Health Care* 2007;**17**:25-9.

17 Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *New Engl J Med* 2013;**368**:33-44.

18 FDA (U.S. Food and Drug Administration). Approval of Sovaldi (sofosbuvir) tablets for the treatment of chronic hepatitis C. 2013. Available at: http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/ucm377920.htm Accessed: 2 Aug. 2014.

19 European Association for the Study of the Liver (EASL). EASL Recommendations on Treatment of Hepatitis C 2015. *J Hepatol* 2015;**63**:199–236.

20 American Association for the Study of Liver Diseases (AASLD). Summary of recommendations for patients who are initiating therapy for HCV infection by HCV genotype. 2015. Available at: http://www.hcvguidelines.org/printpdf/full-report/initial-treatment-box-summary-recommendations-patients-who-are-initiating-therapy-hcv Accessed: 28 Aug. 2015.

21 Krajden M, Montaner JSG. The curability of hepatitis C: implications for a public health response. *BC Med J* 2013;**55**:243.

22 Fraser I, Burger JR, Lubbe MS, Dranitsaris G, Sonderup MW, Stander MP. Cost-effectiveness modeling of sofosbuvir-containing regimens for chronic genotype 5 hepatitis C virus infection in South Africa. *Pharmacoeconomics* [In press].

23 Franciscus A. HCV Diagnostic Tools: grading & staging a liver biopsy. Available at: http://hcvadvocate.org/hepatitis/factsheets_pdf/grade_stage.pdf Accessed: 2 Mar. 2015.

24 Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. *Clin Infect Dis* 2011;**52**:889-900.

25 Prabdial-Sing N, Puren A, Schoub B. The status of hepatitis C – the silent "volcano" in South Africa. *Euro Surveill* 2013;**11**(1):22-5.

26 Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014;**370**:1889-98.

27 Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014;**370**:1483-93.

28 Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 2014;**370**:1879-88.

29 Kapoor R, Kohli A, Sidharthan S, Sims Z, Petersen TL, Osinusi A, et al. All-oral treatment for genotype 4 chronic hepatitis C infection with sofosbuvir and ledipasvir: interim results from the NIAID SYNERGY trial. *Hepatology* 2014;**60**:321A.

30 Gane EJ, Hyland RH, An D, Svarovskaia ES, Pang PS, Symonds WT, et al. High efficacy of LDV/SOF regimens for 12 weeks for patients with HCV genotype 3 or 6 infection. *Hepatology* 2014;**60**:1274A.

31 Abergel A, Loustaud-Ratti V, Metivier S, Jiang D, Kersey K, Knox SJ, et al. Ledipasvir/Sofosbuvir for the treatment of patients with chronic genotype 4 or 5 HCV infection. Paper presented at The International Liver Congress 2015: 50th annual meeting of the European association for the Study of the Liver (EASL), Vienna, Austria; April 22-26. Available at: http://natap.org/2015/EASL/EASL_80.htm Accessed: 21 Aug. 2015.

32 TreeAge Pro 2014, R1.2.TreeAge Software, Williamstown, MA; software available at http://www.treeage.com.

33 Hatzakis A, Chulanov V, Gadano AC, Bergin C, Ben-Ari Z, Mossong J, et al. The present and future disease burden of hepatitis C virus (HCV) infections with today's treatment paradigm – volume 2. *J Viral Hepat* 2015;**22**:26-45.

34 Thein HH, Krahn M, Kaldor JM, Dore GJ. Estimation of utilities for chronic hepatitis C from SF-36 scores. *Am J Gastroenterol* 2005;**100**:643-51.

35 Alawazi W, Cunningham M, Dearden J, Foster GR. Systematic review: outcome of compensated cirrhosis due to chronic hepatitis C infection. *Alim Pharmacol Ther* 2013;**32**:344-55.

36 Sweeting M, De Angelis D, Neal KR, Ramsay ME, Irving W, Wright M, et al. Estimated progression rates in three United Kingdom hepatitis C cohorts differed according to method of recruitment. *J Clin Epidemiol* 2006;**59**:144–52.

37 Saab S, Hunt D, Stone M, McClune A, Tong M. Timing of hepatitis C antiviral therapy in patients with advanced liver disease: a decision analysis model. *Liver Transpl* 2010;**16**:748–59.

38 Hutchinson S, Bird S, Goldberg D. Modeling the current and future disease burden of hepatitis C among injection drug users in Scotland. *Hepatology* 2005;**42**:711–23.

39 Actuarial Society of South Africa. Actuarial Society of South Africa HIV demographic model 2008 version. 2008. Available at: http://aids.actuarialsociety.org.za/Models-3145.htm Accessed: 1 Feb 2015.

40 D'Heygere F, George C, Van Vlierberghe H, Decaestecker J, Nakad A, Adler M, et al. Efficacy of interferon-based antiviral therapy in patients with chronic hepatitis C infected with genotype 5: a meta-analysis of two large prospective clinical trials. *J Med Virol* 2011;**83**:815-9.

41 Saraswat V, Norris S, de Knegt RJ, Sanchez Avila JF, Sonderup M, Zuckerman E, et al. Historical epidemiology of hepatitis C virus (HCV) in select countries – volume 2. *J Viral Hepat* 2015;**22**:6-25.

42 Ghany MG, Strader DB, Thomas DL, Seeff LB. American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009;**49**:1335-74.

43 United Network for Organ Sharing (UNOS). Transplant Living. 2015. Available at: http://www.transplantliving.org/before-the-transplant/financing-a-transplant/the-costs/ Accessed: 10 Aug. 2015.

Table 1 — Model parameters

Parameter	Base Case		Reference
Current estimated burden of HCV in South Africa			
Country's population	51,000,000		[33]
Total viremic infections	393,800		[33]
New infections	6,940		[33]
Diagnosed viremic			
Total cases	55,500		[33]
Annual newly diagnosed	2,600		[33]
Newly diagnosed rate	0.7%		[33]
Treatment rate	0.18% of total diagnosed cases		
HCV natural history	Annual probability	Range	
CHC → cirrhosis[a]	0.011	(0.005 – 0.018)	[34]
Cirrhosis → decompensated cirrhosis	0.064	(0.030 – 0.070)	[35]
Cirrhosis → HCC	0.036	(0.015 – 0.040)	[35]
Decompensated cirrhosis → HCC	0.068	(0.041 – 0.099)	[36,37]
Decomp. cirrhosis → liver-related death	0.168	(0.120 – 0.400)	[38]
HCC → liver-related death	0.605	(0.300 – 0.800)	[38]
Mortality unrelated to HCV			[39]
Effectiveness of treatment (Probability of SVR)			
Standard of care (peg-INF/RBV)	55%	(0.45 – 0.65)	[40]
Sofosbuvir-based regimens	92%	(0.89 – 0.99)	[31]

CHC, chronic hepatitis C; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; peg-INF, pegylated-interferon; RBV, ribavirin; SOC, standard of care; SOF, sofosbuvir; SVR, sustained virologic response

[a]Annual probability of CHC to cirrhosis was calculated from assumed probability of 20% over 20 years

Table 2 — Estimated burden of hepatitis C virus infection in South Africa.

	Current estimated cases	Estimated number of cases in 2035[a]	
		SOC	SOF-based
Total viremic infections	393 800	290 368	290 325
Total diagnosed cases	55 500	72 211	72 168
Undiagnosed viremic infections	338 300	218 157	218 157
Diagnosed CHC (Treatment naïve)	9 380	37 857	37 853
Compensated cirrhosis	39 700	25 558	25 527
Decompensated cirrhosis	4 810	6 667	6 661
HCC	1 610	2 129	2 127
Prescribed HCV treatment	100	127	124
Achieved SVR	56	72	114

CHC, chronic hepatitis C; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SOF, sofosbuvir; SOC, standard of care; SVR, sustained virologic response

[a]Estimated future burden of HCV assuming that we continue to treat 0.18% of diagnosed patients per year, with SOC or SOF-based regimens respectively

Table 3 — Total number of cases of decompensated cirrhosis, HCC and liver-related deaths by 2035.

	Current protocol		Proposed protocol	
	SOC	SOF-based	SOC	SOF-based
Decompensated cirrhosis	42085	42070	41777	41574
Number of cases saved		15		203
HCC	34083	34071	33862	33717
Number of cases saved		12		145
Liver-related deaths	57917	57901	57633	57445
Number of cases saved		16		188

HCC, hepatocellular carcinoma; SOF, sofosbuvir; SOC, standard of care

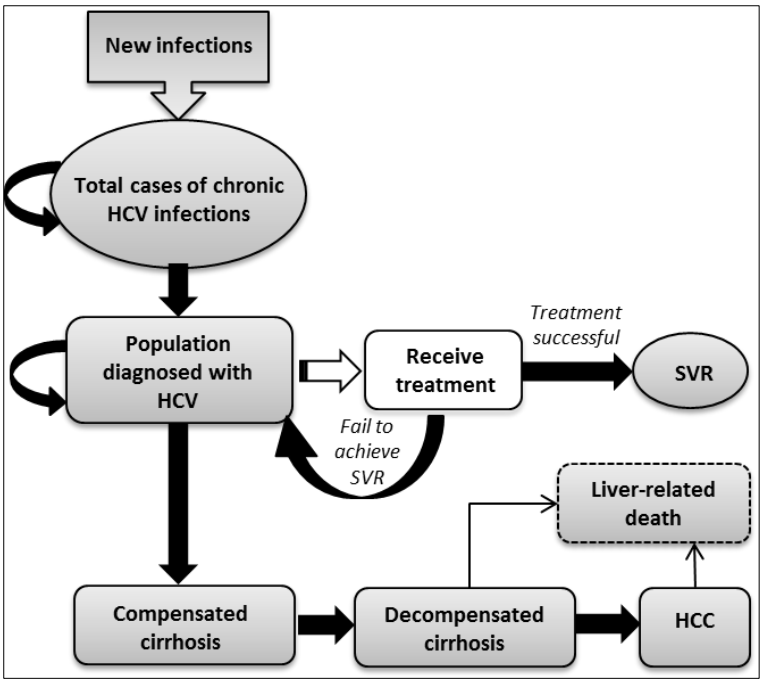


Fig.1 — Simplified structure of Markov model representing HCV infected population in South Africa. HCC, hepatocellular carcinoma; HCV, hepatitis C virus, SVR, sustained virologic response

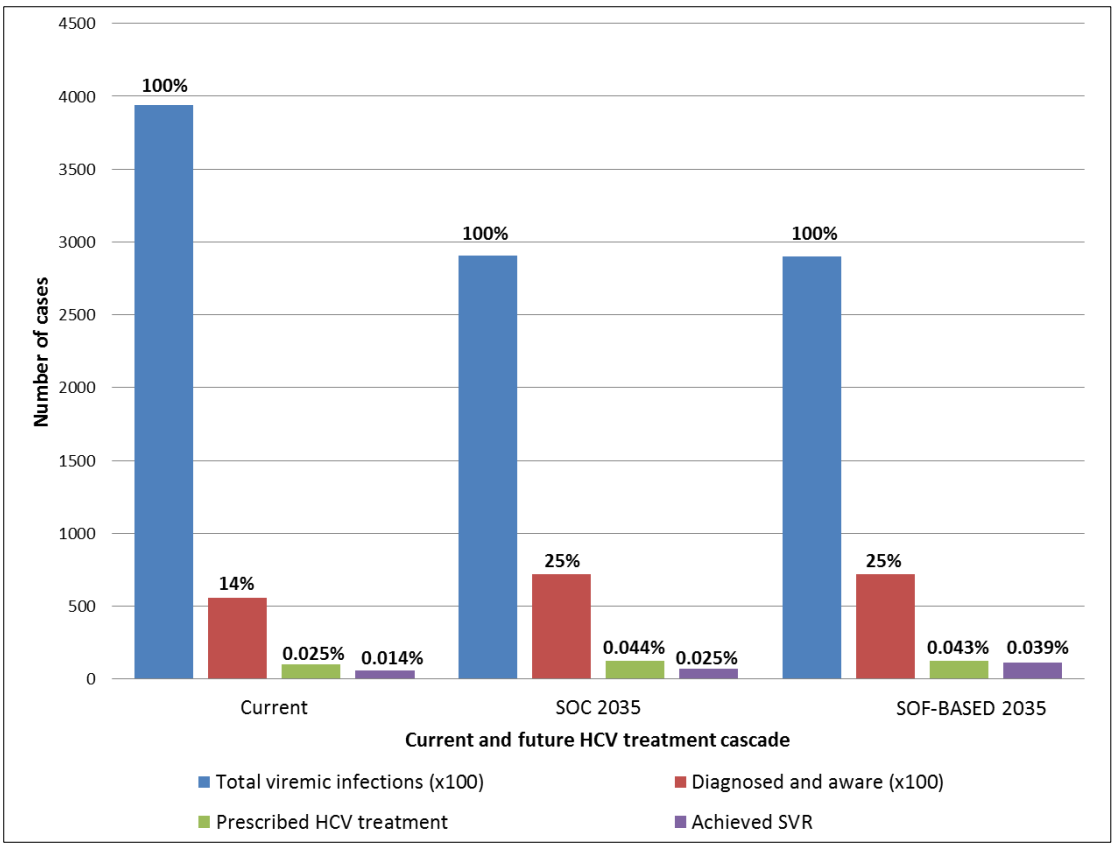


Fig. 2 — Current and future treatment cascade of HCV in South Africa, based on the current treatment paradigm. HCV, hepatitis C virus; SOC, standard of care; SOF, sofosbuvir; SVR, sustained virologic response

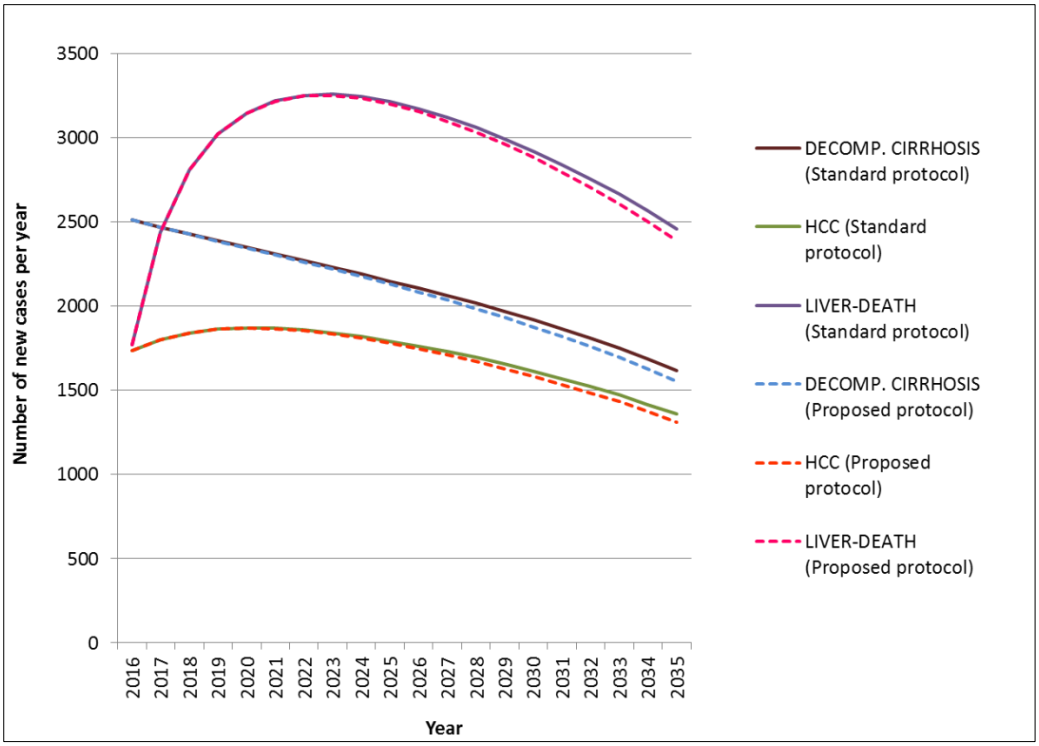


Fig. 3 — Incidence of new cases of decompensated cirrhosis, HCC and liver-related death. Decomp, decompensated; HCC, hepatocellular carcinoma

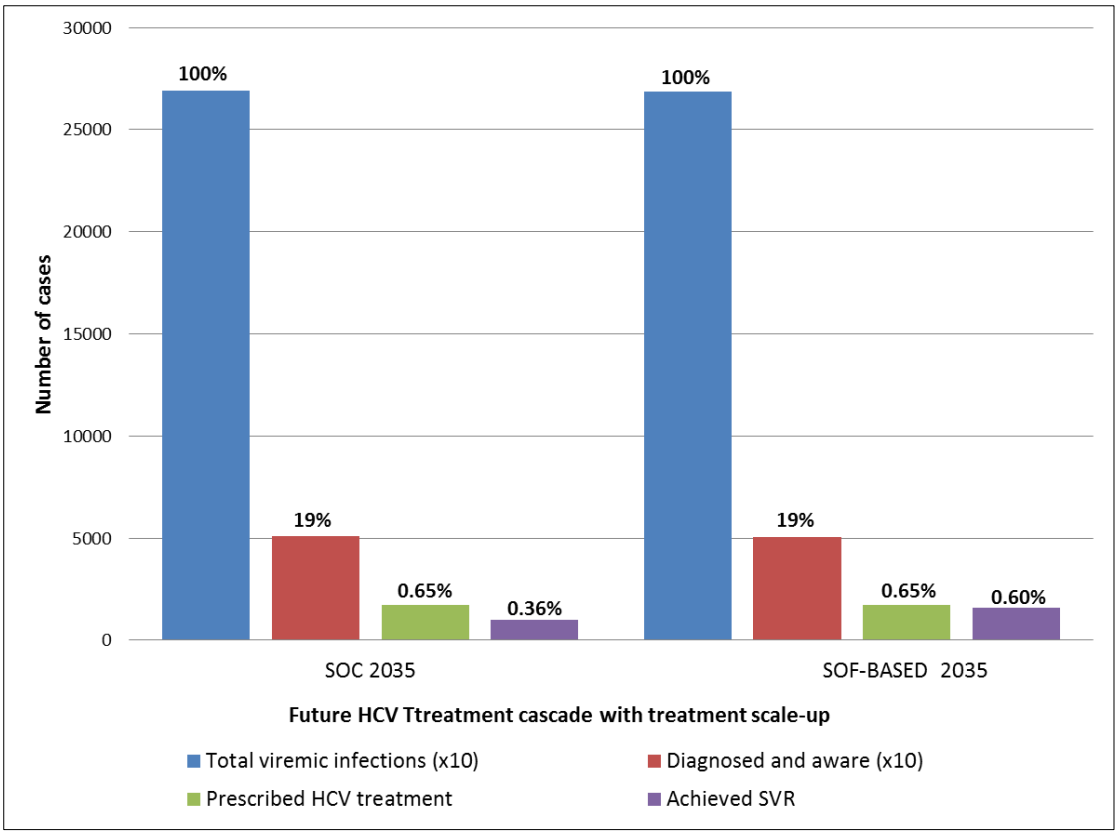


Fig. 4 —Future HCV-treatment cascade, assuming proposed treatment protocol: SOC *vs* SOF-based regimens. SOF, sofosbuvir; SOC, standard of care; SVR, sustained virologic response

3.4 Manuscript 3

Article title:

Budget impact analysis of sofosbuvir-based regimens for chronic hepatitis C virus infection in South Africa

Running heading: Budget impact of sofosbuvir-based regimens in South Africa

Authors:

I Fraser[1] *BPharm, MPharm*, JR Burger[1] *BPharm, MPharm, PhD*, MS Lubbe[1] *BPharm, MPharm &* MP Stander[2] *MBChB, MBA*

Affiliation:

[1]Medicine Usage in South Africa (MUSA), North-West University (Potchefstroom campus), Potchefstroom, South Africa

[2]HEXOR (Pty) Ltd, Midrand, Johannesburg, South Africa

Word count (Abstract):

272

Word count (Text):

4951

Title: Budget impact of sofosbuvir-based regimens for chronic hepatitis C virus infection in South Africa

Running heading: Budget impact of sofosbuvir-based regimens in South Africa

Authors:

I Fraser[a] *BPharm, MPharm*, JR Burger[a] *MPharm, PhD*, MS Lubbe[a] *MPharm, PhD*, & MP Stander[b] *MBChB*

Affiliation:

[a]Niche area: Medicine Usage in South Africa (MUSA), North-West University (Potchefstroom campus), Potchefstroom, South Africa

[b]Researcher: HEXOR (Pty) Ltd, Block J, Central Park, 400 16th Road, Midrand, 1685, Johannesburg, South Africa

Corresponding Author:

Fraser, Ilanca

Mailing address: Medicine usage in South Africa (MUSA), Faculty of Health Sciences, North-West University, Potchefstroom Campus, Potchefstroom, South Africa, 2520

Degrees: BPharm, MPharm

Institution: North-West University, Potchefstroom Campus

Phone: +27 18 299 2285

Fax: +27 87 231 4105

E-mail address: ilancaroux@gmail.com

Word count (manuscript text): 4 951

INTRODUCTION

Chronic hepatitis C (CHC) causes significant morbidity and mortality and is globally one of the leading causes of cirrhosis, primary hepatocellular carcinoma and liver transplants.[1] In addition to being physically catastrophic, hepatitis C also represents a significant economic burden — as healthcare costs associated with the management of the long-term consequences of hepatitis C can be substantial.[2] In 2013, the World Health Organization described the global hepatitis C epidemic as a 'viral time bomb', which poses major public health, economic and social crises, particularly in low and middle income countries.[3] The clinical and economic impact of chronic hepatitis C virus (HCV) infection is expected to grow considerably over the next decade as the global population ages and a large number of individuals who acquired the virus in the 1960s through to the 1980s begin to develop advanced liver disease.[4] As these numbers continue to grow, effective treatment and care of HCV will become more crucial in addressing the financial implications currently associated with the disease. It is therefore essentialfor countries to estimate the resources required to implement planned hepatitis C prevention, screening, and treatment strategies and their expected health, societal, and financial benefits to mobilise domestic and international funding.[2]

South Africa currently has a two-tiered healthcare financing system, with a relatively large proportion of funding allocated through medical aid, various hospital care plans and out-of-pocket payments. The other 'non-contributory' portion is funded through the treasury from general taxes and is mainly for public sector users.[5] In 2013, 48.4% of the total health expenditure went towards the public health sector.[6] The South African constitution protects the rights of all its citizens, including access to health care. As public beneficiaries have no alternative service, government is obliged to fund and provide merely those services which are needed by the served population, at all levels of care, and cannot be used to subsidise frivolous health demands.[7] Some of the biggest challenges facing the health sector relate to the prevention and control of epidemics and the allocation of resources for healthcare.[8] According to the 2014/2015 healthcare budget, the South African Department of Health will continue to focus on increasing life expectancy and improving quality-of-life for South Africans through sustaining the expansion of the HIV/AIDS treatment and prevention programme, revitalising public health care facilities, and ensuring the provision of specialised tertiary hospital services over the medium term.[9] Spending on these three areas takes up 85.2% of the department's total budget over the medium term expenditure framework (MTEF) period. The primary cost drivers of the national healthcare budget are HIV and AIDS, followed by tuberculosis and maternal and child health. The proposed budget for these indicators, as published by the National Treasury, is R14.4 billion (US$1.23 billion)[a] for 2015/2016, R16 billion (US$1.36 billion) for 2016/2017 and R18 billion (US$1.53 billion) for 2017/2018 — a total of almost R50 billion over 3 years.[9] The importance of eradicating HIV/AIDS notwithstanding, management of the HIV/AIDS epidemic should not obscure the effects of other chronic disease epidemics on the health system such as alcohol abuse, and viral hepatitis.[8]

Recent advances and the continued development of new direct acting antivirals (DAAs) with greater cure rates have the potential to cure more than 90% of HCV infection and end the HCV epidemic. Of the recently

[a] 1USD = 11.73276ZAR [average exchange rate for first quarter of 2015]

developed DAAs, sofosbuvir has drawn the most attention, because it is the first new DAA that the FDA approved for the treatment of genotypes 1-4.[10] It is also the first DAA to be included in the EASL and AASLD guidelines for the treatment of all six HCV genotypes.[11,12] With cure rates and side effect profiles better than previously observed for hepatitis C, sofosbuvir have been hailed as a 'miracle cure'. Not only was sofosbuvir the first new DAA to be approved as part of an interferon-free regimen (for HCV genotypes 2 and 3), it was also the first DAA with proven efficacy for HCV genotype 5, the predominant genotype in South Africa (SA).[13] The addition of inhibitor sofosbuvir to the current standard of care (SOC) in South Africa, *viz.* the combination of pegylated interferon (peg-INF) and ribavirin (RBV),[14] increases the cure rate to >90% and shortens the treatment duration to 12 weeks.[13] Less than a year after the approval of sofosbuvir, an all-oral, fixed-dose combination of sofosbuvir and ledipasvir (LDV) was approved by the FDA for HCV.[15] For patients ineligible, intolerant or unwilling to take interferon-based regimens, this combination represents a significant advance. Moreover, the combination of sofosbuvir-ledipasvir has demonstrated SVR rates of >95% in genotypes 1 and 4-6 irrespective of cirrhosis status.[16-21] Given the potential for near universal HCV curability and the human and societal costs of untreated HCV, a strategic and proactive response is required to eradicate the HCV epidemic.[22]

Lessons learnt from the HIV/AIDS epidemic should be applied to stop HCV in its tracks — the first and most important of which is "treatment saves lives".[23] HIV treatment is a unique tool in the HIV/AIDS response, preventing illness and death, averting new infections and saving money. Overwhelming evidence indicates that rapidly scaling up quality-assured HIV treatment will prevent millions of people from dying, prevent millions of HIV transmissions, save money and lay the foundation for the end of the AIDS epidemic.[24] SA — which has the third highest HIV prevalence in the world — has made remarkable progress in the response to the AIDS epidemic in a short period of time. In response to the WHO treatment targets, the percentage of eligible adults and children receiving antiretroviral therapy increased from 58.3% to >85% from 2010 to 2013.[25] A new narrative on HIV treatment in the post-2015 era is nothing less than the end of the AIDS epidemic by 2030. The aim of the new 90-90-90 target for HIV treatment scale-up beyond 2015, established by UNAIDS, is that by 2020, 90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive antiretroviral therapy and that 90% of all people receiving antiretroviral therapy will have viral suppression.[26] This target is ambitious, but is believed to be achievable. The HCV burden in SA may not be as substantial as the HIV/AIDS burden, but the lessons learnt from our struggle with HIV should be applied in this instance — the issues are intrinsically the same and warrant no different a response. A 90-90-90 approach to HCV could potentially eradicate the epidemic by 2020, but engagement from government, civil society, donors, and policymakers is needed to generate political commitment, mobilise resources, and reduce diagnostic and medicine costs for HCV. The goal of this budget impact analysis was to estimate the financial consequences of adoption and diffusion of sofosbuvir-based regimens within the South African healthcare setting when aiming for the same 90-90-90 target by 2020.

We adopted the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) guidelines for developing the budget impact analysis (BIA),[27] and considered the perspective of the budget holder, which in this case is the South African government. Currently, there is no predetermined annual or projected future budget for HCV treatment and management in SA. In order to evaluate the budget impact of sofosbuvir-based

regimens, we first needed to determine the estimated expenditure on HCV treatment in SA based on the current treatment paradigm. HCV remains underdiagnosed and underreported in SA, and the total economic burden of the disease in unknown. However, a recent study estimated that in 2011, one hundred patients received CHC treatment in SA.[28] To estimate the annual and five-year cumulative budget for HCV in SA, we assumed that the number of treated patients have remained constant since 2011 and would remain constant until 2020. This was not meant to be a realistic scenario, but was rather a baseline to estimate the expenditure on HCV for the next five years, based on the current estimated treatment paradigm, and compare the impact of sofosbuvir-based therapy *viz.* sofosbuvir triple therapy (sofosbuvir in combination with peg-INF and RBV) or sofosbuvir-ledipasvir on this budget for HCV treatment in SA. This model also does not imply that the current treatment paradigm will remain stagnant. Instead, the scenarios shown represent how the current presumed annual budget would be impacted if we changed the treatment protocol of HCV from SOC to sofosbuvir-based regimens, and estimate the resources that would be required if we were to drastically scale up HCV treatment over the next five years in the same way as the 90-90-90 treatment target proposed for ending the HIV/AIDS epidemic *viz*. by 2020, 90% of all patients with HCV in SA should be diagnosed, 90% of all diagnosed patients should be treated and 90% of those treated should have sustained virologic response (SVR).

METHODS

We adapted a previously developed decision-analytic Markov-based model of the natural history of HCV infection and progression toward advanced liver disease. The model was previously described in detail.[29] In brief, the model consists of an initial decision tree — in which patients are eligible to receive treatment — and a state-transition Markov model to simulate the clinical course of patients with chronic HCV infection, and project patients' outcomes. Three treatment strategies were considered for this analysis: i) sofosbuvir-ledipasvir (SOF/LDV) monotherapy; ii) sofosbuvir triple therapy (SOF-TT); and iii) SOC (peg-INF + RBV). Health states included in this model were CHC without cirrhosis, compensated cirrhosis, decompensated cirrhosis, HCC, SVR, liver-related death and non-liver related death. For the purpose of this model, decompensated cirrhosis included ascites, esophageal varices and hepatic encephalopathy. **Figure 1** is a simplified illustration of the model.

<<Insert Figure 1>>

Figure 1. Simplified illustration of model. *CHC* chronic hepatitis C, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *SVR* sustained virologic response, *Tx* treatment

Base-case population

For the base case analysis, we considered a cohort of one hundred treatment-naive patients with chronic HCV infection residing in South Africa. Baseline characteristics for the target population were based on the patient demographics of a South African HCV cohort and are shown in **Table 1**. The cohort was characterised by age, sex and according to the presence/absence of cirrhosis.[30]

<<Insert Table 1>>

Antiviral treatment

We simulated three treatment scenarios in our model: i) treatment with SOF/LDV; ii) treatment with SOF-TT; and iii) treatment with SOC. To be consistent with current guidelines, we assumed a 12-week treatment period for SOF-TT and SOF/LDV and a 48 week treatment period for SOC, respectively.[13,14] Dosing and administration of both sofosbuvir-based regimens were based on published AASLD and EASL guidelines,[11,12] whereas dosing and administration of SOC was based on the current South African hepatitis C management guidelines.[14] In the decision-tree, patients in the first arm of the model received SOF/LDV, patients in the second arm received SOF-TT and patients in the third arm received SOC. Patients in the SOF/LDV arm without cirrhosis received a single tablet of SOF/LDV (400 mg / 90 mg) once a day for 12 weeks, whereas patients with cirrhosis received daily SOF/LDV plus daily weighted based RBV. Patients in the SOF-TT arm received 400 mg SOF orally, daily, along with daily weight based RBV and weekly peg-INF,[11,12] and patients in the SOC arm were assumed to receive daily RBV and 180 μg peg-INF weekly.[14] The primary efficacy measure used in the model was SVR, 12 weeks and 24 weeks after completion of treatment for sofosbuvir-based treatments and SOC respectively. We applied the 12-week stopping rule to patients who received SOC, *viz.* patients who achieve EVR by week 12 completed the full 48 week treatment period and patients who did not achieve EVR stopped treatment after 12 weeks.[38] In the absence of head-to-head trials, response rates for SOF-TT were taken from the NEUTRINO trial, the first sofosbuvir trial to involve all of the HCV genotypes, including HCV genotype 5, the predominant genotype in South Africa, whereas response rates for SOF/LDV were based on ION-1,[16,17] ION-2,[18] ION-3,[19] and SYNERGY[20] trials, as well as the open-label study conducted by Abergel *et al.* (2015) in France.[21] Response rates of SOC were based on the pooled results from the BERNAR-1 and BERNAR-2 RCT's.[37] SVR rates used in our model are shown in **Table 1**.

Natural history model

Following the decision-tree, we constructed a Markov model to simulate the natural history of HCV infection and progression toward advanced liver disease. The specific objectives of this analysis was firstly to estimate the total expenditure associated with treating and managing CHC in SA based on the current assumed protocol, and secondly, to estimate the required annual and cumulative budget to treat ~90% of all the patients diagnosed with HCV by 2020. The model started with the annual number of patients who receive HCV treatment. For the base case analysis, this was assumed to be 100 new patients each year for five annual cycles. At the beginning of each cycle, 100 new patients entered the model with a confirmed diagnosis of CHC and initiated treatment upon entering the model. For all treatment arms, the aim of treatment was SVR, and based on the efficacy rates of each treatment option modeled, treatment could either be successful (achieved SVR) or unsuccessful (failed to achieve SVR). Patients were assumed to complete only one course of treatment before achieving SVR. Patients who achieved SVR were assumed to maintain SVR and not experience further disease progression until they died, thus, we assumed that SVR eliminates the risk of progressive liver disease. Patients who did not achieve SVR were assumed to be at risk of progressive liver disease. Failure to achieve SVR after 12 weeks (sofosbuvir-based regimens) or 48 weeks (SOC) was considered as treatment failure. Patients who failed to achieve SVR could follow one of three different paths at the end of each one year cycle: i) continue in the same health state without suffering from any event; ii) die of non-liver related causes (all-cause mortality); or iii) progress to the next health state in the natural history model, based on their transition probabilities, irrespective

of the treatment option chosen. Due to a lack of data, retreatment, relapse or recurrence was not considered in this model. Patients who failed to achieve SVR moved between defined health states on an annual basis according to annual transition probabilities, based on best available evidence (**Table 1**). Non-liver death could occur from any state and was calculated by applying age- and sex-specific rates of mortality, calculated as a multiple of the mortality in the general population of the same sex for a specific age.[36] Liver-related death was only possible from decompensated cirrhosis and HCC states. TreeAge Pro Healthcare, 2014 software[39], was used for model creation and analysis. The model structure, inputs and assumptions were validated by independent clinical hepatologists. After five cycles were complete, the model yielded an average lifetime cost for each treatment strategy which we used to perform the budget impact analysis.

Data sources

Transition probabilities and background mortality

Annual transition probabilities for progressing from one disease state to the next were derived from literature.[31-35] Base-case values and ranges are shown in **Table 1.** Probabilities for HCV-related death were also taken from literature, whereas sex- and age-specific mortality rates from causes other than HCV were taken from the Actuarial Society of South Africa (ASSA) HIV demographic model: 2008 version.[36]

Medical costs

Costs used in this model are shown in **Table 2**. Following recommendations of the ISPOR BIA Good Practice Task Force,[27] we considered all direct disease costs associated with chronic HCV infection to estimate the budget impact of sofosbuvir-based regimens, including diagnostic costs, drug regimen, treatment monitoring and health state (downstream liver-disease complications). Monitoring costs and recommended follow-up of patients were based on typical South African management of HCV and was confirmed by independent South African hepatologists.

<<Insert Table 2>>

In addition to receiving drug-treatment, all patients underwent baseline testing and diagnoses upon entering the model. Patients in both arms of the model acquired a once-off cost for pathology (including HCV antibody, HCV PCR & viral load, HCV genotyping, HBV sAg, HBV sAb, HBV core antibody (total), HIV-test (rapid and Western Blot technique), HAV-immunity (HAV IgG), TFT, LFT, FBC, U&E, INR, AFP and iron studies, abdominal ultrasound)[b], the cost of a liver biopsy and the cost of a consultation with a specialist (hepatologist), irrespective of the treatment option chosen. Costs of laboratory tests, radiological examination and consultations were based on the prices in the Referencing Price List (RPL), and were calculated according to specified monitoring resource use.[40] The latest RPL values (2009) were inflated using published annual medical inflation numbers from Statistic South Africa (STATS SA) and total monitoring costs over the treatment period were aggregated from calculated totals.[41] Drug costs included the costs of peg-INF, RBV, sofosbuvir and

[b] PCR = polymerase chain reaction, HBV sAg = hepatitis B virus serum antigen, HCV sAb = hepatitis B virus serum antibody, HIV = human immunodeficiency virus, HAV IgG = hepatitis A virus immunoglobulin G, TFT = thyroid function test, LFT = liver function tests, FBC = full blood count, U&E = urea and electrolytes, INR = international normalised ratio, AFP = alpha fetoprotein

SOF/LDV, and drug regimen costs were based on unit drug costs, indicated drug dosing and therapy duration. Unit prices of peg-INF and RBV were taken from the Official Pharmaceutical Bluebook.[42] The medicine price used to populate the model was a composite of single exit price (SEP), value added tax (VAT) and the prescribed professional dispensing fee. The total cost of drug treatment and total monitoring costs were added to calculate a total annual treatment cost for cirrhotic and non-cirrhotic patients in each treatment arm. Patients who failed to achieve SVR continued to receive costs associated with follow-up and advanced disease states. All costs were converted to a 2015 baseline by using published annual medical inflation numbers from STATS SA (STATS SA, 2009 – 2015) and expressed in South African Rand (ZAR) and United States Dollars (US$).

In the United States, sofosbuvir and SOF/LDV have been priced at US$84,000 (~R985,552) and US$94,500 (~R1,108,746) for a 12-week course, respectively. Sofosbuvir and SOF/LDV is yet to be registered in SA and the price at which these drugs will be made available in this country have not been formalised. However, SA is included in the list of countries for distribution of the generic version of sofosbuvir and SOF/LDV, and it will almost certainly be able to have access to the drug at a lower price.[43,44] Indications are that South Africa will be benchmarked with the BRICS countries[45] and hence we predicted that sofosbuvir will be sold at a cost of R82,129.32 (US$7,000) for a 12-week course in SA, the same price as agreed in Brazil[46], and SOF/LDV will be sold at a price of R123,193 (US$10,500) for 12 weeks. A recent cost-effectiveness analysis of sofosbuvir-containing regimens for HCV genotype 5 infection in South Africa showed that at a price of R123,193, SOF/LDV dominates (i.e. is less costly and more effective), SOF-TT and SOC. At a price of R82,129.32 for 12 weeks, sofosbuvir is less cost-effective than SOF/LDV, but still dominates the current SOC[29]. This cost-effectiveness analysis, however, does not provide the impact of new therapies on payers' budgets.

RESULTS

Results from the base case analysis are presented in **Table 3**. Table 3 shows a breakdown of the estimated expenditure on HCV in SA over the next five years, assuming that we treat 100 new patients with chronic HCV infection each year with the SOC, SOF-TT or SOF/LDV, respectively.

<<Insert Table 3>>

According to our analysis, the annual budget required to actively treat and monitor 100 new CHC patients in SA with the current SOC, and to follow-up those who failed treatment is approximately R29 000 000 (US$2 471 712). The estimated cumulative cost over five years is estimated at R145 104 298 (US$12 367 448). The base case analysis also shows the incremental budget impact if we changed the treatment protocol from SOC to either of the sofosbuvir-based regimes. The required budget for treating 100 patients with SOF/LDV or SOF-TT, would be between ~R22 900 000 (US$1 951 800) and ~R23 800 000 (US$2 028 508) per year, or R114 220 546 (US$9 735 181) and R118 765 505 (US$10 122 555) over five years for SOF/LDV and SOF-TT, respectively. The incremental budget impact for treating patients with SOF/LDV or SOF-TT instead of SOC, is roughly between -R5 000 000 (-US$426 157) and -R6 000 000 (US$511 389) per year, or -R26 338 793 (US$2 244 893) and -R30 883 752 (US$2 632 267) over five years, which represents a significant cost-saving over SOC. Without increasing the HCV budget, but changing the current treatment

protocol from SOC to SOF-based regimens, the cost-saving awarded by sofosbuvir-based regimes would allow an additional 22 to 28 CHC patients to receive treatment with SOF-TT or SOF/LDV, per year.

In order to estimate the resources that would be required if we were to drastically scale up HCV treatment over the next five years in the same way as the 90-90-90 treatment target proposed the HIV/AIDS epidemic, we first need to estimate the number of patients with HCV infection that should be treated by 2020. The exact prevalence of HCV in South Africa is currently unknown. However, a recent study estimated the total number of viremic infections at 393 800.[28] If we were to achieve to diagnose at least 90% of the current estimated infections and treat 90% of those diagnosed by 2020, we need to treat 318 978 patients over the next five years. Figure 2 shows the proposed approach to scaling up treatment over the next five years to reach this target.

<<Insert Figure 2>>

Figure 2. Number of patients needed to treat per year to reach target by 2020

In order to reach 318 978 treated patients by 2020, the number of patients treated per year needs to be drastically scaled up from the current protocol; from 100 to over 10 000 in the first year, and thereafter doubling the number of patients annually over the next four years **(Figure 2)**. Assuming the proposed scale-up approach as presented in Figure 2, we estimated the annual costs and the cumulative costs needed to reach this target by 2020. These costs are presented in Table 4.

<<Insert Table 4>>

Table 4 shows that the initial cost to scale-up treatment from 100 to ~10 000 per year, using sofosbuvir-based therapies instead of SOC, would increase the budget for HCV from an estimated R29 million per annum to >R2 billion. Thereafter, the annual budget would need to be doubled each year over the next four years, reaching a total of between R37.5 billion and R39 billion (~US$3 billion) in 2020. In order to reach a 90-90-90 target, *viz.* treat at least 90% of all patients diagnosed with chronic HCV infection in SA with SOF-TT, a total of R75.7 billion (US$6 billion) would need to be budgeted for HCV over the next five years. Opting to treat patients with SOF/LDV instead of SOF-TT would save almost R3 billion (US$256 million) over five years.

DISCUSSION

We have previously reported on the economic impact of the new treatment modalities that are available for the treatment of HCV[29]. In the latter study we showed that the use of sofosbuvir-based regimens were dominant economic strategies compared to SOC, *viz.* it had increased efficacy at a lower cost. In considering the financial impact of adopting sofosbuvir-based regimens as a treatment strategy in SA, we considered three treatment options. We have estimated the total average cost for SOF/LDV, SOF-TT (for 12 weeks) and SOC (response guided therapy). As a framework for our analysis, we considered two strategies.

Firstly we looked at a status quo strategy where a limited number of patients are treated with different treatment regimens. Secondly we attempted to draw from the lessons learnt from the global response to combating the HIV epidemic. Specifically we attempted to adopt a 90:90:90 strategy with the goal to eradicate HCV and stop transmission and to quantify what monetary resources will be required to implement this strategy.

Our results demonstrate that therapy with the fixed-dose combination of SOF/LDV or SOF-TT, respectively, is notably less costly than response-guided therapy with SOC. The incremental cost-savings are between R5 million and R6 million (~US$426 000 – US$511 000). These savings can primarily be ascribed to shortened treatment duration with sofosbuvir-based regimens (12 weeks compared to 48 weeks with SOC). Even though sofosbuvir is more costly than peg-INF and RBV [(R82 129 (US$7 000) for 12 weeks *vs.* R44 000 (US$3 750) for peg-INF and R4 200 – R5 100 (~US$400) for RBV for 12 weeks)], the addition of sofosbuvir to peg-INF/RBV reduces the treatment duration by 75%, consequently eliminating the costs associated with 36 weeks of peg-INF/RBV —which in itself is still a costly combination. Our results also suggest that 12 weeks with SOF-TT is more costly than 12 weeks with SOF/LDV. This is because SOF/LDV offers further cost-savings over SOF-TT as, even though it has the higher unit cost than sofosbuvir [R 1467 (US$125) *vs.* R978 (US$83)], it can be used without peg-INF/RBV in most patients. The observed cost-savings between sofosbuvir-based regimens and SOC can also be explained by the differing rates with which costs are accumulated under the different treatments: costs associated with clinical monitoring and follow-up of sofosbuvir-based regimens are relatively small [(R8 869 (US$756) – R10 130 (US$863) per patient per year] compared with the costs of SOC (R17 709 or US$1 509 per patient per year), and thus have little relative impact on total average cost estimates. Furthermore, because of the increased efficacy of sofosbuvir-based regimens, there is a significant reduction in the number of patients who require follow-up after treatment failure and who consequently progress to more advanced stages of liver disease. The costs associated with monitoring patients who have failed treatment and the costs of managing advance liver disease, including decompensated cirrhosis and hepatocellular carcinoma, is reduced by >88% when patients are treated with SOF/LDV instead of SOC. These results clearly demonstrate that savings awarded by sofosbuvir-based regimens will open up access to care to at least 127 patients over a 5 year period without any additional financial resource investment.

In a growing number of countries, the foundations for ending the AIDS epidemic are being established by scaling up HIV treatment, combined with expanding access to other essential programmatic activities.[9] HIV/AIDS is the primary cost driver of the South African national healthcare budget.[9] The consolidated nominal (national and provincial) health HIV and AIDS spending in South Africa was estimated at R10 billion in 2012/2013; R11.7 billion in 2013/2014 and R13.6 billion in 2014/2015. The budget for HIV/AIDS in 2015/2016 is estimated to be R15.3 billion.[47] In nominal terms, the consolidated government budget allocated for 2013/2014 was R1.05 trillion and is expected to grow to R1.23 trillion in 2015/2016. The consolidated national and provincial health budget was R133.3 billion in 2013/2014 and is estimated to grow further in real terms by 3% in 2014/15. This indicates, that year-on-year, for the 2013/14 – 2015/16 medium term, the consolidated health budget receives an annual average share of 11.3% as a share of total consolidated government. Interestingly the consolidated national and provincial health HIV/AIDS allocations grow from year to year as part of the consolidated health expenditure, from 8.8% in 2013/2014 and 10% in 2015/2016,

despite the slow growth of the overall health share in the total national expenditure.[47] The consolidated health HIV/AIDS spending also grows as a share in the consolidated government budget, from 0.95 per cent in 2012/2013 to 1.15% in 2015/2016. These figures indicate the health HIV and AIDS allocations are increasing in the budget, which should be accompanied by increasing health budget resources overall.

Hopes for ending the HCV epidemic will depend in large measure on the South African government's ability to provide HCV treatment to all who need it. Considering the significant budget allocations toward HIV/AIDS, drastically scaling up HCV treatment does not seem out of reach. To put the results of our analysis into perspective, the proposed budget for HCV for 2015/2016 (~R2.4 billion) represents a share of 1.7% of the total healthcare budget (R137.3 billion), compared to 10% for HIV/AIDS, and 15.7% of the total budget allocated for HIV/AIDS (R15.3 billion). Depending on the per cent increase in the consolidated health budget over the next five years, spending on HCV could represent approximately 3%, 6%, 12% and 24% of the total healthcare budget from 2016/2017 – 2019/2010, when treatment is scaled up according the values shown in Table 4. In order for the South African government to continue the HIV/AIDS treatment scale up and also adopt a drastic approach to scaling up HCV treatment in South Africa, more resources need to be sourced to increase the general health budget. Investments in the HCV-sector from development partners, private healthcare sector and the public sector itself can help to strengthen the health sector generally, and calls for constant monitoring to guarantee effective and efficient prevention of new HCV-infections and mitigation of the impact of HCV amongst those already affected by the disease.

Limitations

Our study has several limitations. Firstly, the current budget of HCV was estimated based on the assumption that only 100 patients receive treatment each year. This could be significantly more, which would impact on the overall budget and the number of additional patients reported to gain access to treatment in the case of a strategy stage. Secondly, the BIA assumed that SA would access sofosbuvir and SOF/LDV at the same prices reported for Brazil. However, these prices have not been confirmed for SA, and further reductions in prices could significantly impact the results of our analysis. The BIA did not take into account health-system costs that might be necessary to implement a strategy toward a 90-90-90 treatment scale-up, or the impact of such a drastic scale-up on the South African health system, in particular, human resources. Further research is necessary to address these shortcomings.

CONCLUSION

The use of sofosbuvir-based regimens therapies could substantially reduce HCV-related complications and might be cost-effective in the majority of patients with CHC in SA. However, treating all treatment-eligible patients in SA would have a significant budgetary impact on both private and government providers, and additional resources are needed to manage this epidemic.

REFERENCES

1 Blachier M, Leleu H, Peck-Radosavljevic M. The burden of liver disease in Europe: a review of available epidemiological data. European Association for the Study of the Liver 2013. Available from http://www.easl.eu/medias/EASLimg/Discover/EU/54ae845caec619f_file.pdf

2 The Economist Intelligence Unit. The silent pandemic: tackling hepatitis C with policy innovation. 2012. Available from https://www.janssen.ie/sites/stage-janssen-ie.emea.cl.datapipe.net.pdf

3 Open Society Institute (OSI). War on drugs: report of the Global Commission on Drug Policy. 2011. Available from http://www.refworld.org/docid/4e3250d32.html

4 McHutchison JG, Bacon BR. Chronic Hepatitis C: an age wave of disease burden. Am J Manag Care 2005;11:S286-S295.

5 Archer, C. The role of private specialists in an NHI system. 2013. Available form http://www.hsf.org.za/siteworkspace/cms-news-march-2013-nhi-final-website-1.pdf

6 The World Bank. 2013. Health expenditure, public (% of total health expenditure). 2013. Available from http://data.worldbank.org/indicator/SH.XPD.PUBL/countries

7 Van den Heever A. Strategic health reform and "National Health Insurance" Available from http://www.hsf.org.za/siteworkspace/cms-news-march-2013-nhi-final-website-1.pdf

8 Harrison D. An overview of health and health care in South Africa 1994 – 2010: priorities, progress and prospects for new gains. 2009. Available from http://ftp.bhfglobal.com/files/bhf/overview1994-2010.pdf

9 The National Treasury. Estimates of National Expenditure. 2015. Available from http://www.treasury.gov.za/documents/national%20budget/2015/ene/FullENE.pdf

10 Leof A, Gerrity M, Thielke A, King V. Sofosbuvir for the treatment of hepatitis C and evaluation of the 2014 American Association for the Study of Liver Diseases treatment guidelines. 2014. Portland.

11 European Association for the Study of the Liver (EASL). EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatology. 2015;63:199–236.

12 American Association for the Study of Liver Diseases (AASLD). Summary of recommendations for patients who are initiating therapy for HCV infection by HCV genotype. 2015. Available from http://www.hcvguidelines.org/printpdf/full-report/initial-treatment-box-summary-recommendations-patients-who-are-initiating-therapy-hcv

13 Lawitz E, Mangia A, Wyles D, Rodriguez-Torres, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. New Eng J Med. 2014;368(1):33-44.

14 Botha JF, Kassianides C, Schneider HR, et al. South African hepatitis C management guidelines 2010. SA Gastroenterol. 2010;8(1). Available from http://www.sages.co.za/images/hcvjfb.pdf

15 FDA (US Food and Drug Administration). FDA approves first combination pill to treat hepatitis C. 2014. Available from http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm418365.htm

16 Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370:1889-98.

17 Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014;370:1483-93.

18 Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014;370:1879-88.

19 Kapoor R, Kohli A, Sidharthan S, et al. All-oral treatment for genotype 4 chronic hepatitis C infection with sofosbuvir and ledipasvir: interim results from the NIAID SYNERGY trial. Hepatology. 2014;60:321A.

20 Gane EJ, Hyland RH, An D, et al. High efficacy of LDV/SOF regimens for 12 weeks for patients with HCV genotype 3 or 6 infection. Hepatology. 2014;60:1274A.

21 Abergel A, Loustaud-Ratti V, Metivier S, et al. Ledipasvir/Sofosbuvir for the treatment of patients with chronic genotype 4 or 5 HCV infection. Paper presented at The International Liver Congress 2015: 50th annual meeting of the European association for the Study of the Liver (EASL), Vienna, Austria; April 22-26. Available from http://natap.org/2015/EASL/EASL_80.htm

22 Krajden M, Montaner JSG. The curability of hepatitis C: implications for a public health response. BC Med J. 2013;55:243.

23 Thomas DL. Highly active anti-hepatitis C therapy: seven lessons from HIV. Antivir Ther. 2012;17(600):1183-88.

24 UNAIDS. Treatment 2015. Available from http://www.unaids.org/sites/default/files/media_asset/JC2484_treatment-2015_en_1.pdf

25 South African National AIDS Council. Global AIDS response progress report. 2012. Available from http://www.unaids.org/sites/default/files/country/documents//ce_ZA_Narrative_Report.pdf

26 UNAIDS. 90-90-90: An ambitious treatment target to help end the AIDS epidemic. 2014. Available from http://www.unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf

27 Sullivan SD, Mauskopf JA, Augustovksi F, et al. Budget Impact Analysis: principles of good practice. Report of the ISPOR 2012 Budget Impact Analysis good practice II task force. Value in health. 2014;17:5-14.

28 Saraswat V, Norris S, de Knegt RJ, et al. Historical epidemiology of hepatitis C virus (HCV) in select countries – volume 2. J Viral Hep. 2015;22:6-25.

29 Fraser I, Burger JR, Lubbe MS, et al. Cost effectiveness modelling of sofosbuvir triple therapy for chronic genotype 5 hepatitis C virus infection in South Africa. Pharmacoeconomics. [In press].

30 Sonderup MW, Abuelhassan W, Spearman W. IL28B polymorphisms are not predictive in hepatitis C genotype 5 infected South African patients. 2012. Paper presented at 63rd Annual Meeting of the American Association for the Study of Liver Diseases, Boston, MA, 9-13 November. http://onlinelibrary.wiley.com/doi/10.1002/hep.26040/epdf Date of access: 17 Feb. 2015.

31 Alberti A, Chemello L, Benvegnhù L. Natural history of hepatitis C. J Hepatology. 1999;31(Suppl. 1):11-24.

32 Alawazi W, Cunningham M, Dearden J, Foster GR. Systematic review: outcome of compensated cirrhosis due to chronic hepatitis C infection. Alim Pharmacol Ther. 2013;32:344-55.

33 Sweeting M, De Angelis D, Neal KR, et al. Estimated progression rates in three United Kingdom hepatitis C cohorts differed according to method of recruitment. J Clin Epidemiol. 2006;59:144–52.

34 Saab S, Hunt D, Stone M, et al. Timing of hepatitis C antiviral therapy in patients with advanced liver disease: a decision analysis model. Liver Transplant. 2010;16:748–59.

35 Hutchinson S, Bird S, Goldberg D. Modeling the current and future disease burden of hepatitis C among injection drug users in Scotland. Hepatology. 2005;42:711–23.

36 Actuarial Society of South Africa. Actuarial Society of South Africa HIV demographic model 2008 version. 2008. Available from http://aids.actuarialsociety.org.za/Models-3145.htm

37 D'Heygere F, George C, Van Vlierberghe H, et al. Efficacy of interferon-based antiviral therapy in patients with chronic hepatitis C infected with genotype 5: a meta-analysis of two large prospective clinical trials. J Viral Hepat. 2011;83:815-9.

38 Ghany MG, Strader DB, Thomas DL, Seeff LB. American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009;49:1335-74.

39 TreeAge Pro 2014, R1.2.TreeAge Software, Williamstown, MA; software available at http://www.treeage.com.

40 Council for Medical Schemes. Reference Price List (RPL). National reference price list for services by medical practitioners, effective from 1 January 2009. Available from http://wcawca.co.za/files/bhf_2009_medical_practitioners.pdf

41 Statistics South Africa (STATS SA). Statistical Release P0141: Consumer Price Index (CPI). 2015. Available from http://www.statssa.gov.za

42 The Official Pharmaceutical Bluebook. 2015. Available from http://www.pbb.co.za/

43 Gilead Sciences, Inc. Gilead announces generic licensing agreements to increase access to hepatitis C treatments in developing countries. 2014. Available from http://www.gilead.com/news/press-releases/2014/9/gilead-announces-generic-licensing-agreements-to-increase-access-to-hepatitis-c-treatments-in-developing-countries

44 Gilead Sciences, Inc. Chronic hepatitis C treatment expansion: generic manufacturing for developing countries. 2014. Available from http://www.gilead.com/~/media/Files/pdfs/other/HCVGenericAgreementFactSheet.pdf

45 South Africa. BRICS (Brazil, Russia, India, China, South Africa). 2015. Available from http://www.gov.za/about-government/brics-brazil-russia-india-china-south-africa

46 GTPI (The Working Group on Intellectual Property of the Brazilian Network for the Integration of Peoples). Brazil is excluded from license authorizing production of generic medicine for hepatitis C. 2014. Available from http://www.deolhonaspatentes.org.br/media/file/GTPI_statement_Gilead_license_sofosbuvir.pdf

47 Ndlovu N, Vilakazi M, Majozi M, Sithole F, Mbatha K, Guthrie T. Trends in national and provincial health and HIV/AIDS budgeting and spending in South Africa. Available from http://cegaa.org/resources/docs/healthbudget2014.pdf

Table 1. Model parameter values and ranges

Variable	Base Case		Reference
Cohort characteristics			
Start age	52 years		[30]
Weight (males)	80 kg		[30]
Weight (females)	60 kg		[30]
Gender distribution	55% male; 45% female		[30]
Disease stage distribution	80% non-cirrhotic; 20% cirrhotic		[30]
HCV natural history	**Annual probability**	**Range**	
CHC → cirrhosis[1]	0.011	(0.005 – 0.018)	[31]
Cirrhosis → decompensated cirrhosis	0.064	(0.030 – 0.070)	[32]
Cirrhosis → HCC	0.036	(0.015 – 0.040)	[32]
Decompensated cirrhosis → HCC	0.068	(0.041 – 0.099)	[33,34]
Decomp. cirrhosis → liver-related death	0.168	(0.120 – 0.400)	[35]
HCC → liver-related death	0.605	(0.300 – 0.800)	[35]
Mortality unrelated to HCV			[36]
Effectiveness of treatment (Probability of SVR)			
Standard of care (peg-INF/RBV)			
CHC, no cirrhosis	55%	(0.45 – 0.65)	[37]
Compensated cirrhosis[2]	40%	(0.30 – 0.50)	[37]
Sofosbuvir + peg-INF/RBV			
CHC, no cirrhosis	92%	(0.89 – 0.99)	[13]
Compensated cirrhosis	80%	(0.67 – 0.89)	[13]
Sofosbuvir + ledipasvir			
CHC, no cirrhosis	95%	(0.90 – 0.99)	[16-21]
Compensated cirrhosis	95%	(0.85 – 0.97)	[16-21]

CHC chronic hepatitis C, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *peg-INF* pegylated-interferon, *RBV ribavirin, SOC* standard of care, *SOF* sofosbuvir, *SVR* sustained virologic response

[1]Annual probability of CHC to cirrhosis was calculated from assumed probability of 20% over 20 years.

Table 2. Total annual cost of HCV management during each modeled health state

Variable	Cost (ZAR)	Cost (US$)
Diagnosis / Baseline	96 493	8 224
Chronic hepatitis C without cirrhosis		
During treatment with SOC (48 weeks completed)	213 572	18 203
During treatment with SOC (12 week stopping rule applied)[a]	61 138	5 211
During treatment with SOF-TT	141 005	12 018
During treatment with SOF/LDV	132 062	11 256
Annual follow-up after treatment failed	2 174	185
Compensated cirrhosis		
During treatment with SOC (48 weeks)	216 322	18 437
During treatment with SOC (12 week stopping rule applied)[a]	62 972	5 367
During treatment with SOF-TT	14 ,005	12 018
During treatment with SOF/LDV	136 782	11 658
Annual follow-up after treatment failed	4 619	394
Decompensated cirrhosis[b]		
Ascites	69 625	5 934
Esophageal varices[c]	102 572	8 742
Hepatic encephalopathy	226 825	19 333
HCC	227 694	19 430
Liver biopsy[d]	86 653	7 386
SVR (with cirrhosis)[e]	849 – 1 698	72 – 145

[a]The 12 week stopping rule was applied to patients who failed to achieve EVR. Costs applied to patients who discontinued treatment after 12 weeks was calculated as 12 weeks' drug cots and two-thirds of monitoring costs associated with SOC, for both cirrhotic and non-cirrhotic patients

[b]The total annual cost of decompensated cirrhosis is a weighted average between the average annual cost of ascites, variceal bleed and hepatic encephalopathy; calculated by multiplying the average annual cost for each sequale by fix proportions derived from literature: ascites, 62%; variceal hemorrhage, 28% and hepatic encephalopathy, 10%.

[c]The cost for esophageal varices is a weighted average between the average annual cost of bleeding (R362,309.00) and non-bleeding (R32,083.00) varices, assuming that, on average, varices has a 30% chance of bleeding.

[d]Patients without cirrhosis who did not achieve SVR get a liver biopsy every five years after treatment failure, whereas patients with compensated cirrhosis get a liver biopsy every three years after treatment failure

[e]For patients with cirrhosis who achieve SVR, the cost of HCC screening (using AFP and liver ultrasound) every six to twelve months was included

AFP alpha fetoprotein, *HCC* hepatocellular carcinoma, *SOC* standard of care, *SOF/LDV* sofosbuvir-ledipasvir, *SOF-TT* sofosbuvir triple therapy

Table 3. Estimated expenditure on HCV

Year		SOF/LDV		SOF-TT		SOC	
		Cost per year (ZAR)	**Cost per year (US$)**	**Cost per year (ZAR)**	**Cost per year (US$)**	**Cost per year (ZAR)**	**Cost per year (US$)**
1	Diagnostic costs	9 613 385	819 363	9 613 385	819 363	9 613 385	819 363
	DAA	12 319 300	1 049 992	8 212 931	700 000	0	0
	Peg-INF/RBV	0	0	4 874 589	415 468	17 421 780	1 484 883
	Monitoring costs	886 903	75 592	1 012 962	86 336	1 770 884	150 935
	Total per year	**22 819 588**	**1 944 946**	**23 713 867**	**2 021 167**	**28 806 049**	**2 455 181**
	Cumulative cost	**22 819 588**	**1 944 946**	**23 713 867**	**2 021 167**	**28 806 049**	**2 455 181**
2	Diagnostic costs	9 613 385	819 363	9 613 385	819 363	9 613 385	819 363
	DAA	12 319 300	1 049 992	8 212 931	700 000	0	0
	Peg-INF/RBV	0	0	4 874 589	415 468	17 421 780	1 484 883
	Monitoring costs	886 903	75 592	1 012 962	86 336	1 770 884	150 935
	Follow-up costs	10 798	920	17 277	1 473	94 596	8 063
	Total per year	**22 830 386**	1 945 867	**23 731 144**	2 022 640	**28 900 645**	2 463 244
	Cumulative cost	**45 649 974**	3 890 813	**47 445 011**	4 043 806	**57 706 693**	4 918 424
3	Diagnostic costs	9 613 385	819 363	9 613 385	819 363	9 613 385	819 363
	DAA	12 319 300	1 049 992	8 212 931	700 000	0	0
	Peg-INF/RBV	0	0	4 874 589	415 468	17 421 780	1 484 883
	Monitoring costs	886 903	75 592	1 012 962	86 336	1 770 884	150 935
	Follow-up costs	21 575	1 839	34 521	2 942	189 004	16 109
	Total per year	**22 841 163**	**1 946 785**	**23 748 388**	**2 024 109**	**28 995 053**	**2 471 290**
	Cumulative cost	**68 491 138**	**5 837 598**	**71 193 399**	**6 067 916**	**86 701 747**	**7 389 715**
4	Diagnostic costs	9 613 385	819 363	9 613 385	819 363	9 613 385	819 363
	DAA	12 319 300	1 049 992	8 212 931	700 000	0	0
	Peg-INF/RBV	0	0	4 874 589	415 468	17 421 780	1 484 883
	Monitoring costs	886 903	75 592	1 012 962	86 336	1 770 884	150 935
	Follow-up costs	45 935	3 915	73 495	6 264	402 396	34 297
	Total per year	**22 865 523**	**1 948 861**	**23 787 362**	**2 027 431**	**29 208 445**	**2 489 478**
	Cumulative cost	**91 356 660**	**7 786 459**	**94 980 761**	**8 095 347**	**115 901 191**	**9 878 425**
5	Diagnostic costs	9 613 385	819 363	9 613 385	819 363	9 613 385	819 363
	DAA	12 319 300	1 049 992	8 212 931	700 000	0	0
	Peg-INF/RBV		819 363	4 874 588	415 468	17 421 780	1 484 883
	Monitoring costs	886 903	1 049 992	1 012 962	86 336	1 770 884	150 935
	Follow-up costs	44 298	0	70 877	6041	388 058	33 075
	Total per year	**22 863 886**	**75 592**	**23 784 744**	**2 027 208**	**29 194 107**	**2 488 256**
	Cumulative cost	**114 220 546**	**1 944 946**	**118 765 505**	**10 122 555**	**145 104 298**	**12 367 448**

DAA direct acting antiviral *peg-INF* pegylated interferon *RBV* ribavirin *SOF/LDV* sofosbuvir-ledipasivr *SOF-TT* sofosbuvir triple therapy (sofosbuvir + peg-INF + RBV)

In the SOF/LDV arm, the price of the DAA refers to the price of fixed-dose combination of sofosbuvir-ledipasvir, and in the SOF-TT the price of the DAA refers to the price of sofosbuvir

Table 4. Estimated budget to achieve 90-90-90 target over the next five years

		Sofosbuvir-ledipasvir		Sofosbuvir triple therapy	
Year	**% Diagnosed**	**Annual cost**	**Cumulative cost**	**Annual cost**	**Cumulative cost**
1	10 290	2 348 135 605	2 348 135 605	2 440 156 914	2 440 156 914
2	20 580	4 697 382 366	7 045 517 972	4 882 091 678	7 322 248 593
3	41 160	9 395 873 181	16 441 391 153	9 765 956 874	17 088 205 467
4	82 320	18 794 725 891	3 523 611 7044	19 536 680 994	36 624 886 461
5	164 640	37 586 955 635	72 823 072 680	39 069 368 152	75 694 254 613

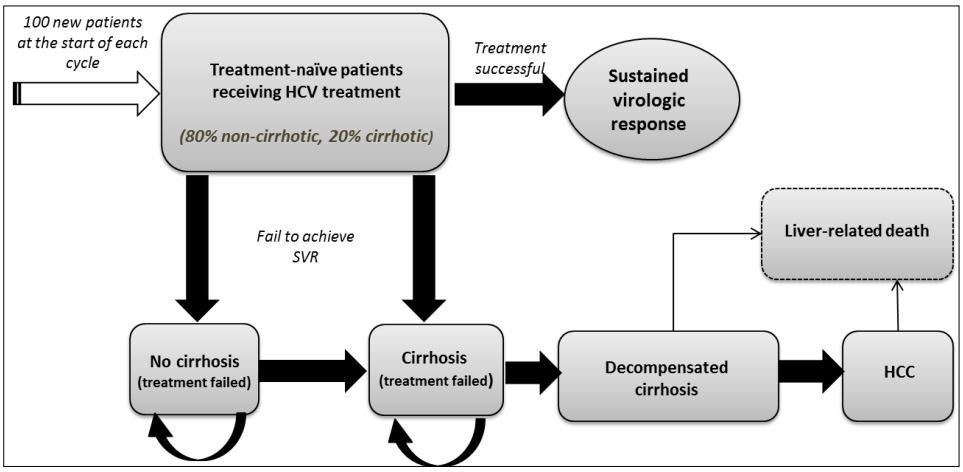


Figure 1. Simplified illustration of model. *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus

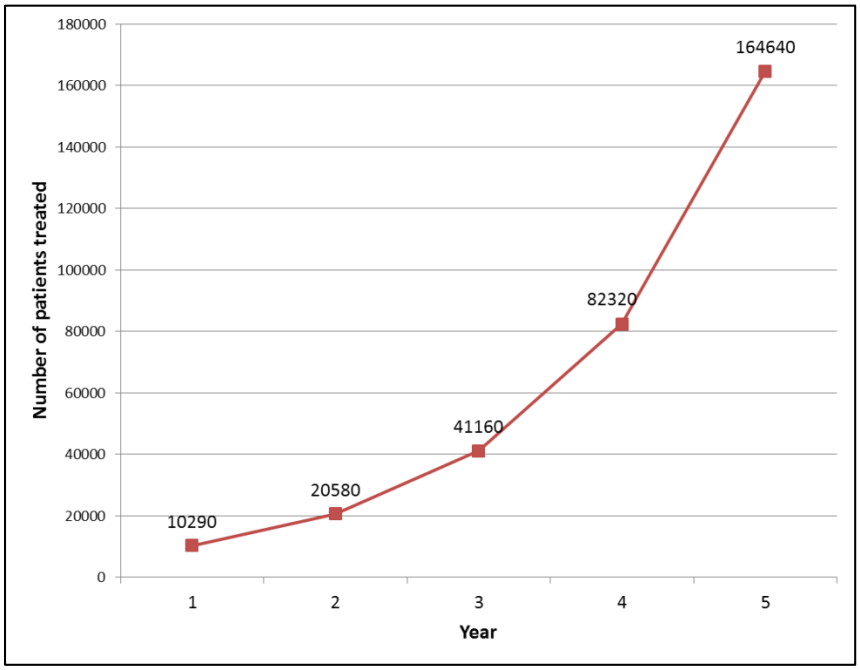


Figure 2. Number of patients needed to treat per year to reach target by 2020

3.5 Chapter summary

In this chapter, three manuscripts were presented addressing the objectives of the empirical investigation. The next chapter, which concludes the study, focuses on the conclusion, strengths and limitations of the study, and recommendations for future studies.

CHAPTER 4

The purpose of this chapter is to draw conclusions from the study with regard to the specific objectives outlined. This chapter begins with a brief overview of the content of the thesis and a summary of findings from the study. The strengths and limitations of findings of the study will be discussed and the chapter will conclude with recommendations for future studies.

4.1 Content of thesis

The thesis consisted of four chapters: Chapter one provided an introduction and overview of the study. The chapter reflected on the background and motivation for the study, research questions, research objectives and the method of study employed. Chapter one concluded with the general division of chapters in the thesis.

Chapter two represented the literature review of this study. This chapter provided a general summary of hepatitis C virus (HCV) infection. This included defining HCV infection and discussing relevant aspects of the disease; including clinical features of the disease, routes of transmission, incubation period, risk factors, prevention, complications, diagnosis and testing, treatment and response. This was followed by an investigation into the current status of hepatitis C by determining global and national prevalence and epidemiology of chronic HCV infection and the different HCV genotypes and their geographical distributions. By determining the main disease states of chronic hepatitis C virus infection, as well as the annual transition probabilities from one disease state to the next, the patient journey of an individual with hepatitis C infection was determined. The literature review of chapter two finished with a description of the concept of “health-related quality-of-life” and determination of the health state utilities in patients with HCV infection for use in cost-effectiveness analyses.

The objectives of the literature review also included determining the direct medical expenses involved during each disease state and determining the effectiveness of the two competing treatment strategies investigated in this study by means of published clinical trial data. This formed an integral part of the first two objectives of the empirical phase, i.e. *i) Building a Markov model on TreeAge Pro Healthcare, 2014 software (TreeAge Pro 2014, R1.2), based on the natural history/disease states of chronic HCV infection identified in the literature review* and *ii) Populating the model with data, including annual transition probabilities, cost data, effectiveness data, health state utility values and background mortality rates,* and was therefore included in the literature review / introduction of the first manuscript.

Chapter three represented the results and discussions section of the thesis and was presented in the form of manuscripts. Three manuscripts were presented with the following titles:

- Manuscript 1: Cost-effectiveness modelling of sofosbuvir-containing regimens for chronic genotype 5 hepatitis C virus infection in South Africa.
- Manuscript 2: Public health impact of sofosbuvir-based regimens for chronic hepatitis C virus infection in South Africa.
- Manuscript 3: Budget impact analysis of sofosbuvir-based regimens for chronic hepatitis C in South Africa.

4.2 Conclusions from the study

The general aim of this research project was to determine the cost-effectiveness of sofosbuvir (either with pegylated interferon and ribavirin or with ledipasvir) for the treatment of hepatitis C in South Africa, by constructing a decision-analytical model utilising TreeAge Pro Healthcare 2014 software (TreeAge Pro 2014, R1.2).

The study was conducted in two phases; a literature review (phase one) and an empirical study (phase two). The empirical study focused on the construction of the decision-analytic Markov model using TreeAge Pro Healthcare 2014 Software and using the resulting model to run various analyses. The project had both literature and empirical objectives and the conclusions from the specific research objectives follow in the subsequent paragraphs.

4.2.1 Conclusions from the literature review

The objectives of the literature review were outlined in paragraph 1.4.2.1 of chapter one. These objectives were achieved in Chapter two of this thesis, with the exception of objectives (v) and (vi), which were achieved in Manuscript one of chapter three.

(i) Defining HCV infection and researching all relevant aspects on the subject of the disease; including clinical features of the disease, routes of transmission, incubation period, risk factors, prevention, complications, diagnosis and testing, treatment and response

HCV infection is defined as an infection with the hepatitis C virus, an enveloped single-stranded ribonucleic acid (RNA) virus that belongs to the *Flaviviridae* family of RNA viruses (McPhee *et al.,* 2008:571) (refer to section 2.1). HCV is a blood-borne virus generally transmitted through exposure to infected blood (WHO, 2002) (refer to section 2.1.5). The incubation period for HCV infection is usually 14 to 140 days, with an average of 45 days (CDC, 2012; Immunization Action Coalition; McPhee *et al*., 2008:572; WHO, 2012;

WHO, 2013). Seroconversion normally occurs 32 to 46 days after viraemia and the period of communicability spans from one to several weeks before onset of the first symptoms, and in some persons, it may persist indefinitely (Maasoumy & Wedemeyer, 2012:403; WHO, 2002:19) (refer to section 2.1.7). Because HCV is transmitted through exposure to infectious blood, those generally at risk of contracting HCV include current or former injection drug users; recipients of clotting factor concentrates before 1987; recipients of blood transfusions or donated organs before July 1992; long-term haemodialysis patients; persons with known exposures to HCV (e.g. healthcare workers after needle stick injuries, recipients of blood or organs from a donor who later tested positive for HCV), and infants born to infected mothers (CDC, 2012) (refer to section 2.1.6).

There are presently no vaccine and no post-exposure prophylaxis available for hepatitis C infection. Education, prevention and effective management are therefore fundamental to reducing transmission of the virus. The need for safer blood supply and injection practices in healthcare in developing countries should also be recognised (Parini, 2001:19; Pears, 2010:55) (refer to section 2.1.8).

Diagnosis of chronic hepatitis C infection is made when HCV RNA persists for more than six months. Traditional liver function tests and HCV antibody diagnostic tests (serologic assays that detect specific antibodies to the HCV and molecular assays that detect viral nucleic acid (HCV RNA) are used in the diagnosis of chronic HCV infection (Botha *et al.,* 2010). Liver biopsy is the gold standard for staging liver disease in an individual with chronic hepatitis C infection, but is only used selectively, as it is an expensive procedure that has occasional complications and poor patient acceptance because of the risk of bleeding and post-procedural pain (Saadeh *et al*., 2001) (refer to section 2.1.9).

HCV infection causes hepatitis C, a liver disease defined as *"inflammation of the liver from any cause, characterized by diffuse or patchy necrosis"* (Beers *et al*., 2006:219). Hepatitis C is generally considered to be a progressive disease, however, it can be either acute or chronic (Beers *et al*., 2006:219; Parini, 2001:20). Patients in whom HCV infection persists for longer than six months, are considered chronic HCV carriers and approximately 75-85% of newly infected patients will progress to chronic hepatitis C; defined as *"a state in which symptoms of hepatitis continue for several months and may increase in severity"* (Mosby's Dictionary of Medicine, Nursing & Health Professions, 2006:382) (refer to section 2.1.2).

Approximately 80% of people infected with HCV are asymptomatic following initial infection (Immunization Action Coalition; CDC, 2012). However, patients can present with flu-like symptoms, myalgia, arthralgia, easy fatigability, upper respiratory symptoms and anorexia. Distaste for smoking, nausea and vomiting, abdominal pain and low-grade fever are fairly

common symptoms of hepatitis C. Jaundice may develop within the first few days after exposure to the virus, albeit only in a small percentage of patients (McPhee *et al.,* 2008:572; Parini, 2001:20; Poll, 2012:397) (refer to section 2.1.4).

Morbidity and mortality associated with chronic liver disease tends to develop decades after initial infection with HCV (Shepard *et al.,* 2005:558). Liver cirrhosis, hepatic decompensation and development of HCC are some of the consequences of chronic HCV infection; causing significant liver-related morbidity and mortality (Maasoumy & Wedemeyer, 2012:401) (refer to section 2.1.10). The goal of HCV treatment is to achieve a SVR, which is defined as undetectable HCV RNA six months after cessation of therapy, leading to HCV clearance. SVR is associated with an improved histological outcome and a reduction of morbidity and mortality (Wendt & Bourlière, 2013:191) (refer to section 2.4).

The standard of care therapy for patients with chronic HCV infection has been the use of both peg-INF and RBV. These drugs are administered for either 48 weeks (HCV genotypes 1, 4, 5, and 6) or for 24 weeks (HCV genotypes 2 and 3), producing SVR rates of 40%-50% in those with genotype 1 and of 80% or more in those with genotypes 2 and 3 infections. Once achieved, an SVR is associated with long-term clearance of HCV infection, which is regarded as a virologic 'cure', as well as with improved morbidity and mortality (refer to section 2.4).

(ii) Investigating the current status of hepatitis C by determining global and national prevalence and epidemiology of chronic HCV infection

Current estimates indicate that approximately 130-150 million people globally are chronically infected with HCV, reflecting a global HCV prevalence of 3% (WHO, 2013). Global estimates further indicate that 54 000 deaths and 955 000 disability-adjusted-life-years were associated with HCV infection in 2011 and that more than 350 000 people die from hepatitis C-related liver diseases annually (Khayriyyah *et al*., 2013:1333; WHO, 2013) (refer to section 2.2).

Although HCV has a global distribution, there is a large degree of geographic variability in its spread. Studies indicate that HCV prevalence is generally low (<1.5%) in regions like high-income Asia Pacific, high-income North-America and Tropical Latin America. Prevalence is marginally higher (≤2%) in Andean, Central and Southern Latin America, Southeast Asia and East sub-Saharan Africa. Europe, Central-, South- and West sub-Saharan African countries, Australasia, Oceania and the Caribbean have a moderate HCV prevalence (>2%; <3%), whereas Central- East- and South Asia, North Africa and the Middle East are estimated to have high a prevalence (>3.5%). Prevalence rates of anti-HCV for Western Pacific region ranges from 2.5% - 4.9% (Averhoff, 2012:S12; Hanafiah *et al.,* 2013:1333; Lavancy, 2011:110). Egypt has the highest HCV prevalence in the world (>14.7%) (Mohamoud *et al*., 2013:288). The exact

extent of the burden of HCV in South Africa is not well known, however, it is estimated to be low (0.1–1.7%) (refer to section 2.2).

(iii) Investigating different HCV genotypes and their geographical distributions

There are substantial regional differences in the distribution of the different HCV genotypes (Pybus *et al.,* 2001). Genotype 1a is common in the United States and Northern Europe, whereas genotype 1b has a worldwide distribution and is often found to be the most common genotype. Genotypes 2a and 2b are also found worldwide and are relatively common in North America, Europe, and Japan, whereas genotype 3 is found in India, the USA and Europe. Genotype 4a is most common in North Africa and the Middle East — with a proportion ranging from 36%-100% of all HCV cases, whereas genotype 6 occurs in Hong Kong and Southeast Asia (Antaki *et al.,* 2009:343; Simmonds, 2004). Genotype 5 is relatively uncommon and has been thought to be confined to the northern part of South Africa for many years, however, new evidence suggest that the epidemiology of genotype 5 is more diverse than originally thought, as pockets of genotype 5 can be found worldwide (Verbeeck *et al.,* 2008:170 (refer to section 2.2.4).

(iv) Characterising the patient journey of an individual with hepatitis C infection; by determining the main disease states of chronic hepatitis C virus infection, as well as the annual transition probabilities from one disease state to the next

To determine the expected health-economic outcomes in patients with CHC, a decision-analytic model was developed to simulate the disease progression of chronic HCV infection. The individual course of CHC is highly variable and this has challenged the development of a universal model describing the natural history of HCV infection (Alberti *et al*., 1993:17; Marcellin, 1999:9). Despite these limitations, however, many attempts have been made to describe the natural history of HCV infection. Based on published literature, the main disease states in the natural history of HCV infection was identified and used to construct a Markov model. Main health states identified included: active chronic hepatitis C (CHC without cirrhosis), compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma. Although not necessarily considered 'disease states', for the purpose of the cost-effectiveness model, sustained virological response (SVR) without cirrhosis, SVR with cirrhosis, non-liver related death and liver-related death was included. Focussing on systematic reviews, the annual probabilities for transitioning from each disease state to the next was identified. The annual transition probabilities identified were: for progressing from CHC to cirrhosis, 0.011% per year (20% over 20 years); for progressing from cirrhosis to decompensated cirrhosis, 0.064%; for progressing from cirrhosis to HCC, 0.036%; and for progressing from decompensated cirrhosis

to HCC, 0.068%. The annual probabilities for liver-related death due to decompensated cirrhosis or HCC were identified as 0.168% and 0.605%, respectively (refer to section 2.1.11).

(v) Determining the medical expenses involved (direct medical) during each disease state

This objective was achieved as part of the objectives of the empirical phase and was reported in the 'methods' section of manuscript 1, as well as the online resource for manuscript 1. According to the South African third-party payer's perspective, only direct costs was considered in the model — in particular, the drug costs (peg-INF, RBV, SOF) and the costs associated with disease management (i.e. diagnostic tests, routine blood tests, outpatient visits, hospitalisation etc.). The model accounted for three types of HCV-related cost, *viz.* drug regimen, treatment monitoring and health state (downstream liver-disease complications). In addition to the cost of drug-treatment, costs for baseline testing and diagnosis were also considered for all patients assumed to receive treatment in the model.

The cost of baseline testing or diagnoses included costs for pathology (including HCV antibody, hepatitis C virus polymerase chain reaction (PCR) and viral load, HCV genotyping, hepatitis B virus serum antigen, hepatitis B virus serum antibody, hepatitis B virus core antibody (total), human immunodeficiency virus-test (rapid and Western Blot technique), hepatitis A virus-immunity (HAV IgG), thyroid function tests, liver function tests, full blood count, urea and electrolytes, international normalised ratio, alpha fetoprotein and iron studies, abdominal ultrasound), the cost of a liver biopsy and the cost of a consultation with a specialist (hepatologist), irrespective of the treatment option chosen (refer to manuscript 1 and online resource for manuscript 1).

Monitoring costs and recommended follow-up of patients were based on typical South African management of HCV and was confirmed by expert opinion (independent South African hepatologists). Costs of laboratory tests, radiological examination and consultations were based on the prices in the Referencing Price List (RPL), and were calculated according to specified monitoring resource use. The latest RPL values (2009) were inflated using published annual medical inflation numbers from Statistics South Africa and total monitoring costs over the treatment period were aggregated from calculated totals. Monitoring costs, including costs of pathology tests and doctors consultations were derived from the Referencing Price List (RPL).

Drug costs included the costs of peg-INF, RBV and SOF and drug regimen costs were based on unit drug costs, indicated drug dosing and therapy duration. Unit prices of peg-INF and RBV were taken from the Official Pharmaceutical Bluebook. The medicine price used to populate the model was a composite of single exit price (SEP) (including value added tax (VAT)) and the

prescribed professional dispensing fee. A detailed description of drug and monitoring costs was presented in the online resource of manuscript 1.

(vi) Determining the effectiveness of the three competing treatment strategies by means of published clinical trial data

This objective was achieved as part of the objectives of the empirical phase and was reported in the methods section of manuscript 1. Clinical inputs for treatment efficacy and duration for sofosbuvir-based treatment were derived from the phase III NEUTRINO clinical trial and the open-label study by Abergel *et al.* (2015), whereas SVR rates for peg-INF/RBV were derived from a meta-analysis of two large Belgium phase III/IV prospective RCTs — the BERNAR-1 and BERNAR-2 trials.

Based on data from the NEUTRINO trial, the French open-label study and the BERNAR-1 and BERNAR-2 trials, the effectives, or SVR rates for each of the competing treatment strategies in the treatment of HCV-G5 patients, were identified as follows: The SVR rate of sofosbuvir triple therapy is 92% (0.89% – 0.99%) in CHC patients without cirrhosis and 80% (0.67% – 0.89%) in patients with cirrhosis. The SVR rate of sofosbuvir-ledipasvir is 95% in non-cirrhotic and cirrhotic patients, whereas the SVR rate of peg-INF/RBV (SOC) is 55% (0.45% – 0.65%) in CHC patients without cirrhosis and 40% (0.30% – 0.50%) in patients with cirrhosis (refer to Table 1 of manuscript 1).

(vii) Describing the concept of health-related quality-of-life, and determining health state utilities, or health-related quality-of-life (HRQoL), in patients with HCV infection

HRQoL is defined as *"the value assigned to duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy"* (Patrick & Erickson *as quoted by* Feeny, 2000:II-152).

In section 2.5 it was established that measurement of HRQoL is done by means of standardized, self-administered questionnaires, and that there are two basic types of HRQoL questionnaires: generic questionnaires and disease specific questionnaires. Utility measures are a third type of HRQoL questionnaires that measures HRQoL from a cost-effectiveness perspective (Gutteling *et al.*, 2007:228).

In health economics, utilities are cardinal values that reflect an individual's preferences for a specific level of health status or different health outcomes. They are measured on an interval scale with zero reflecting states of health equivalent to death and one reflecting perfect health. Health utilities are typically combined with survival estimates and aggregated across individuals

to generate quality-adjusted life years (QALYs) for use in cost-utility analyses of healthcare interventions (Torrance, 1986:2).

HRQoL of patients with chronic liver disease has been shown to be impaired, especially in those patients with hepatitis C. Beside specific complications of cirrhosis; such as hepatic encephalopathy, ascites and variceal bleeds, symptoms such as abdominal pain, muscle cramps, fatigue, depression and anxiety have also been associated with reduced HRQoL in patients with CHC. Concern about complications of the disease, decreased sexual interest, loneliness and hopelessness has also been implicated in decreased HRQoL (Gutteling *et al*., 2006:1629; Younossi *et al*., 1999:297). Few estimates exist for utility measures for liver disease in the literature, and to date, health utilities for patients suffering from chronic HCV infection in South Africa have not been determined. Consequently, for the model health utility values taken from literature as efficacy measures were employed, such as:

SVR (without cirrhosis) = 1; CHC (without cirrhosis) = 0.790 (0.74 – 0.82); CHC (while on treatment with SOC) = 0.430 (0.28 – 0.58); CHC (while on treatment with SOF) = 0.650 (0.43 – 0.86); CHC (while on treatment with SOF/LDV) = 0.750 (0.59 – 0.91); Compensated cirrhosis = 0.748 (0.74 – 0.77); Cirrhosis (while on treatment with SOC) = 0.430 (0.28 – 0.58); Cirrhosis (while on treatment with SOF) = 0.650 (0.43 – 0.86); Cirrhosis while on treatment with SOF/LDV + RBV = 0.701 (0.55 – 0.85); Decompensated cirrhosis = 0.672 (0.60 – 0.69); HCC = 0.610 (0.20 – 0.67) and SVR (with cirrhosis) = 0.87 (0.82 – 0.89).

Herewith the objectives set for the literature review were met and the overall conclusion drawn from the literature review can be summarised as follows:

The number of cases of chronic hepatitis C are increasing and with it, manifesting their most serious symptoms. Hepatitis C related complications are estimated to continue to rise, peaking in about 2030. The problem is turning into a burning public health concern that threatens to pressurise already stretched researchers, patients, and the healthcare system.

The current standard of care for HCV-G5 infection in South Africa is the combination of peg-INF/RBV — a lengthy treatment option with often severe side-effects that only cures approximately 50% of patients was established. With improved efficacy and safety, sofosbuvir is a game changer in the management of HCV, and as the first direct-acting antiviral to be included in the treatment guidelines for HCV-G5 infection, sofosbuvir represents renewed hope for patients with this HCV genotype. In combination with ledipasvir, sofosbuvir further increases treatment success rates (compared to sofosbuvir + peg-INF/RBV) and offers a significant advance for patients unable, or unwilling to use peg-INF. However, sofosbuvir is associated with a considerable cost, driving concerns that the price for sofosbuvir and drugs like *Harvoni*®

that contain sofosbuvir, will render these drugs completely inaccessible to the vast majority of HCV infected patients residing in low- and middle-income countries.

Sofosbuvir and SOF/LDV is yet to be registered in South Africa, but their approval is imminent. The only draw-back of these drugs is the exceptionally high cost at which it was launched in the US and other European countries, which has raised questions as to its cost-effectiveness. Given the absence of prospective, long-term studies on sofosbuvir that include cost data in South Africa and the fact that concerns about cost are dominating decisions about treatment, it was concluded that economic modelling of sofosbuvir (either in combination with peg-INF/RBV or ledipasvir) may empower policy-makers to make informed decisions about the treatment of chronic HCV infection and serve to aid in allocating resources for maximal collective health benefits.

4.2.2 Conclusions from the empirical investigation

Following the objectives of the pharmacoeconomic model already met in the literature phase, the specific objectives of the empirical phase included:

(i) Building a Markov model on TreeAge Pro Healthcare, 2014 software (TreeAge Pro 2014, R1.2), based on the natural history/disease states of chronic HCV infection identified in the literature review

(ii) Populating the model with data, including annual transition probabilities, cost data, effectiveness data, health state utility values and background mortality rates

(iii) Running the model through TreeAge Pro Healthcare, 2014 software (TreeAge Pro 2014, R1.2) to yield results based on cost-effectiveness and analysing these results

(iv) Using the results to compare the three alternative HCV treatment strategies based on cost-effectiveness and incremental cost-effectiveness ratios

(v) Determining whether the modelled price for sofosbuvir and SOF/LDV will be cost-effective for HCV infection in South Africa based on the willingness-to-pay threshold of R200 000.00 through sensitivity analyses

These objectives were met in manuscript 1, which comprised a health economic analysis of sofosbuvir-containing regimens for the treatment of patients with HCV-G5.

A decision-analytic Markov model of the natural history of HCV infection and progression toward advanced liver disease was constructed, so as to evaluate the cost-effectiveness of sofosbuvir-

containing regimens versus the current SOC for treatment-naive patients with chronic HCV-G5 in the South African context.

The natural history model simulated the journey of a hypothetical cohort of patients with chronic HCV-G5 infection through defined health states over a lifetime period until death. The modelled cohort moved between defined health states on an annual basis according to annual transition probabilities. Health states included in the model were CHC without cirrhosis, compensated cirrhosis, decompensated cirrhosis, HCC, SVR without cirrhosis, SVR with cirrhosis, liver-related death and non-liver related death.

The model allowed for antiviral treatment to be applied at two progressive states of the disease: CHC without cirrhosis and compensated cirrhosis. Patients initiated treatment as they entered the model. Treatment strategies for HCV-G5 infection included i) SOC (with peg-INF and RBV); ii) sofosbuvir triple therapy (SOF-TT) (with sofosbuvir plus peg-INF and RBV) and iii) sofosbuvir-ledipasvir (SOF/LDV) as an interferon-free regimen. To be consistent with current guidelines, it was assumed that SOC was administered for 48 weeks. Using the EASL and AASLD guidelines, it was assumed SOF-TT and SOF/LDV was administered for 12 weeks. Patients who achieved SVR were assumed to maintain SVR and experience no further disease progression until their death. Every patient who survived each one year cycle received one life year gained (LYG). TreeAge Pro Healthcare, 2014 software, was used for model creation and analysis.

In the study, a cohort of hypothetical treatment-naive HIV-negative patients with chronic HCV-G5 infection was considered. Baseline characteristics for the study population were based on the patient demographics of a South African HCV cohort. The cohort was characterised by age, sex and according to the presence/absence of cirrhosis. The cohort was not stratified according to ethnicity or IL-28B genotype. The annual transition probabilities for progressing from one disease state to the next and probabilities for HCV-related death were derived from published literature, whereas sex- and age-specific mortality rates from causes other than HCV were taken from the Actuarial Society of South Africa (ASSA) HIV demographic model: 2008 version. The primary efficacy measure used in the model was SVR, 12 weeks and 24 weeks after completion of treatment for sofosbuvir-containing regimens and SOC, respectively. SVR rates for patients who initiated treatment while in the ‘compensated cirrhosis’ state were considered to be lower than for patients who initiated treatment while in the ‘CHC without cirrhosis’ state. Response rates of sofosbuvir triple therapy were based on the results of the NEUTRINO trial, whereas treatment efficacy of SOF/LDV was based on the results of the small open-label study conducted in France (Abergel *et al.*, 2015). SVR rates of SOC were based on pooled results from the BERNAR-1 and BERNAR-2 RCT’s. For base case analysis, the following SVR rates was assumed: 95% for SOF/LDV in both cirrhotic and non-cirrhotic patients; 92% and 80% for

SOF-TT in non-cirrhotic and cirrhotic patients, respectively; and 55% and 40% for SOC in non-cirrhotic and cirrhotic patients, respectively.

In the absence of South African specific utility data, two systematic reviews and one original study were used as references for health state utility values used in the model. The model accounted for three types of HCV-related cost: drug regimen, treatment monitoring and health state (downstream liver-disease complications). Costs of treatment cycles were expressed in South African Rand (ZAR) and United States Dollars (US$) at 2015 value.

According to the South African third-party payer's perspective, only direct health care costs were considered — in particular, drug costs and the costs associated with disease management (diagnostic tests, routine blood tests, outpatient visits, hospitalisation, etc.) (refer to section 4.3.1). At the time of the analysis, sofosbuvir and SOF/LDV had not been registered in South Africa and its pricing had not yet been established. However, because South Africa is included in the list of countries for distribution of the generic version of sofosbuvir and SOF/LDV, it will almost certainly be able to have access to the drug at a lower price. Reliable indications were that South Africa will be benchmarked with the BRICS countries and a cost of R82 129.32 (US$7 000) for a 12 week course of sofosbuvir and cost of R123 193 (US$10 500) was assumed in the base case analysis, which is on par with the pricing of these drugs in Brazil, one of the BRICS countries.

In the analysis, comparisons of health and economic outcomes were made across treatment regimens for the modelled cohort. The long-term health economic outcomes included discounted and undiscounted life-time costs (in ZAR and US$), discounted and undiscounted life-years gained (LYG), discounted and undiscounted QALYs and incremental lifetime cost per QALY gained [incremental cost-effectiveness ratios (ICERs)]. The primary outcome was QALYs, calculated by applying utility values to life years gained (LYG). The incremental lifetime cost per QALY gained for sofosbuvir triple therapy was compared against the willingness-to-pay (WTP) threshold of R200 000 (~US$17 046) per QALY.

The cost-effectiveness model demonstrated that in South Africa, the SOF/LDV combination yields the most favourable future health economic outcomes compared with the current SOC. Compared with SOC and SOF-TT, SOF/LDV was associated with the lowest incidence of liver disease complications and HCV-related deaths, due to increased efficacy in both cirrhotic and non-cirrhotic patients, with an estimated percentage reduction in these sequelae of >90% for SOF/LDV *vs.* SOC. The strategy of treating patients with SOF/LDV produced an overall SVR rate of 93.8% compared to an overall SVR rate of 88.5% and 52.3% in patients treated with SOF-TT and SOC, respectively. In addition to a higher SVR rate, patients treated with SOF/LDV lived 0.15 and 0.64 years longer, and gained 0.25 and 1.9 more QALYs than those

treated with SOF-TT and SOC, respectively. SOF/LDV was associated with the lowest discounted lifetime cost (R241,561 or ~US$20,589), followed by SOF-TT (R263,132 or ~US$22,472). Findings from the analysis, relating to the lifetime incremental cost per QALY gained for patients infected with HCV-G5, indicated that at a price of R123 193 (US$10 500), sofosbuvir in combination with ledipasvir dominates both SOF-TT and SOC *viz.* it is less costly and more effective. At a price of R82 129 (US$7 000) for 12 weeks, sofosbuvir in combination with peg-IFN/RBV dominates SOC. The total discounted lifetime cost of patients treated with SOC (R392 127) (~US$33 422) was almost 32% and 38% higher than those of patients treated with SOF-TT (R263 132 or ~US$22 472) and SOF/LDV (R241,560.54 or ~US$20,588.55), respectively. Results from the sub-group analysis relating to the SOF/LDV arm showed that treating cirrhotic patients with 24 weeks monotherapy is less cost-effective than 12 weeks SOF/LDV+RBV, but still more cost effective than SOF-TT and SOC overall. Results from the sensitivity analysis indicates that SOF/LDV continued to be a cost-effective strategy even when key clinical and cost parameters were adjusted across wide, yet plausible, ranges.

Based on the results from the cost-effectiveness model it was concluded that, the fixed-dose combination of sofosbuvir and ledipasvir might be a cost-effective strategy for patients with chronic HCV-G5 infection in South Africa at a price of R123 193 (US$10 500) for 12 weeks.

(vi) Quantifying the public health impact of the use of sofosbuvir-based regimens compared to current HCV treatments from a South African private sector third-party payer's perspective

This objective was met in manuscript 2. The aim of manuscript 2 was to project the impact of the use of sofosbuvir-based regimens in South African patients with chronic HCV infection on the size of the HCV-infected population, as well as on the number of cases of advanced liver-disease and liver-related deaths, compared to the current SOC.

The Markov model constructed for the cost-effectiveness analyses was adapted to produce a dynamic population Markov model to represent the HCV-infected population in South Africa to estimate the impact of sofosbuvir-based regimens on the future burden of HCV.

Health states included in this disease-progression model were: i) new infections; ii) undiagnosed viremic infections; iii) diagnosed CHC (treatment naïve); iv) diagnosed CHC (treatment failed); v) compensated cirrhosis; vi) decompensated cirrhosis; vii) HCC; viii) SVR; ix) liver-related death, and x) non liver-related death. The model started with the annual number of new infections that progressed to chronic HCV infection. The progression of new cases along with all cases of current chronic HCV infections was followed for twenty annual cycles. During this time the population could change in size due to new infections, or due to patients being removed from the cohort because of death from liver disease or other causes.

Baseline characteristics for the study population were based on the patient demographics of a South African HCV cohort. This model considered sofosbuvir-based regimens (SOF-TT and SOF/LDV) *vs.* SOC. Dosing and administration of the treatment alternatives and annual transition probabilities remained unchanged from the cost-effectiveness model. For the SOF arm, we assumed an average SVR rate of SOF-TT and SOF/LDV over all genotypes. Costs were not considered in this analysis, and because QALYs were not calculated for this analysis, utility values were irrelevant. Once again, the primary efficacy measure used in the model was SVR. Patients were assumed to complete only one course of treatment before achieving SVR and patients who achieved SVR were assumed to maintain SVR and experience no further disease progression until their death. Patients who failed to achieve SVR returned to the diagnosed CHC (treatment failed) state where they could follow one of three different paths in each cycle, based on their transition probabilities: i) continue in the same health state without suffering from any event; ii) progress to the next health state in the natural history model, or iii) die of non-liver related causes. Death from other causes (non-liver related) was possible from all health states, whereas liver-related mortality was only possible from decompensated and HCC states. Every patient who survived each one year cycle received one life year gained (LYG). The primary endpoint of the model was the number of cases of advanced liver-disease and number of liver-related deaths projected to be prevented by SOF-based regimens *vs.* SOC over the next two decades.

The baseline prevalence and incidence were based on the results of a recent study reporting on the current and future disease burden of HCV in South Africa (Hatzakis *et al*., 2015). Based on findings from Hatzakis *et al.* (2015), a baseline viremic prevalence of 0.77% and a baseline incidence of 6 940 new infections per year was assumed. The annual diagnosis rate for HCV was assumed to be 0.7%. For the purpose of this analysis, the annual number of new infections and newly diagnosed cases were assumed to have remained unchanged from the last reported year. Saraswat *et al*. (2015) indicated that 100 patients were treated for CHC in South Africa in 2011. Based on this report, and the assumptions that: i) only patients who have been diagnosed with CHC can receive treatment, and ii) the number of treated patients remained constant after the last reported year, an annual treatment rate for CHC in South Africa was calculated as 0.18%.

As part of the public health impact analysis, a treatment cascade of the current HCV situation in South Africa was developed. Based on the estimated published by Hatzakis *et al*. (2015) and Saraswat *et al*. (2015), only 1% of all diagnosed HCV-patients, or 0.025% of the total population with chronic HCV infection are currently receiving treatment in South Africa.

From the results of the base case analysis it is evident that, assuming only 0.18% of all diagnosed patients are treated every year for the next 20 years, the South African HCV

treatment cascade will not look much different by 2035, irrespective of the treatment option chosen. These results also showed that, even though the total number of viremic infections is estimated to decrease over the next two decades, cases of advanced liver disease will continue to rise over the next two decades, with a ~32% increase in the number of HCC cases and a ~39% increase in decompensated cirrhosis cases, irrespective of the treatment option chosen. Results also show an increase of 58.5% in the number of liver-related deaths from 1 550 in 2015 to ~2 458 in 2035.

Results from the base case analysis furthermore indicated that treating 0.18% of all diagnosed patients per year is not enough to show any benefit of using sofosbuvir over the current SOC. Results from the sub-group analysis, however, showed that if policy-makers and physicians were to aim to scale up active treatment of HCV to at least 10% of all diagnosed non-cirrhotic CHC patients annually — assuming that newly diagnosed patients are also eligible for treatment — the impact of antiviral therapy on chronic HCV-infections and the added benefit of treating patients with sofosbuvir-based regimens instead of the current SOC becomes visible. By treating at least 10% of all diagnosed non-cirrhotic CHC patients annually for the next 20 years with sofosbuvir-based regimens, a total of 203 cases of decompensated cirrhosis, 145 cases of HCC and 188 liver-related deaths could be avoided over the next two decades. Furthermore, the incidence of new cases will start to decline faster, reducing the increase in liver-related morbidity and mortality with 5%.

With the proposed HCV treatment scale-up, the annual treatment rate of HCV in South Africa could increase from 0.025% to 0.65% over the next two decades. Furthermore, opting to treat patients with sofosbuvir-based regimens instead of SOC (i.e. peg-INF/RBV), will almost double the annual percentage of patients who achieve SVR; curing 0.60% (1 601 out of 268 563) of the total HCV infected population compared to 0.36% (978 out of 269 075) if practitioners continue to treat patients with SOC. These numbers seem low, but considering the considerable costs associated with treating decompensated cirrhosis and HCC, this could have a significant impact on healthcare budgets in the long term.

The conclusions drawn from the public health impact analysis were the following:

Even though the total number of HCV infections in South Africa is expected to decline, HCV-related morbidity and mortality is expected to increase as the population ages and patients with chronic infection progress to more advanced liver-disease. The current treatment paradigm in South Africa is insufficient to control the HCV disease burden and this failure of policy-makers to control hepatitis disease could have great significance for future costs to health and welfare budgets. Increased treatment and/or higher efficacy therapies are needed to keep the number of HCV infected patients with advanced liver diseases and liver related deaths from increasing.

Studies have shown that sofosbuvir-based regimens not only have to potential to cure almost twice as many patients with chronic HCV infection, but also significantly reduce risks for HCV-related morbidity and mortality in the long term, provided that we treat enough patients early in the disease. However, unless policy-makers in South Africa adopt proven public health strategies to actively identify those infected, ensure appropriate diagnosis and treatment, and provide comprehensive follow-up and support, the individual and public health benefits of curative therapies such as sofosbuvir will fail to materialize.

(vii) Determining the budget impact of sofosbuvir in South Africa as part of the total health budget

This objective was met in manuscript 3. The goal of manuscript 3 was to estimate the financial consequences of adoption and diffusion of sofosbuvir-based regimens within the South African healthcare setting when aiming for the same 90-90-90 target by 2020. As a framework for the analysis, two strategies were considered: the first was to look at a status quo strategy where a limited number of patients are treated with different treatment regimens. The second was an attempt to draw from the lessons learnt from the global response to combating the HIV epidemic, specifically when aiming to adopt a 90:90:90 strategy, with the goal to eradicate HCV and stop transmission, and to quantify what monetary resources will be required to implement this strategy.

The cost-effectiveness model was adapted for the purpose of the budget impact analysis. The model still consisted of an initial decision tree and a state-transition Markov model to simulate the clinical course of patients with chronic HCV infection, and project patients' outcomes. The model considered the same three treatment strategies as for the cost-effectiveness analysis: i) sofosbuvir-ledipasvir (SOF/LDV) monotherapy; ii) sofosbuvir triple therapy (SOF-TT) and iii) SOC (peg-INF + RBV). Health states included in this model were CHC without cirrhosis, compensated cirrhosis, decompensated cirrhosis, HCC, SVR, liver-related death and non-liver related death.

For the base case analysis a cohort of one hundred treatment-naive patients with chronic HCV infection living in South Africa was considered, and baseline characteristics for the target population were based on the patient demographics of a South African HCV cohort. Similar to the cost-effectiveness and public health impact analyses, the primary efficacy measure used in the model was SVR, 12 weeks and 24 weeks after completion of treatment for sofosbuvir-containing regimens and SOC, respectively. In the absence of head-to-head trials, response rates for SOF-TT were taken from the NEUTRINO trial, whereas response rates for SOF/LDV were based on ION-1, ION-2, ION-3, and SYNERGY trials, as well as the open-label study conducted by Abergel *et al.* (2015) in France. Response rates of SOC were based on the

pooled results from the BERNAR-1 and BERNAR-2 RCT's. Dosing and administration of the treatment alternatives, annual transition probabilities remained unchanged from the previous models.

The model started with the annual number of patients who receive HCV treatment. For the base case analysis, this was assumed to be 100 new patients each year for five annual cycles. At the beginning of each cycle, 100 new patients entered the model with a confirmed diagnosis of CHC and initiated treatment upon entering the model. For all treatment arms, the aim of treatment was SVR, and based on the efficacy rates of each treatment option modeled, treatment could either be successful (achieved SVR) or unsuccessful (failed to achieve SVR). Patients who achieved SVR were assumed to maintain SVR and not experience further disease progression until they died, whereas patients who failed to achieve SVR could follow one of three different paths at the end of each one year cycle: i) continue in the same health state without suffering from any event; ii) die of non-liver related causes (all-cause mortality) or iii) progress to the next health state in the natural history model, based on their transition probabilities, irrespective of the treatment option chosen. After five cycles were complete, the model yielded an average lifetime cost for each treatment strategy which was then used to perform the budget impact analysis.

Following recommendations of the ISPOR Budget Impact Analysis Good Practice Task Force, all direct disease costs associated with chronic HCV infection were considered to estimate the budget impact of sofosbuvir-based regimens, including diagnostic costs, drug regimen, treatment monitoring and health state (downstream liver-disease complications) costs. In addition to receiving drug-treatment, all patients underwent baseline testing and diagnoses upon entering the model. Patients in both arms of the model acquired a once-off cost for pathology, the cost of a liver biopsy and the cost of a consultation with a specialist (hepatologist), irrespective of the treatment option chosen. Costs of laboratory tests, radiological examination and consultations were based on the prices in the Referencing Price List (RPL), and were calculated according to specified monitoring resource use. The latest RPL values (2009) were inflated using published annual medical inflation numbers from Statistic South Africa (STATS SA) and total monitoring costs over the treatment period were aggregated from calculated totals. Drug costs included the costs of peg-INF, RBV, sofosbuvir and SOF/LDV, and drug regimen costs were based on unit drug costs, indicated drug dosing and therapy duration. Unit prices of peg-INF and RBV were taken from the Official Pharmaceutical Bluebook. The total cost of drug treatment and total monitoring costs were added to calculate a total annual treatment cost for cirrhotic and non-cirrhotic patients in each treatment arm. Patients who failed to achieve SVR continued to receive costs associated with follow-up and advanced disease states. All costs were converted to a 2015 baseline by using published

annual medical inflation numbers from STATS SA (STATS SA, 2009 – 2015) and expressed in South African Rand (ZAR) and United States Dollars (US$).

Results from the analysis showed that the annual budget required to actively treat and monitor 100 new CHC patients in South Africa with the current SOC, and to follow-up those who failed treatment is approximately R29 000 000 (US$2 471 712). The estimated cumulative cost over five years was estimated at R145 104 298 (US$12 367 448). The base case analysis also showed the incremental budget impact if the treatment protocol were changed from SOC to either of the sofosbuvir-based regimes: the required budget for treating 100 patients with SOF/LDV or SOF-TT, would be between ~R22 900 000 (US$1 951 800) and ~R23 800 000 (US$2 028 508) per year, or R114 220 546 (US$9 735 181) and R118 765 505 (US$10 122 555) over five years for SOF/LDV and SOF-TT, respectively. The incremental budget impact for treating patients with SOF/LDV or SOF-TT instead of SOC, was estimated at between -R5 000 000 (-US$426 157) and -R6 000 000 (US$511 389) per year, or -R26 338 793 (US$2 244 893) and -R30 883 752 (US$2 632 267) over five years, which represents a significant cost-saving over SOC. Without increasing the HCV budget, but changing the current treatment protocol from SOC to SOF-based regimens, the cost-saving awarded by sofosbuvir-based regimes would allow an additional 22 to 28 CHC patients to receive treatment with SOF-TT or SOF/LDV, per year.

The results further showed that in order to achieve the goal of diagnosing at least 90% of the current estimated infections, and treating 90% of those diagnosed by 2020 (i.e. treating ~80% of all current infections), a total of 318 978 patients need to receive antiviral treatment over the next five years. In order to reach 318 978 treated patients by 2020, the number of patients treated per year needs to be drastically scaled up from the current protocol; from 100 to over 10 000 in the first year, and thereafter doubling the number of patients annually over the next four years. The initial cost to scale-up treatment from 100 to ~10 000 per year, using sofosbuvir-based therapies instead of SOC, would increase the budget for HCV from an estimated R29 million per annum to >R2 billion. Thereafter, the annual budget would need to be doubled each year over the next four years, reaching a total of between R37.5 billion and R39 billion (~US$3 billion) in 2020. In order to reach a 90-90-90 target, *viz.* treat at least 90% of all patients diagnosed with chronic HCV infection in SA with SOF-TT, a total of R75.7 billion (US$6 billion) would need to be budgeted for HCV over the next five years.

The conclusions drawn from the budget impact analysis were the following:

The use of sofosbuvir-based regimens therapies could substantially reduce HCV-related complications and might be cost-effective in the majority of patients with CHC in SA. Therapy

with the fixed-dose combination of SOF/LDV or SOF-TT, respectively, is notably less costly than response-guided therapy with SOC, with incremental cost savings between R5 million and R6 million (~US$426 000 – US$511 000). Savings awarded by sofosbuvir-based regimens will open up access to care to at least 127 patients over a 5 year period without any additional financial resource investment. However, treating all treatment-eligible patients in SA would have a significant budgetary impact on both private and government providers, and additional resources are needed to manage this epidemic.

4.3 Study strengths and limitations

4.3.1 Study strengths

Health care payers, policy decision-makers and patients stand to benefit from this study, as the model developed during this study will predominantly serve as a normative decision making aid for policy makers; to inform funding decisions on competing courses of actions regarding the treatment of hepatitis C infection.

For both the public and private healthcare sectors, the determination of a cost-effective price for sofosbuvir, and other drugs containing sofosbuvir as a primary ingredient, might aid in pricing discussions with pharmaceutical companies designated to supply generics of these drugs to South Africa. The more cost-effective the price, the more patients could benefit from a life-saving treatment on a constrained healthcare budget. Given the absence of prospective, long-term studies on sofosbuvir that include cost data in South Africa and the fact that concerns about cost are dominating decisions about treatment, further economic modelling of treatment strategies may serve to aid in allocating resources for maximal collective health benefits (Koff & Seeff, 1995:1882; Gellad *et al*., 2012:1189).

The value of this study therefore lies in empowering policy-makers to make informed decisions about the treatment of hepatitis C infection.

4.3.2 Study limitations

Potential limitations of this study exist. Firstly, the model is largely populated with clinical trial data, which does not necessarily represent a real world environment. Real-world efficacy rates and patient adherence associated with the modelled treatment regimens may be substantially lower and the frequency of side-effects may be higher than reported in clinical trial settings. In general, data from clinical trials are not directly transferable to clinical practice, since trial patients are healthier, show greater adherence to trial protocol, and are more closely monitored. The model also used aggregate, rather than individual patient data. Subsequently, the results reflected group averages rather than individual data. Moreover, we efficacy rates for each

treatment arm in the models were derived from separate studies, as no head-to-head clinical trials including SOF/LDV, SOF/LDV and SOC were available at the time of this analysis. Also, as patients' demographical and clinical characteristics are different across clinical trials, efficacy rates are influenced.

Secondly, the model only considers a treatment-naive cohort and does not demonstrate if there is a difference in the cost-effectiveness of sofosbuvir-containing regimens in treatment-experienced patients, or how retreating treatment-experienced patients with sofosbuvir-containing regimens would influence the future HCV burden. Fibrosis progression was considered to be linear in non-cirrhotic patients; however, studies have shown that fibrosis progression accelerates in the latter stages of chronic hepatitis C (Zarski *et al*., 2003:309). The model only compensated for accelerated fibrosis progression with increasing age, by discriminating cohorts according to age. The model also disregarded the effect of risk factors such as increased alcohol consumption on fibrosis progression, since the model did not include comorbidities or associated risk factors. Another element not addressed by this model is the potential contribution of extrahepatic manifestations of HCV infection. All of this might underestimate the rate of all-cause mortality, as studies have indicated increased all-cause mortality in HCV populations due to increased co-morbidities (El-Kamary *et al.*, 2011:150). In addition, the model does not consider the progression of cured HCV patients. More advanced patients may continue their disease progression after achieving SVR, although at a slower rate.

Because the model only considered a HIV-negative cohort, it did not take HIV/AIDS into account as a potential confounder of treatment efficacy. This might be important for South Africa, as an estimated 12.2% of the South African population (6.4 million persons) are HIV positive, and studies have indicated a significantly higher prevalence of HCV among HIV infected patients as compared to HIV negative patients (13.4% *vs.* 1.73%) (Parboosing, 2008; Shisana *et al*., 2014). Notwithstanding evidence on improved efficacy of sofosbuvir and SOF/LDV in HIV-infected cohorts over the current SOC (CinicalTrials.gov, 2014; Molina *et al*., 2015:1104), efficacy data of sofosbuvir and SOF/LDV in HIV-positive HCV genotype 5 are unavailable.

Very little epidemiology data is available for HCV in South Africa. Prevalence and incidence data were taken from published literature and the consensus numbers reported in these studies may not be representative of the true state of HCV infection South Africa. For the public health impact analysis, the model used the annual number of new cases and tracked their progression over time. A key limitation of this analysis was the assumption that the number of new cases of HCV, and the number of newly diagnosed cases will remain constant after the last reported year. Higher numbers of new infections in 2015 and beyond could thus result in higher total numbers of infections in 2035. A further limitation is the assumption that sufficient numbers of

diagnosed patients will be available for treatment, however, in reality, as the diagnosis rate increases, it will become more difficult to find undiagnosed patients. In addition, diagnosed patients may not have easy access to care. The data presented in manuscript two may overestimate the reduction in HCC and decompensated cirrhosis cases, as the scope of the analysis was limited to HCV viremic individuals.

The base case analyses of both the public health impact and the budget impact analyses assumed that only 100 patients in South Africa receive treatment for HCV per year. Because there is no central registry in South Africa recording and/or monitoring treatment of HCV infected patients, treatment rates were based on results from study that utilised drug sales data and expert panel to estimates. These estimates may over or under-estimate the total number of treated patients in South Africa. This highlights the need for more robust epidemiology studies to quantify HCV in the general population.

4.4 Recommendations

Data on all aspects of HCV in South Africa is rare; including epidemiology data, data on the number of patients receiving treatment, efficacy of treatment and utility values of patients with HCV. South Africa has a rather unique HCV population, in that HCV genotype 5 is the prevalent genotype in South Africa. Given its almost endemic nature to South Africa, it is less well studied and epidemiological data describing the characteristics of chronic HCV infection in South Africa is limited. This study highlights the need for more robust HCV epidemiology analyses that take into consideration the general population and subpopulations that may not be captured in a national study. Future studies are recommended to collect data required for a detailed analysis of HCV disease burden; including anti-HCV and viremic prevalence, the number previously and newly diagnosed, the annual number of treated patients and the genotype distribution. Ideally, future research will also include a HRQoL study in South African patients with HCV infection, which can be utilised to calculate utility values for use in further pharmacoeconomic analyses.

Furthermore, HCV genotypes 4, 5 and 6 are spreading outside their main foci and reaching western countries, and so they should not be neglected by the medical community. These three genotypes represent more than 20% of all HCV cases worldwide and prospective studies are needed, especially in HCV-G5 and HCV-G6, to determine optimal duration of treatment and efficacy rates of newer anti-HCV drugs in these genotypes (Antaki *et al.,* 2009:351).

Other sofosbuvir combinations are currently being tested in on-going trials and further guideline adaptations for HCV-G5 may follow in the near future. Even though these drugs remain unregistered and unavailable in South Africa, with recent findings on the efficacy of drugs like

Harvoni® in HCV-G5, future research is warranted on the cost-effectiveness of other sofosbuvir-containing regimens for treating HCV in SA.

4.5 Chapter summary

This final chapter completes the study by correlating the achievements of the study to the specific objectives outlined from the beginning of the study. The strengths and limitations were described, and recommendations for future research were made. Hereby the objectives set for this study were met.

REFERENCES

AASLD (American Association for the Study of Liver Diseases). 2015. Summary of recommendations for patients who are initiating therapy for HCV infection by HCV genotype. http://www.hcvguidelines.org/printpdf/full-report/initial-treatment-box-summary-recommendations-patients-who-are-initiating-therapy-hcv Date of access: 28 Aug. 2015.

Abergel, A., Loustaud-Ratti, V., Metivier, S., Jiang, D., Kersey, K., Knox, S.J., Svarovskaia, E., Pang, P.S., Samuel, D. & Asselah, T. 2015. Ledipasvir/Sofosbuvir for the treatment of patients with chronic genotype 4 or 5 HCV infection. Paper presented at The International Liver Congress 2015: 50th annual meeting of the European association for the Study of the Liver (EASL), Vienna, Austria; April 22-26. http://natap.org/2015/EASL/EASL_80.htm Date of access: 21 Aug. 2015.

Abuelhassan, W. 2012. Review: hepatitis C virus infection in 2012 and beyond. *South African journal of epidemiology and infection,* 27(3):93-97.

Acts ***see*** South Africa.

Ademi, Z., Hansoo, K., Zomer, E., Reid, C.M., Hollingsworth, B. & Liew, D. 2012. Overview of pharmacoeconomic modelling methods. *British journal of clinical pharmacology,* 75(4):944-950.

Afdhal, N., Zeuzem, S., Kwo, P., Chojkier, M., Gitlin, N., Puoti, M., Romero-Gomez, M., Zarski, J., Agarwal, K., Buggisch, P., Foster, G.R., Bräu, N., Buti, M., Jacobson, I.M., Subramanian, G.M., Ding, X., Mo, H., Yang, J.C., Pang, P.S., Symonds, W.T., McHutchison, J.G., Muir, A.J., Mangia, A., & Marcellin, P. 2014a. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *The New England journal of medicine,* 370(20):1889-1898.

Afdhal, N., Reddy, K.R., Nelson, D.R., Lawitz, E., Gordon, S.C., Schiff, E., Nahass, R., Ghalib, R., Gitlin, N., Herring, R., Lalezari, J., Younes, Z.H., Pockros, P.J., Di Bisceglie, A.M., Arora, S., Subramanian, G.M., Zhu, Y., Dvory-Sobol, H., Yang, J.C., Pang, P.S., Symonds, W.T., McHutchison, J.G., Muir, A.J., Sulkowski, M. & Kwo, P. ION-2 Investigators. 2014b. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *The New England journal of medicine,* 370(16):1483-1493.

Akpan, N. 2013. Hepatitis C cure? Sofosbuvir plus ribavirin eliminate liver infection in promising NIH trial. *Medical Daily,* 27 Aug. http://www.medicaldaily.com/hepatitis-c-cure-sofosbuvir-plus-ribavirin-eliminate-liver-infection-promising-nih-trial-254613 Date of access: 9 Sep. 2014.

Alawazi, W., Cunningham, M., Dearden, J. & Foster, G.R. 2013. Systematic review: outcome of compensated cirrhosis due to chronic hepatitis C infection. *Alimentary pharmacology & therapeutics,* 32(3):344-355.

Alberti, A., Chemello, L. & Benvegnhù, L. 1993. Natural history of hepatitis C. *Journal of hepatology,* 31(Suppl. 1):11-24.

Aleem, I.S., Schemitsch, E.H. & Hanson, B.P. 2009. What is clinical decision analysis study? *Indian journal of orthopedics,* 42(2):137-139.

Alexopoulou, A. & Papatheodoridis, G.V. 2014. Current progress in the treatment of chronic hepatitis C. *World journal of gastroenterology,* 18(42):6060-6069.

Alter, M.J. 2011. HCV routes of transmission: what goes around comes around. *Seminars in liver disease,* 31(4):340-346.

Alter, M.J., Kruszon-Morgan, D., Naina, O.V., McQuillan, G.M., Gao, F., Moyer, L.A., Kaslow, R.A. & Margolis, H.S. 1999. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *The New England journal of medicine,* 341(8):556-562.

Andrei, G. & De Clercq, E. 1993. Molecular approaches for the treatment of hemorrhagic fever virus infections. *Antiviral research,* 22(1):45-75.

Antaki, N., Craxi, A., Kamal, S., Moucari, R., Van der Merwe, S., Haffar, S., Gadano, A., Zein, N., Lai, C.L., Pawlotsky, Heathcote, E.J., Dusheiko, G. & Marcellin, P. 2009a. The neglected hepatitis C virus genotypes 4, 5 and 6: an international consensus report. *Liver international,* 30(3):342-355.

Antaki, N., Hermes, A., Hadad, M., Ftayeh, M., Antaki, F., Abdo, N. & Kebbewar, K. 2009b. Efficacy of interferon plus ribavirin in the treatment of heaptitis C virus genotype 5. *Journal of viral hepatology,* 15(5):383-386.

Aragon, G. & Younossi, Z.M. 2010. When and how to evaluate mildly elevated liver enzymes in apparently healthy patients. *Cleveland Clinic journal of medicine,* 77(3):195-204.

Archer, C. 2013. The role of private specialists in an NHI system. http://www.hsf.org.za/siteworkspace/cms-news-march-2013-nhi-final-website-1.pdf Date of access: 15 Aug. 2013.

Arenas-Guzman, R., Tosti, A., Hay, R. & Haneke, E. 2005. Pharmacoeconomics: an aid to better decision-making. *Journal of the European Academy of Dermatology and Venereology,* 19(1):34-39.

Armstrong, G.L. 2003. Commentary: modelling the epidemiology of hepatitis C and its complications. *International journal of epidemiology,* 32(5):725-726.

Ascione, A., Tartaglione, M.T. & Di Constanzo, G.G. 2007. Natural history of chronic hepatitis C virus infection. *Digestive and liver disease*, 39(Suppl. 1):S4-S7.

ASSA (Actuarial Society of South Africa). 2008. Actuarial Society of South Africa HIV demographic model 2008 version. 2008. http://aids.actuarialsociety.org.za/Models-3145.htm Date of access: 1 Feb. 2015.

Au, J.S. & Pockros, P.J. 2014. Novel therapeutic approaches for hepatitis C. *Nature,* 90(1):78-88.

Averhoff, F.M., Glass, N. & Holtzman, D. 2012. Global burden of hepatitis C: considerations for healthcare providers in the United States. *Clinical infectious diseases,* 55(Suppl 1):S10-S15.

Backus, L.I., Boothroyd, D.B., Phillips, B.R., Belperio, P., Halloran, J. & Mole, L.A. 2011. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clinical gastroenterology and hepatology,* 9(6):509-516.

Barrett, P. & Langreth, R. 2015. Pharma execs don't know why anyone is upset by a $94,500 miracle cure. http://www.bloomberg.com/news/articles/2015-06-03/specialty-drug-costs-gilead-s-hepatitis-c-cures-spur-backlash Date of access: 19 Sep. 2015.

Beers, M.H., *ed*. 2006. The Merck manual of diagnosis and therapy. 18th ed. Whitehouse Station, NJ: Merck Research Laboratories.

Bertoletti, A. & Ferrari, C. 2003. Kinetics of the immune response during HBV and HCV infection. *Hepatology,* 38(1):4-13.

Bestmed Medical Scheme. 2015. Comparative guide 2015. http://www.bestmed.co.za/Documents/ComparativeGuides/Pulse-BULKUntabbedComparativeGuideLRFinal.pdf Date of access: 12 Oct. 2015.

Bica, I., McGovern, B., Dhar, R., Stone, D., McGowan, K. & Scheib, R. 2001. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clinical infectious diseases*, 32(3):492-497.

Blachier, M., Leleu, H. & Peck-Radosavljevic, M. 2013. The burden of liver disease in Europe: a review of available epidemiological data. European Association for the Study of the Liver 2013. http://www.easl.eu/medias/EASLimg/Discover/EU/54ae845caec619f_file.pdf Date of access: 17 Jun. 2015.

Bonny, C., Fontaine, H., Poynard, T., Hézode, C., Larrey, D., Marcellin, P., Bourlière, M., Bronowicki, J.P., Merle, P., Zarski, J.P., Sapey, T., Guillemard, C., Ughetto, S., Henquell, C., Nicolas, C., Roche, C., Randl, K., Bommelaer, G. & Abergel, A. 2006. Effectiveness of interferon plus ribavirin combination in the treatment of naive patients with hepatitis C virus type 5: a French multicentre retrospective study. *Alimentary pharmacology & therapeutics,* 24(4):593-600.

Bootman, J.L. & Skrepnek, G.H. 2012. Achieving value: the role of pharmacoeconomics. *Pharmaceuticals policy and law,* 14:3-6.

Bootman, J.L., Townsend, R.J. & McGhan, W.F. 1996. Introduction to pharmacoeconomics. (*In* Bootman, J.L., Townsend, R.J. & McGhan, W.F., *eds.* Principles of pharmacoeconomics. 2nd ed. Cincinnati, OH: Harvey Whitney. p. 5-19).

Boskey, E. 2015. About health: treatment naïve. http://std.about.com/od/T-Z/g/Treatment-Naive.htm Date of access: 16 Mar. 2016.

Botha, J.F., Kassianides, C., Schneider, H.R., Song, E., Spearman, W. & van der Merwe, S.W. 2010. South African hepatitis C management guidelines 2010. *South African gastroenterology review*, 8(1). http://www.sages.co.za/images/hcvjfb.pdf Date of access: 12 Dec. 2014.

Bourliere, M., Khaloun, A. & Wartelle-Bladou, C. 2011. Chronic hepatitis C: treatments of the future. *Clinics and research in hepatology and gastroenterology,* 35(2):S85-S96.

Bowling, A. 1999. Health-related quality of life: a discussion of the concept, its use and measurement background: The “Quality of Life”. http://info.worldbank.org/etools/docs/library/48475/m2s5bowling.pdf Date of access: 16 Sep. 2014.

CADTH (Canadian Agency for Drugs and Technologies in Health). 2015. CADTH therapeutic review: drugs for chronic hepatitis C infection: recommendations report. https://www.cadth.ca/sites/default/files/pdf/TR0008_HepatitisC_RecsReport_e.pdf Date of access: 18 Mar. 2016.

CDC (Centers for Disease Control and Prevention). 1998. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR 1998;47(No. RR–19). http://www.cdc.gov/mmwr/preview/mmwrhtml/00055154.htm Date of access: 19 Sep. 2014.

CDC (Centers for Disease Control and Prevention). 2012. The ABCs of hepatitis. http://www.cdc.gov/hepatitis/Resources/Professionals/PDFs/ABCTable.pdf Date of access: 28 Apr. 2015.

CDC (Centers for Disease Control and Prevention). 2013. Interpretation of results of tests for hepatitis C virus (HCV) infection and further actions. http://www.cdc.gov/hepatitis/hcv/pdfs/hcv_graph.pdf Date of access: 28 Apr. 2015.

Chhatwal, J., Kanwal, F., Roberts, M.S. & Dunn, M.A. 2015. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. *Annals of internal medicine,* 162(6):397-406.

Chen, S.L. & Morgan, T.R. 2006. The natural history of hepatitis C virus (HCV) infection. *International journal of medical sciences*, 3(2):47-52.

Chong, C.A., Gulamhussein, A., Heathcote, E.J., Lilly, L., Sherman, M., Naglie, G. & Krahn, M. 2003. Health-state utilities and quality of life in hepatitis C patients. *American journal of gastroenterology,* 98(3):630-638.

Choo, Q.L., Kuo, G., Weiner, A.J., Overby, L.R., Bradley, D.W. & Houghton, M. 1989. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science,* 244(4902):359-362.

Choo, Q.L., Richman, K.H., Han, J.H., Berger, K., Lee, C., Dong, C., Gallegos, C., Coit, D., Medina-Selby, R. & Barr, P.J. 1991. Genetic organization and diversity of the hepatitis C virus. *Proceedings of the National Academy of Sciences of the United States of America,* 88(6):2451-2455.

ClinicalTrials.gov. 2014. Efficacy and safety of sofosbuvir plus ribavirin in chronic genotype 1, 2 and 3 hepatitis C Virus (HCV) and human immunodeficiency virus (HIV) co-infected adults. https://clinicaltrials.gov/show/NCT01667731 Date of access: 24 Aug. 2015.

ClinicalTrials.gov. 2015. Ledipasvir/Sofosbuvir fixed-dose combination with ribavirin or GS-9669 in subjects with chronic genotype 1 HCV infection. https://clinicaltrials.gov/ct2/show/NCT01984294 Date of access: 7 Jun. 2015.

CMS (Council for Medical Schemes). 2003. Recommendations of the committee on standardisation of data and billing practices. http://www.medicalschemes.com/publications/ZipPublications/Presentations%20And%20Reports/StandardisationManual.pdf Date of access: 12 Oct. 2015.

CMS (Council for Medical Schemes). 2009. Reference Price List (RPL). National reference price list for services by medical practitioners, effective from 1 January 2009. http://wcawca.co.za/files/bhf_2009_medical_practitioners.pdf Date of access: 10 Oct. 2014.

CMS (Council for Medical Schemes). 2015a. Acts and regulations. http://www.medicalschemes.com/publications.aspx Date of access: 10 Jan. 2015.

CMS (Council for Medical Schemes). 2015b. Questions. https://www.medicalschemes.com/medical_schemes_pmb/questions.htm Date of access: 8 Sept. 2015.

Corbett, R., Cohen, C., Kugelmas, M., Luken, K. & Riley, L. 2006. Reading the signs: choices in hepatitis C care. *Journal of the American Academy of Nurse Practitioners,* 18(Suppl. S1):1-16.

Cox, A.L., Netski, D.M., Mosbruger, T., Sherman, S.G., Strathdee, S., Ompad, D., Vlahov, D., Chien, D., Shyamala, V., Ray, S.C. & Thomas, D.L. 2005. Prospective evaluation of community-acquired acute-phase hepatitis c virus infection. *Clinical infectious diseases,* 40(7):951-958.

David, M., Petricoin ,E., Benjamin, C., Pine, R., Weber, M. & Larner, A. 1995. Requirement for MAP kinase (ERK2) activity in interferon alpha- and interferon betastimulated gene expression through STAT proteins. *Science*, 269(5231):1721-1723.

Davis, G.L., Albright, J.E., Cook, S.F. & Rosenberg, D.M. 2003. Projecting future complications of chronic hepatitis C in the United States. *Liver transplantation,* 9(4):331-338.

Davis, G.L. 2002. Monitoring of viral levels during therapy of hepatitis C. *Hepatology,* 36(Suppl. 1):S145-S151.

De Groote, K., Michielsen, P. & Delwaide, J. 2014. Cost-effectiveness model for sofosbuvir in chronic hepatitis C. Paper presented at the 17th Annual European ISPOR Congress, Amsterdam, The Netherlands; November 8-12, 2014. http://orbi.ulg.ac.be/bitstream/2268/174731/1/ISPOR%20poster_BE_FINALversie(b)%20(voorkeur).pdf Date of access: 20 Aug. 2015.

Delwaide, J., Gerard, C., Reenaers, C., Vaira, D., Bataille, C., Servais, B., Maes, B., Belaiche, J. & Hepatotropes, G.L. Groupe Liegeois D'etudes Des Virus Hepatotropes (GLEVE). 2005. Hepatitis C virus genotype 5 in southern belgium: epidemiological characteristics and response to therapy. *Digestive diseases and sciences,* 50(12):2348-2251.

Deuffic-Burban, S., Poynard, T. & Valleron, A.J. 2002. Quantification of fibrosis progression in patients with chronic hepatitis C using a Markov model. *Journal of viral hepatology*, 9(2):114-122.

Deuffic-Burban, S., Schwarzinger M, Obach, D., Mallet, V., Pol, S., Pageaux, G.P., Canva, V., Deltenre, P., Roudot-Thoraval, F., Larrey, D., Dhumeaux, D., Mathurin, P. & Yazdanpanah, Y. 2014. Should we await IFN-free regimens to treat HCV genotype 1 treatment-naive patients? A cost-effectiveness analysis (ANRS 95141). *Journal of hepatology,* 61(1):7-14.

D'Heygere, F., George, C., Nevens, F., Van Vlierberghe, H. & Van Der Meeren, O . 2005. Patients infected with HCV-5 present the same response rate as patients infected with HCV-1: results from the Belgian randomised trial for naive and relapsers (BERNAR-1). Paper

presented at the 40th annual meeting of the European-Association-for-the-Study-of-the-Liver, Paris, France; April 13-17, 2005. *Journal of hepatology,* 42:203.

D'Heygere, F., George, C., Van Vlierberghe, H., Decaestecker, J., Nakad, A., Adler, M., Delwaide, J., Laureys, A. & Nevens, F. 2011. Efficacy of interferon-based antiviral therapy in patients with chronic hepatitis C infected with genotype 5: A meta-analysis of two large prospective clinical trials. *Journal of viral hepatology,* 83(5):815-819.

Dillon, J. 2007. Management of hepatitis C. *Primary health care,* 17(5):25-29.

Dinner, K., Donaldson, T., Potts, J., Sirna, J. & Wong, T. 2005. Hepatitis C: a public health perspective and related implications for physicians. *Royal College Outlook,* 2:20-22.

Discovery Health Medical Scheme. 2015. Saver and core series: health plan guide. https://www.discovery.co.za/discovery_coza/web/linked_content/pdfs/financial_advisers/health/core_and_saver_plan_brochure.pdf Date of access: 13 Oct. 2015.

EASL (European Association for the Study of the Liver). 2015. EASL recommendations on treatment of hepatitis C. *Journal of hepatology,* 63(Suppl. 1):199-236.

Eddy, D.M., Hollingworth, W., Caro, J.J., Tsevat, J., McDonald, K.M. & Wong, J.B. 2012. Model Transparency and Validation: A report of the ISPOR-SMDM modeling good research practices Task Force–7. Medical decision making, 32(5):733-743.

El-Kamary, S.S., Jhaveri, R. & Shardell, M.D. 2011. All-Cause, liver-Related, and non–liver-related mortality among HCV-infected individuals in the general US population. *Clinical infectious diseases,* 53(2):150-157.

FDA (U.S. Food and Drug Administration). 2013. Approval of Sovaldi (sofosbuvir) tablets for the treatment of chronic hepatitis C. http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/ucm377920.htm Date of access: 2 Aug. 2014.

FDA (U.S. Food and Drug Administration). 2014. FDA approves first combination pill to treat hepatitis C. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm418365.htm Date of access: 13 Nov. 2014.

Feeny, D. 2000. A utility approach to the assessment of health-related quality of life. *Medical care*, 38(9):II-151-II-154.

Ferenci, P., Lafer, H., Scherzer, T.M., Maieron, A., Hofer, H., Stauber, R., Gschwantler, M., Brunner, H., Wenisch, C., Bischof, M., Strasser, M., Datz, C., Vogel, W., Löschenberger, K. & Steindl-Munda, P. Austrian Hepatitis Study Group. 2010. Peginterferon alfa-2a/ribavirin for 48 or 72 weeks in hepatitis C genotypes 1 and 4 patients with slow virologic response. *Gastroenterology,* 138(2):503-512.

Ferreira, P.L., Ferreira, L.N. & Pereira, L.N. 2008. How consistent are health utility values? *Quality of life research*, 17(7):1031-1042.

FEROZSONS Laboratories Ltd. 2014. Ferozsons Lab, Gilead Sciences sign agreement. News center: 20 Jun. 2014. http://www.ferozsons-labs.com/index.php?option=com_news&view=news&news_id=78# Date of ccess: 20 Aug. 2015.

Fick, M. & Hirschler, B. 2014. Gilead offers Egypt new hepatitis C drug at 99 percent discount. *Reuters*, 21 Mar. http://www.reuters.com/article/2014/03/21/us-hepatitis-egypt-gilead-sciences-idUSBREA2K1VF20140321 Date of access: 20 Aug. 2015.

Flinn, R. & Armstrong, D. 2012. Abbott's hepatitis C drugs clear virus in 99% of patients. *Bloomberg*, 15 Oct. http://www.bloomberg.com/news/2012-10-15/abbott-s-hepatitis-c-drugs-clear-virus-in-99-of-patients.html Date of access: 13 Oct. 2013.

Ford, N., Singh, K., Cooke, G.S., Mills, E.J., Von Schoen-Angerer, T., Kamarulzaman, A. & Du Cross, P. 2012. Expanding access to treatment for hepatitis C in resource-limited settings: lessons from HIV/AIDS. *Clinical infectious diseases,* 54(10):1465-1472.

Foster, G.R. 2010. Pegylated interferons for the treatment of chronic hepatitis: pharmacological and clinical differences between peginterferon-α-2a and peginterferon-α-2b. *Drugs,* 70(2):147-165.

Franciscus, A. 2007. HCV diagnostic tools: grading & staging a liver biopsy. http://hcvadvocate.org/hepatitis/factsheets_pdf/grade_stage.pdf Date of access: 2 Mar. 2015.

Fried, M.W., Hadziyannis, S.J., Shiffman, M.L., Messinger, D. & Zeuzem, S. 2011. Rapid virological response is the most important predictor of sustained virological response across

genotypes in patients with chronic hepatitis C virus infection. *Journal of hepatology,* 55(1):69-75.

Fried, M.W., Shiffman, M.L., Reddy, K.R., Smith, C., Marinos, G., Goncales, F.L., Jr., Häussinger, D., Diago, M., Carosi, G., Dhumeaux, D., Craxi, A., Lin, A., Hoffman, J. & Yu, J. 2001. Peginterferon alfa-2a and ribavirin for chronic hepatitis C virus infection. *The New England journal of medicine*, 347(13):975-982.

Gane, E.J., Hyland, R.H. An, D., Svarovskaia, E.S., Pang, P.S. & Symonds, W.T. 2014. High efficacy of LDV/SOF regimens for 12 weeks for patients with HCV genotype 3 or 6 infection. *Hepatology,* 60:1274A.

García-Carrasco, M. & Escárcega, R.O. 2006. Extrahepatic autoimmune manifestations of chronic hepatitis C virus infection. *Annals of hepatology*, 5(3):161-163.

Gededzha, M.P., Mphanhlele, M.J., Lukhwareni, A. & Selabe, S.G. 2010. Should routine serological screening for HCV be mandatory in HIV/AIDS patients enrolling for HAART in South Africa? *South African medical journal*, 100(12):814-815.

Gededzha, M.P., Selabe, S.G., Kyaw, T., Rakgole, J.N., Blackard, J.T. & Mphahlele, M.J. 2012. Introduction of new subtypes and variants of hepatitis C virus genotype 4 in South Africa. *Journal of medical virology,* 84(4):601-607.

Gellad, Z.F., Reed, S.D. & Muir, A.J. 2012. Economic evaluation of direct-antiviral therapy in chronic hepatitis C. *Antiviral therapy,* 17:1189-1199.

Gilead Sciences, Inc. 2013. Gilead Announces New Sustained Viral Response Data for Sofosbuvir-Based Regimens in Genotype 3-Infected Hepatitis C Patients. http://www.gilead.com/news/press-releases/2013/11/gilead-announces-new-sustained-viral-response-data-for-sofosbuvirbased-regimens-in-genotype-3infected-hepatitis-c-patients Date of access: 12 Feb. 2014.

Gilead Sciences, Inc. 2014a. Gilead announces generic licensing agreements to increase access to hepatitis C treatments in developing countries. http://www.gilead.com/news/press-releases/2014/9/gilead-announces-generic-licensing-agreements-to-increase-access-to-hepatitis-c-treatments-in-developing-countries Date of access: 25 May 2015.

Gilead Sciences, Inc. 2014c. Chronic hepatitis C treatment expansion: generic manufacturing for developing countries. 2014. http://www.gilead.com/~/media/Files/pdfs/other/HCVGenericAgreementFactSheet.pdf Date of access: 6 Nov. 2014.

Gilead Sciences, Inc. 2014b. Gilead announces phase 2 data for investigational all-oral regimen of sofosbuvir plus GS-5816 for the treatment of chronic hepatitis C. http://www.gilead.com/news/press-releases/2014/11/gilead-announces-phase-2-data-for-investigational-alloral-regimen-of-sofosbuvir-plus-gs5816-for-the-treatment-of-chronic-hepatitis-c Date of access: 15 Feb. 2015.

Gilead Sciences, Inc. 2015a. Sovaldi®. Highlights of prescribing information. http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf Date of access: 10 Apr. 2015.

Gilead Scineces, Inc. 2015b. Gilead announces SVR12 rates from phase 3 study evaluating Harvoni® for the treatment of chronic hepatitis C in patients co-Infected with HIV. http://www. Date of access: 4 Mar. 2015.

Ghany, M.G., Strader, D.B., Thomas, D.L. & Seeff, L.B. 2009. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*, 49(4):1335-1374.

Gravitz, L. 2011. A smouldering public-health crisis. *Nature,* 474(7350):S2-S4.

Grebely, J. & Dore, G.J. 2011. What is killing people with hepatitis C virus infection? *Seminars in liver disease,* 31(4):331-339.

GTPI (The Working Group on Intellectual Property of the Brazilian Network for the Integration of Peoples). 2014. Brazil is excluded from license authorizing production of generic medicine for hepatitis C. http://www.deolhonaspatentes.org.br/media/file/GTPI_statement_Gilead_license_sofosbuvir.pdf Date of access: 20 Aug. 2015.

Gutteling, J.J., De Man, R.A., Busschbach, J.J.V. & Darlington, A.S.E. 2007. Overview of research on health-related quality of life in patients with chronic liver disease. *The journal of medicine,* 65(7):227-234.

Gutteling, J.J., De Man, R.A., Van der Plas, S.M., Schalm, S.W., Busschbach, J.J.V. & Darlington, A.S.E. 2006. Determinants of quality of life in chronic liver patients. *Alimentary pharmacology & therapeutics,* 23(11):1629-1635.

Guyatt, G.H., Juniper, E.F., Walter, S.D., Griffith, L.E. & Goldstein, R.S. 1998. Interpreting treatment effects in randomized trials. *British medical journal,* 316(Feb):690-693.

Hagan, H., Snyder, N., Hough, E., Yu, T., McKeirnan, S., Boase, J. & Duchin, J. 2002. Case-reporting of acute hepatitis B and C among injection drug users. *Journal of urban health,* 79(4):579–585.

Harrison, D. 2009. An overview of health and health care in South Africa 1994 – 2010: priorities, progress and prospects for new gains. http://ftp.bhfglobal.com/files/bhf/overview1994-2010.pdf Date of access: 12 Oct. 2015.

Hay, J. & Jackson, J. 1999. Panel 2: Methodological issues in conducting pharmacoeconomic evaluations – modeling studies. *Value in health,* 2(2):78-81.

Henquell, C., Cartan, C., Abergel, A., Lauricese, H., Regagnon, C., De Champs, C. 2004. High prevalence of hepatitis C virus type 5 in Central France evidenced by a prospective study from 1996 to 2002. *Journal of clinical microbiology*, 42(7):3030-3035.

Hoofnagle, J.H. 1997. Hepatitis C: the clinical spectrum of disease. *Hepatology*, 26(3 Suppl. 1):15S-20S.

Hoofnagle, J.H., Ghany, M.G., Kleiner, D.E., Doo, E., Heller, T., Promrat, K., Ong, J., Khokhar, F., Soza, A., Herion, D., Park, Y., Everhart, J.E. & Liang, T.J. 2003. Maintenance therapy with ribavirin in patients with chronic hepatitis C who fail to respond to combination therapy with interferon alfa and ribavirin. *Hepatology,* 38(1):66-74.

Houghton, M. 2009. Discovery of the hepatitis C virus. *Liver international*, 29(s1):82-88.

Hsu, P.C., Krajden, M., Yoshida, E.M., Anderson, F.H., Tomlinson, G.A. & Krahn, M.D. 2009. Does cirrhosis affect quality of life in hepatitis C virus-infected patients? *Liver international,* 29(3):449-458.

Huggins, J.W. 1989. Prospects for treatment of viral hemorrhagic fevers with ribavirin, a broad-spectrum antiviral drug. *Reviews of infectious diseases,* 11(Suppl. 4):S750-S761.

Hutchinson, S., Bird, S. & Goldberg, D. 2005. Modeling the current and future disease burden of hepatitis C among injection drug users in Scotland. *Hepatology,* 42(3):711-723.

Immunization Action Coalition. 2007. Hepatitis A, B and C: learn the differences. http://www.immunize.org/catg.d/p4075.pdf Date of access: 28 Apr. 2015.

Jack, A. 2013. Indian health activists move to prevent Gilead's drug patent. *Financial Times*, 24 Nov. http://www.ft.com/intl/cms/s/0/7dd38ee4-551a-11e3-86bc-00144feabdc0.html?siteedition=intl#axzz2ldUq9CwB Date of access: 25 Nov. 2014.

Jacobson, I.M., McHutchison, J.G., Dusheiko, G., Di Bisceglie, A.M., Reddy, K.R., Bzowej, N.H., Marcellin, P., Muir, A.J., Ferenci, P., Flisiak, R., George, J., Rizzetto, M., Shouval, D., Sola, R., Terg, R.A., Yoshida, E.M., Adda, N., Bengtsson, L., Sankoh, A.J., Kieffer, T.L., George, S., Kauffman, R.S. & Zeuzem, S. 2011. Telaprevir for previously untreated chronic hepatitis C virus infection. *The New England journal of medicine,* 364(25):2405-2416.

Hatzakis, A., Chulanov, V., Gadano, A.C., Bergin, C., Ben-Ari, Z. & Mossong, J. 2015. The present and future disease burden of hepatitis C virus (HCV) infections with today's treatment paradigm – volume 2. *Journal of viral hepatology,* 22:26-45.

Jenney, M.E. & Campbell, S. 1997. Measuring quality of life. *Archives of disease in childhood*, 77(4):347-354.

Jones, K. 2007. Doing a literature review in health. (*In* Saks, M. & Allsop, J., *eds.* Researching health: qualitative, quantitative and mixed methods. London: SAGE. p. 32-54).

Jover, R., Pérez-Serra, J., De Vera, F., Alamo, J.M., Munoz, C., Yago, C. 2001. Infection by genotype 5a of HCV in a district of Southeast Spain. *American journal of gastroenterology,* 96(10):3042.

Kanda, T., Yokosuka, O. & Omata, M. 2013. Treatment of hepatitis C virus infection in the future. *Clinical and translational medicine,* 2(9):1-8.

Kang, K. 2013. Abnormality on liver function tests. *Pediatric gastroenterology, hepatology and nutrition,* 16(4):225-232.

Kapoor, R., Kohli, A., Sidharthan, S., Sims, Z., Petersen, T.L., Osinusi, A. 2014. All-oral treatment for genotype 4 chronic hepatitis C infection with sofosbuvir and ledipasvir: interim results from the NIAID SYNERGY trial. *Hepatology*, 60:321A.

Karoney, M.J. & Siika, A.M. 2013. Hepatitis C virus (HCV) infection in Africa: a review. *The Pan African medical journal*, 14:44. http://www.panafrican-med-journal.com/content/article/14/44/full/ Date of access: 9 Sep. 2014

Kenny-Walsh, E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. *The New England journal of medicine,* 340(16):1228-1233.

Kerr, C., Lloyd, A., Ali, S., Goreb, C. & Tyas, D.A. 2012. Impact of treatment attributes of peginterferon for hepatitis C on quality of life and treatment preference. *Health outcomes research in medicine,* 3(3):e153-e167.

Khayrihhay, M.H., Groeger, J., Flaxman, A.D. & Wiersma, S.T. 2013. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology,* 57(1):1333-1342.

Kind, P., Elston Lafata, J., Matuszewski, K. & Raisch, D. 2009. The use of QALYs in clinical and patient decision-making: issues and prospects. *Value Health,* 12(Suppl. 1):S27–S30.

Koff, R.S. & Seeff, L.B. 1995. Economic modeling of treatment in chronic hepatitis B and chronic hepatitis C: promises and limitations. *Hepatology,* 22(6):1880-1882.

Koukoulis, G.K. 2001. Chronic hepatitis C: grading, staging and searching for reliable predictors of outcome. *Human pathology*, 32(9):899-903.

Kowdley, K.V., Gordon, S.C., Reddy, K.R., Rossaro, L., Bernstein, D.E., Lawitz, E., Shiffman, M.L., Schiff, E., Ghalib, R. & Ryan, M. 2014. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *The New England journal of medicine,* 370(20):1879-1888.

Krajden, M. & Montaner, J.S.G. 2013. The curability of hepatitis C: implications for a public health response. *British Columbia medical journal,* 55:243.

Krilov, L.R. 2001. Respiratory syncytial virus: update on infection, treatment, and prevention. *Current infectious disease reports,* 3(3):242-246.

LaFleur Brooks, M. & LaFleur Brooks, D. 2013. Basic medical language. 4th ed. St. Louis, MO: Elsevier.

Lancry, P., O'Connor, R., Stempel, D. & Raz, M. 2001. Using health outcomes data to inform decision-making: healthcare payer perspective. *Pharmacoeconomics*, 19(2):39-47.

Langlet, P., D'Heygere, P., Henrion, J., Adler, M., Delwaide, J., Van Vlierberghe, H., Mulkay, J.P., Lasser, L., Brenard, R., Horsmans, Y., Michielsen, P., Laureys, A. & Nevens, F. 2009. A randomized trial of pegylated-interferon-α-2a plus ribavirin with or without amantadine in treatment-naïve or relapsing chronic hepatitis C patients. *Alimentary pharmacology & therapeutics*, 30(4):352-363.

Lavanchy, D. 2011. Evolving epidemiology of hepatitis C virus. *Clinical microbiology and infection,* 17(2):107–115.

Lawitz, E., Mangia, A., Wyles, D., Rodriguez-Torres, M., THassanein, T., Gordon, S.C., Schultz, M., Davis, M.N., Zeid Kayali, Z., Reddy, K.R., Jacobson, I.M., Kowdley, K.V., Nyberg, L., Subramanian, G.M., Hyland, R.H., Arterburn, S., Jiang, D., McNally, J., Brainard, D., Symonds, W.T., McHutchison, J.G., Sheikh, A.M., Younossi, Z. & Gane, E.J. 2013. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *The New England journal of medicine,* 368(1): 1878-87.

Lawitz, E., Poordad, F.F., Sang, P.S., Hyland, R.H., Ding, X., Mo, H., Symonds, W.T., McHutchison, J.G. & Membreno, F.E. 2014. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. *The Lancet,* 383(9916):515-523.

Lee, R. & Davies, G. 2013. Technology: the cure for rising healthcare costs? *MIT Technology Review*, 3 Sep. http://www.technologyreview.com?view/518946/technology-the-cure-for-rising-healthcare-costs/ Date of access: 11 Nov. 2014.

Lee, L.Y., Tong, C.Y.W., Wong, T. & Wilkonson, M. 2012. New therapies for chronic hepatitis C infection: a systematic review of evidence from clinical trials. *The international journal of clinical practice*, 66(4):342-355.

Legrand-Abravanel, F., Sandres-Sauné, K., Barange, K., Alric, L., Moreau, J., Desmorat, P., Vinel, J.P. & Izopet, J. 2004. Hepatitis C Virus Genotype 5: Epidemiological Characteristics

and Sensitivity to Combination Therapy with Interferon-α plus Ribavirin. *The journal of infectious diseases,* 189(8):1397-1400.

Leof, A., Gerrity, M., Thielke, A. & King, V. 2014. Sofosbuvir for the treatment of hepatitis C and evaluation of the 2014 American Association for the Study of Liver Diseases treatment guidelines. Portland, OR: Center for Evidence Based Policy, Oregon Health & Science University.

Lim, S.S., Vos, T., Flaxman, A.D., Danaei, G., Shibuya, K. & Adair-Rohani, H. 2012. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet,* 380(9859):2224-2260.

Legrand-Abravanel, F., Sandres-Sauné, K., Barange,K., Alric, L., Moreau, J., Desmorat, P., Vinel, J.P. & Izopet, J. 2004. Hepatitis C virus genotype 5: epidemiological characteristics and sensitivity to combination therapy with interferon-a plus ribavirin. *The journal of infectious diseases*, 189(Apr):1397-1400.

Leleu, H., Blachier, M. & Rosa, I. 2015. Cost-effectiveness of sofosbuvir in the treatment of patients with hepatitis C. *Journal of viral hepatitis,* 22(4):376-383.

Lindenbach, B.D. & Rice, C.M. 2001. Flaviviridae: the viruses and their replication. (*In* Fields, B.N., Howley, P.M., Griffin, D.E., Lamb, R.A., Martin, M.A., Roizman, B. & Strauss, S.E., *eds*. Fields virology. Philadelphia, PA: Lippincott-Raven. p. 991-1042).

Lodenyo, H., Schoub, B., Ally, R., Kairu, S. & Segal I. 2000. Hepatitis B and C virus infections and liver function in AIDS patients at Chris Hani Baragwanath Hospital, Johannesburg. *East African medical journal*, 77(1):13-15.

Longworth, L & Bryan, S. 2003. An empirical comparison of EQ-5D and SF-6D in liver transplant patients. *Health economics letters,* 7(2):16-22.

Lukhwareni, A., Burnett, R.J., Selabe, S.G., Mzileni, M.O. & Mphahlele, M.J. 2009. Increased detection of HBV DNA in HBsAg-positive and HBsAg-negative South African HIV/AIDS patients enrolling for highly active antiretroviral therapy at a tertiary hospital. *Journal of medical virology,* 81(3):406-412.

Maasoumy, B. & Wedemeyer, H. 2012. Natural history of acute and chronic hepatitis C. *Best practice & research clinical gastroenterology,* 26(1):401–412.

MacKinnon, G.E. 2013. Decision analysis. (*In* MacKinnon, G.E., *ed*. Understanding health outcomes and pharmacoeconomics. Burlington, MA: Jones & Bartlett Learning. p.151-162).

Maheshwari, A., Ray, S. & Thuluvath, P.J. 2008. Acute hepatitis C. *The Lancet*, 372(9635):321-332.

Malone, D.C. 2005. The role of pharmacoeconomic modeling in evidence-based and value-based formulary guideline. *Journal of managed care pharmacy,* 11(4):S7-10.

Manns, M.P., McHutchison, J.G., Gordon, S.C., Rustgi, V.K., Shiffman, M., Reindollar, R., Goodman, Z.D., Koury, K., Ling, M. & Albrecht, J.K. 2001. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. *The Lancet,* 358(9286):958-965.

Marcellin, P. 1999. Hepatitis C: the clinical spectrum of disease. *Journal of hepatology*, 31(Suppl. 1):9-16.

Massard, J., Ratziu, V., Thabut, D., Moussalli, J., Lebray, P., Benhamou, Y. & Poynard, T. 2007. Natural history and predictors of disease severity in chronic hepatitis C. *Journal of hepatology,* 44(Suppl. 1):S19-S24.

Matshidze, P. & Hanmer, L. 2007. Health information systems in the private health sector. (*In* Harrison, S., Bhana, R. & Ntuli, A., *eds*. South African Health Review 2007. Durban: Health Systems Trust. p. 89-102).

McGee, H. & Ring, L. 2010. Quality of Life. (*In* French, D., Vedhara, K., Kaptein, Ad A. & Weinman, J., *eds*. Health pshycology. 2nd ed. Oxford: Blackwell. p. 329-344).

McHutchison, J.G. & Bacon, B.R. 2005. Chronic hepatitis C: an age wave of disease burden. *American journal of managed care,* 11(10):S286-S295.

McLernon, D.J., Dillon, J. & Donnan, P.T. 2008. Health-state utilities in liver disease: a systematic review. *Medical decision making,* 28(4):582-592.

Miller, P. 2005. Role of pharmacoeconomic analysis in R&D decision making: when, where, how? *Pharmacoeconomics*, 23(1):1-12.

Miller, M.F., Haley, C., Koziel, M.J. & Rowley, C.F. 2005. Impact of hepatitis C virus on immune restoration in HIV-infected patients who start highly active antiretroviral therapy: a meta-analysis. *Clinical infectious diseases,* 41(5):713-720.

Milne, R.J. 1998. Pharmacoeconomic models in disease management: a guide for the novice or the perplexed. *Disease management and health outcomes*, 4(3):119-134.

Mohamoud, Y.A., Mumtaz, G.R., Riome, S., Miller, D. & Abu-Raddad, L.J. 2013. The epidemiology of hepatitis C virus in Egypt: a systematic review and data synthesis. *BMC infectious diseases*, 13(288):1-21.

Molina, J.M., Orkin, C., Iser, D.M., Zamora, F.X., Nelson, M., Stephan, C., Massetto, B., Gaggar, A., Ni, L., Svarovskaia, E., Brainard, D., Subramanian, M., McHutchison, J.G., Puoti, M & Rockstroh, J.K. PHOTON-2 study team. 2015. Sofosbuvir plus ribavirin for treatment of hepatitis C virus in patients co-infected with HIV (PHOTON-2): a multicentre, open-label, non-randomised, phase 3 study. *The Lancet,* 385(9973):1098-1106.

Momentum Health. 2015. Focus on the extender option. https://content.momentum.co.za/content/health2015/Focus_Pages/Focus_on_the_Extender_Option_2015.pdf Date of access: 8 Sep. 2015.

Mosby's dictionary of medicine, nursing & health professions. 2006. 7th ed. St. Louis, MO: Mosby Elsevier.

Muller, O., Corrah, T., Katabira, E., Plummer, F. & Mabey, D. 1998. Antiretroviral therapy in sub-Saharan Africa. *The Lancet*, 351(9095):68.

Myers, R.P., Shah, H., Burak, K.W., Cooper, C. & Feld, J.J. 2015. An update on the management of chronic hepatitis C: 2015 consensus guidelines from the Canadian Association for the Study of the Liver. *Canadian journal of gastroenterology and hepatology*. In Press. http://www.liver.ca/files/Professional_Education___Partnerships/Information___Resources_for_HCP/CASL_Hep_C_Consensus_Guidelines_Update_-_Jan_2015.pdf Date of access: 13 Mar. 2016.

Naggie, S., Cooper, C., Saag, M., Workowski, K., Ruane, P., Towner, W.J., Marks, K., Luetkemeyer, A., Baden, R.P., Sax, P.E., Gane, E., Santana-Bagur, J., Stamm, L.M., Yang, J.C., German, P., Dvory-Sobol, H., Ni, L., Pang, P.S., McHutchison, J.G., Stedman, C.A.M., Morales-Ramirez, J.O., Bräu, N., Jayaweera, D., Colson, A.E., Tebas, P., Wong, D.K., Dieterich, D. & Sulkowski, M., for the ION-4 Investigators. 2015. Ledipasvir and Sofosbuvir for HCV in Patients Coinfected with HIV-1. *The New England journal of medicine,* 373(8):705-713.NATCO Pharma Ltd. 2015.

NATCO receives generic sofosbuvir (Sovaldi®) approval for India. News and announcements: 11 Mar. 2015. http://natcopharma.co.in/about/news/#news1 Date of access: 20 Aug. 2015.

National Center for Pharmacoeconomics (NCPE Ireland). 2014. Cost effectiveness of sofosbuvir (in combination with either ribavirin or pegylated interferon + ribavirin) (Sovaldi®) for the treatment of hepatitis C infection. http://www.ncpe.ie/wp-content/uploads/2014/03/Summary-Report-for-Sofosbuvir-Sovaldi-For-website1.pdf Date of access: 18 Jun. 2015.

Ndlovu, N., Vilakazi, M., Majozi, M., Sithole, F., Mbatha, K. & Guthrie, T. 2014. Trends in national and provincial health and HIV/AIDS budgeting and spending in South Africa. Available from http://cegaa.org/resources/docs/healthbudget2014.pdf Date of access: 14 Nov. 2015.

Nevens, F., Van Vlierberghe, H., D'Heygere, F., Delwaide, J., Adler, M., Henrion, J., Lenaerts, A., Hendlisz, A., Michielsen, P., Bastens, B., Brenard, R. & Laureys, A.; The BERNAR-1 Study Group. 2010. A randomized, open-label multicenter study evaluating the efficacy of peginterferon alfa-2a versus interferon alfa-2a, in combination with ribavirin, in naïve and relapsed chronic hepatitis C patients. *Acta gastro-enterologica Belgica*, 73(2):223-228.

NHRPL (National Health Referencing Price List). 2015. http://www.bhfglobal.com/national-health-reference-price-list-nhrpl Date of access: 3 Feb. 2015.

NICE (National Institute for Health and Care Excellence. 2015a. NICE guidance recommends sofosbuvir (Sovaldi, Gilead Sciences) and simeprevir (Olysio, Janssen) for treating hepatitis C. https://www.nice.org.uk/news/press-and-media/nice-guidance-recommends-sofosbuvir-sovaldi-gilead-sciences-and-simeprevir-olysio-janssen-for-treating-hepatitis-c). Date of access: 29 Mar. 2016

NICE (National Institute for Health and Care Excellence). 2015b. NICE recommends three new treatment options for hepatitis C in draft guidance. 2015b. https://www.nice.org.uk/news/press-and-media/nice-recommends-new-treatment-options-for-hepatitis-c Date of access: 29 Mar. 2016

OANDA currency converter. 2015. Average exchange rate for the first quarter of 2015. http://www.oanda.com/currency/converter/ Date of access: 3 May 2015.

OSI (Open Society Institute). 2011. War on drugs: report of the Global Commission on Drug Policy. http://www.refworld.org/docid/4e3250d32.html Date of access: 23 Jul. 2015.

Oxford dictionary of nursing. 2003. 4th ed. Oxford: Oxford University Press.

Oxford University Press. 2016. Oxford dictionaries. http://www.oxforddictionaries.com/definition/english/budget Date of access: 15 Mar. 2016.

Ozaras, R. & Tahan, V. 2009. Acute hepatitis C: prevention and treatment. *Expert review of anti-infective therapy*, 7(3):351-361.

Palella, F.J., Jr., Baker, R.K., Moorman, A.C., Chmiel, J.S., Wood, K.C., Brooks, J.T., Holmberg, S.D. HIV Outpatient Study Investigators. 2006. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *Journal of acquired immune deficiency syndromes,* 43(1):27-34.

Parboosing, R. 2008. Clinical and epidemiological aspects of HIV and hepatitis C virus co-infection in KwaZulu-Natal Province of South Africa. Durban: UKZN. (Thesis — MMed).

Parini, S. 2001. Hepatitis: speaking out about the silent epidemic. *Nursing management,* 32(6):17-24.

Patrick, D.L. & Erickson, P. 1993. Health status and health policy: quality of life in health care evaluation and resource allocation. New York, NY: Oxford University Press.

Pearlman, B.L. & Traub, N. 2011. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. *Clinical infectious diseases,* 52(7):889-900.

Pears, E. 2010. Hepatitis C virus infection: risk factors, diagnosis and management. *Nursing standard,* 25(15-17):49-56.

Petta, S., Cabibbo, G., Enea, M., Macaluso, F.S., Plaia, A., Bruno, R., Gasbarrini, A., Crax, A. & Camm, C. 2014. Cost-effectiveness of sofosbuvir-based triple therapy for untreated patients with genotype 1 chronic hepatitis C. *Hepatology,* 59(5):1692-1705.

Pfeil, A.M., Reich, O., Guerra, I.M., Cure, S., Negro, F., Müllhaupt, B., Lavanchy, D. & Schwenkglenks, M. 2015. Cost-effectiveness analysis of sofosbuvir compared to current standard treatment in Swiss patients with chronic hepatitis C. *PLoS One,* 10(5): e0126984.

Pharand, C. 2002. How to evaluate pharmacoeconomic data: the example of enoxaparin in acute coronary syndromes. *The Canadian journal of hospital pharmacies,* 55(2):114-122.

Phillips, C. 2009. What is cost-effectiveness? http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/Cost-effect.pdf Date of access: 3 Feb. 2015.

Poll, R. 2012. Hepatitis C part I: detection and assessment. *Practice nursing,* 23(8):396-400.

Pollack, A. 2013. FDA Approves pill to treat hepatitis C. *NewYork Times*, 7 Dec. http://www.nytimes.com/2013/12/07/business/fda-approves-pill-to-treat-hepatitis-c.html?ref=health Date of access: 9 Dec. 2013.

Poordad, F. & Dieterich, D. 2012. Treating hepatitis C: current standard of care and emerging direct-acting antiviral agents. *Journal of viral hepatology,* 19(7):449-464.

Poordad, F., Lawitz, E., Kowdley, KV., Cohen, D.E., Podsadecki, T., Siggelkow, S., Heckaman, M., Larsen, L., Menon, R., Koev, G., Tripathi, R., Pilot-Matias, T. & Bernstein, B. 2013. Exploratory study of oral combination antiviral therapy for hepatitis C. The New England medical journal, 368(20):45-53.

Poordad, F., McCone, J., Bacon, B.R., Bruno, S., Manns, M.P., Sulkowski, M.S., Jacobson, I.M., Reddy, K.R., Goodman, Z.D., Boparai, N., DiNubile, M.J., Sniukiene, V., Brass, C.A., Albrecht, J.K. & Bronowicki, J.P. 2011. Boceprevir for untreated chronic HCV genotype 1 infection. *The New England journal of medicine,* 364(13):1195-1206.

Poynard, T., Ratziu, V., Charlotte, F., Goodman, Z., McHutchison, J. & Albrecht, J. 2001. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. *Journal of hepatology,* 34(Suppl. 1):730-739.

Prabdial-Sing, N., Puren, A.J., Mahlangu, J., Barrow, P. & Bowyer, S.M. 2008. Hepatitis C virus genotypes in two different patient cohorts in Johannesburg, South Africa. *Archive of virology*, 153(11):2049-2058.

Prabdial-Sing, N., Puren, A. & Schoub, B. 2013. The status of hepatitis C: the silent "volcano" in South Africa. *Communicable diseases surveillance bulletin,* 11(1):22-25.

Pradat, P., Alberti, A., Poynard, T., Esteban J., Weiland, O., Marcellin, P, Badalamenti, S. & Trěpo, C. 2002. Predictive value of ALT levels for histologic findings in chronic hepatitis C: a European collaborative study. *Hepatology*, 36(4.1):973-977.

Pratt, D.S. 2010. Liver chemistry and function tests. (*In* Feldman, M., Friedman, L.S. & Brandt, L.J., *eds.* Sleisenger and Fordtran's gastrointestinal and liver disease. 9th ed. Philadelphia, PA: Elsevier Saunders. p. 1227-1237).

Pybus, O.G., Charleston, M.A., Gupta, S., Rambaut, A., Holmes, E.C. & Harvey, P.H. 2001. The epidemic behaviour of the hepatitis C virus. *Science,* 292(5525):2323-2325.

Quigley, R., den Broeder, L., Furu, P., Bond, A., Cave, B. & Bos, R. 2006. Health impact assessment: international best practice principles. Fargo: International Association for Impact Assessment; Sep, 2006. (Special Publication Series No. 5). http://activelivingresearch.org/files/IAIA_HIABestPractice_0.pdf Date of acces: 15 Mar. 2016.

Rivas, A. 2013. Gilead combination pill cures 95% hepatitis patients; one-a-day 'game-changing' pill comes with few side effects. *Medical daily,* 5 Nov. http://www.medicaldaily.com/gilead-combination-pill-cures-95-hepatitis-c-patients-once-day-game-changing-pill-comes-few-side Date of access: 5 Dec. 2013.

Roberts, M., Russell, L.B., Paltiel, A.D., Chamber, M., McEwan, P. & Krahn, M. 2012. Conceptualizing a model: a report of the ISPOR-SMDM modeling good research practices task force-2. *Value in health*, 15:804-811.

Saab, S., Hunt, D., Stone, M., McClune, A. & Tong M. 2010. Timing of hepatitis C antiviral therapy in patients with advanced liver disease: a decision analysis model. *Liver transplantation,* 16(6):748-759.

Saadeh, S., Cammell, C., Carey, W.D., Younossi, Z., Barnes, D. & Easley, K. 2001. *Hepatology*, 33(1):196-200.

SAMPR (South African Medicine Price Registry). 2014. Database of medicine prices; 28 January 2014. http://www.mpr.gov.za/PublishedDocuments.aspx#DocCatId=21 Date of access: 28 Jan. 2014.

Salomon, J.A., Weinstein, M.A., Hammitt, J.K. & Goldie, S.J. 2003. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. *Journal of the American Medical Association,* 290(2):228-237.

Santantonio, T. & Fasano, M. 2008. Therapy of acute hepatitis C: a review of literature. *Current pharmaceutical design*, 14(17):1686-1689.

Saraswat, V., Norris, S., de Knegt, R.J., Sanchez, A.J.F., Sonderup, M. & Zuckerman, E. 2015. Historical epidemiology of hepatitis C virus (HCV) in select countries – volume 2. *Journal of viral hepatology,* 22:6-25.

Scuffham, P.A., Whitty, J.A., Mitchell, A. & Viney, R. 2008. The use of QALY weights for QALY calculations: a review of industry submissions requesting listing on the Australian pharmaceutical benefits scheme 2002-2004. *Pharmacoeconomics,* 26(4):297-310.

Seeff, L.B. 1997. Natural history of hepatitis C*. Hepatology,* 26(3 Suppl 1):21S-28S.

Seeff, L.B., Hollinger, F.B., Alter, H.J., Wright, E.C., Cain, C.M., Buskell, Z.J., Ishak, K.G., Iber, F.L., Toro, D., Samanta, A., Koretz, R.L., Perrillo, R.P., Goodman, Z.D., Knodell, R.G., Gitnick, G., Morgan, T.R., Schiff, E.R., Lasky, S., Stevens, C., Vlahcevic, R.Z., Weinshel, E., Tanwandee, T., Lin, H.J. & Barbosa, L. 2001. Long-term mortality and morbidity of transfusion-associated non-A, non-B, and type C hepatitis: a National Heart, Lung, and Blood Institute collaborative study. *Hepatology,* 33(2):455-463.

Sharma, P.H., Kalasare, S.N., Kamble, R.A., Powar, P.V. & Ambikar, R.B. 2014. Pharmacoeconomics: analysis of the cost of drug therapy to health care systems and society. *Journal club for pharmaceutical sciences,* 1(I):142-151.

http://www.academia.edu/9197168/Pharmacoeconomics_Analysis_of_The_Cost_of_Drug_Therapy_To_Health_Care_Systems_and_Society Date of access: 3 Feb. 2015.

Shepard, C.W., Finelli, L. & Alter, M.J. 2005. Global epidemiology of hepatitis C virus infection. *Lancet infectious diseases,* 5(1):558-567.

Sherman, K.E., Flamm ,S.L., Afdhal, N.H., Nelson, D.R., Sulkowski, M.S., Everson, G.T., Fried, M.W., Adler, M., Reesink, H.W., Martin, M., Sankoh, A.J., Adda, N., Kauffman, R.S., George, S., Wright, C.I. & Poordad, F. 2011. Response-guided telaprevir combination treatment for hepatitis C virus infection. *The New England journal of medicine*, 365(11):1014-1024.

Shisana, O., Rehle, T., Simbayi, L.C., Zuma, K., Jooste, S., Zungu, N., Labadarios, D., Onoya, D., Ramlagan, S., Mbelle, N., Zuma, K., Van Zyl, J., Davids, A. & Wabiri, N. 2014. South African National HIV Prevalence, Incidence and Behaviour Survey, 2012. Cape Town: HSRC Press. http://www.hsrc.ac.za/uploads/pageContent/4565/SABSSM%20IV%20LEO%20final.pdf Date of access: 15 Jun. 2015.

Sidwell, R.W., Huffman, J.H., Khare, G.P., Allen, L.B., Witkowski, J.T. & Robins, R.K. 1972. Broad-spectrum antiviral activity of Virazole: 1-beta-D-ribofuranosyl-1, 2, 4-triazole-3-carboxamide. *Science,* 177(4050):705-706.

Skripenova, S., Trainer, T.D., Krawitt, E.L. & Blaszyk , H.J. 2007. Variability of grade and stage in simultaneous paired liver biopsies in patients with hepatitis C. *Clinical pathology,* 60(3):321-324.

Smith, B.D., Patel, N., Beckett, G.A., Jewett, A. & Ward, J.W. 2011. Hepatitis C virus antibody prevalence, correlates and predictors among persons born from 1945 through 1965, United States, 1999–2008. *Hepatology,* 54(Suppl. 1554A-5A). (Abstract).

Snyman, J.R., *ed.* 2013. MIMS monthly index of medical specialties. Pretoria: MIMS.

Sonderup, M. 2013. Treating hepatitis B and C (in South Africa). World Hepatitis Day Presentation. http://hcvadvocate.org/hepatitis/factsheets_pdf/grade_stage.pdf Date of access: 17 Feb. 2015.

Sonderup, M., Spearman, W. & Geffen, N. 2011. When the private health sector falls short: Discovery Health and its failure to adequately cover hepatitis B and C.

http://www.quackdown.info/article/when-private-health-sector-falls-short/ Date of access: 29 Aug. 2014.

Sonderup MW, Abuelhassan W, Spearman W. 2012. IL28B polymorphisms are not predictive in hepatitis C genotype 5 infected South African patients. Paper presented at 63rd Annual Meeting of the American Association for the Study of Liver Diseases, Boston, MA, 9-13 November. http://onlinelibrary.wiley.com/doi/10.1002/hep.26040/epdf Date of access: 17 Feb. 2015.

Sonnenberg, F.A. & Beck, J.R. 1993. Markov models in decision making: a practical guide. *Medical decision making,* 13(2):322-338.

Sonnenberg, F.A. & Beck, J.R. 1993. Markov models in medical decision making: a practical guide. *Medical decision making,* 13(4):322-339.

Soriano, V., Sulkowski, M., Bergin, C., Hatzakis, A., Cacoub, P., Katlama, C., Cargnel, A., Mauss, S., Dieterich, D., Moreno, S., Ferrari, C., Poynard, T. & Rockstroh, J. 2002. Care of patients with chronic hepatitis C and HIV co- infection: recommendations from the HIV–HCV International Panel. *AIDS*, 16(6):813-828.

South Africa. 1998. Medical Schemes Act 131 of 1998.

South Africa. 2013. Medicines and Related Substances Act (Act no. 101 of 1965): regulations relating to a transparent pricing system for medicines and schedules substances. (Government notice no. R68). *Government gazette*, 36118, 1 Feb.

South Africa. 2014. Medicines and Related Substances Act (Act no. 101 of 1965): regulations relating to a transparent pricing system for medicines and schedules substances. (Government notice no. R264). *Government gazette,* 37527, 3 Apr.

South Africa. 2015. BRICS (Brazil, Russia, India, China, South Africa). http://www.gov.za/about-government/brics-brazil-russia-india-china-south-africa Date of access: 4 Jul. 2015.

South African National AIDS Council. 2012. Global AIDS response progress report. http://www.unaids.org/sites/default/files/country/documents//ce_ZA_Narrative_Report.pdf Date of access: 10 Sep. 2015.

STATS SA (Statistics South Africa). 2009. Statistical Release P0141. Consumer Price Index (CPI): January 2009. https://www.statssa.gov.za/publications/P0141/P0141January2009.pdf Date of access: 20 Mar. 2015.

STATS SA (Statistics South Africa). 2010. Statistical Release P0141. Consumer Price Index (CPI): January 2010. http://www.statssa.gov.za/publications/P0141/P0141February2010.pdf Date of access: 20 Mar. 2015.

STATS SA (Statistics South Africa). 2011. Statistical Release P0141. Consumer Price Index (CPI): January 2011. https://www.statssa.gov.za/publications/P0141/P0141January2011.pdf Date of access: 20 Mar. 2015.

STATS SA (Statistics South Africa). 2012. Statistical Release P0141. Consumer Price Index (CPI): January 2012. http://www.statssa.gov.za/publications/P0141/P0141January2012.pdf Date of access: 20 Mar. 2015.

STATS SA (Statistics South Africa). 2013. Statistical Release P0141. Consumer Price Index (CPI): January 2013. http://www.statssa.gov.za/publications/P0141/P0141January2013_Tables.pdf Date of access: 20 Mar. 2015.

STATS SA (Statistics South Africa). 2014. Statistical Release P0141. Consumer Price Index (CPI): January 2014. http://www.statssa.gov.za/publications/P0141/P0141January2014.pdf Date of access: 20 Mar. 2015.

STATS SA (Statistics South Africa). 2015. Statistical Release P0141: Consumer Price Index (CPI). http://www.statssa.gov.za/publications/P0141/P0141January2015.pdf Date of access: 20 Mar. 2015.

Standish, R.A., Cholongitas, E., Dhillon, A., Burroughs, A.K. & Dhillon, A.P. 2006. An appraisal of the histopathological assessment of liver fibrosis. *Gut,* 55(4):569-578.

Stedman's Medical Dictionary for the Health Professions and Nursing. 2005. 5th ed. Baltimore, MD: Lippincott Williams & Wilkens.

Stepanova, M., Nader, F., Cure, S., Bourhis, F., Hunt, S. & Younossi, M. 2014. Patients' preferences and health utility assessment with SF-6D and EQ-5D in patients with chronic

hepatitis C treated with sofosbuvir regimens. *Alimentary pharmacology & therapeutics,* 40(6):676-685.

Sullivan, S.D., Mauskopf, J.A., Augustovksi, F., Caro, J., Lee, K.M., Minchin, M., Orlewska, E., Penna, P., Rodriguez Barrios, J.M. & Shau, W.Y. 2014. Budget impact analysis: principles of good practice. Report of the ISPOR 2012 Budget Impact Analysis good practice II task force. *Value in health,* 17:5-14.

Sweeting, M.J., De Angelis, D., Neal, K.R., Ramsay, M.E., Irving, W.L., Wright, M., Brant, L. & Harris, H.E. Trent HCV Study Group; HCV National Register Steering Group. 2006. Estimated progression rates in three United Kingdom hepatitis C cohorts differed according to method of recruitment. *Journal of clinical epidemiology,* 59(2):144-152.

Sweeting, M.J., De Angelis, D., Brant, L.J., Harris, H.E., Mann, A.G. & Ramsay, M.E. 2007. The burden of hepatitis C in England. *Journal of viral hepatology,* 14(8):570-576.

Suh, D., Okpara, I.R.N., Agnese, W.B. & Toscani, M. 2002. Application of pharmacoeconomics to formulary decision making in managed care organizations. *The American journal of managed care,* 8(2):161-169.

TAC (Treatment Action Campaign). 2011. TAC Letter requesting for the designation of treatment for hepatitis B and C as prescribed minimum benefit conditions. http://www.tac.org.za/community/node/3174 Date of access: 12 Oct. 2015.

Taylor, M. 2009. What is sensitivity analysis? http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/What_is_sens_analy.pdf Date of access: 5 Oct. 2014.

Te, H.S., Randall, G. & Jensen, D.M. 2007. Mechanism of action of ribavirin in the treatment of chronic Hepatitis C. *Gatroenterology and hepatology,* 3(3):218-225.

The Economist Intelligence Unit. 2015. The silent pandemic: tackling hepatitis C with policy innovation. 2015. https://www.janssen.ie/sites/stage-janssen-ie.emea.cl.datapipe.net.pdf Date of access: 11 Aug. 2015.

Thein, H.H., Krahn, M., Kaldor, J.M. & Dore. G.J. 2005. Estimation of utilities for chronic hepatitis C from SF-36 scores. *American journal of gastroenterology,* 100(3):643-651.

Thein, H., Yic, Q., Dored G.J. & Krahnabe, M.D. 2008. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS,* 22(15):1979-1991.

Theise, N.D. 2007. Liver biopsy assessment in chronic viral hepatitis: a personal, practical approach. *Modern pathology,* 20(Suppl. 1):S3-S14.

The National Treasury. 2015. Estimates of national expenditure. http://www.treasury.gov.za/documents/national%20budget/2015/ene/FullENE.pdf Date of access: 27 Oct. 2015.

The Official Pharmaceutical Bluebook. 2015. http://www.pbb.co.za/ Date of access: 3 Feb. 2015.

The World Bank. 2014. Health expenditure per capita (current US$). http://data.worldbank.org/indicator/SH.XPD.PCAP Date of access: 10 Jun. 2014.

Thomas, D.L. 2012. Highly active anti-hepatitis C therapy: seven lessons from HIV. *Antiviral therapy,* 7(600):1183-1188.

Thomas, D.L., Astemborski, J., Rai, R.M., Anania, F.A., Schaeffer, M., Galai, N., Nolt, K., Nelson, K.E., Strathdee, S.A., Johnson, L., Laeyendecker, O., Boitnott, J., Wilson, L.E. & Vlahov, D. 2000. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *Journal of the American Medical Association,* 284(4):450-456.

Thwaites, R. & Townsend, R.J. 1998. Pharmacoeconomics in the new millennium. *Pharmacoeconomics,* 13(2):175-180.

Tolley, K. What are health utilities? 2009. http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/Health-util.pdf Date of access: 11 Nov. 2014.

Tong, M.J., Lai, P.P.C., Hwang, S., Lee, S., Co, R.L., Chien, R.N.D. & Kuo, G. 1995. Evaluation of sexual transmission in patients with chronic hepatitis C infection. *Clinical and diagnostic virology,* 3(1):39-47.

Torrance, G.W. 1986. Measurement of health state utilities for economic appraisal. *Journal of health economics*, 5(1):1-30.

TreeAge Pro 2014, R1.2. TreeAge Software, Williamstown, MA; software available at http://www.treeage.com.

TreeAge Software, Inc. 2015. TreeAge Pro Healthcare. https://www.treeage.com/shop/treeage-pro-healthcare/ Date of access: 12 Jan. 2015.

Tso, P. & McGill, J. 2003. The physiology of the liver. (*In* Rhoades, R.A., Tanner, G.A., *eds*. Medical physiology. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins. p. 514-525).

Tucker, T.J., Voight, M., Bird, A., Robson, S., Gibbs, B., Kannemeyer, J., Galloway, M., Kirsch, R.E. & Smuts, H. 1997. Hepatits C virus infection rate in volunteer blood donors from the Western Cape: comparison of screening tests and PCR. *South African medical journal,* 87(5):603-605.

Turner, R., Angus, B.J., Handa, A. & Hatton, C., *eds.* 2009. Clinical skills and examination: the core curriculum. Oxford: Wiley:Blackwell.

UNAIDS (United Nations Programme on HIV/AIDS). 2014. 90-90-90: an ambitious treatment target to help end the AIDS epidemic. http://www.unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf Date of access: 5 Sep. 2015.

UNAIDS (United Nations Programme on HIV/AIDS). 2015. Treatment 2015. http://www.unaids.org/sites/default/files/media_asset/JC2484_treatment-2015_en_1.pdf Date of access: 1 Sept. 2015.

UNOS (United Network for Organ Sharing). Transplant living. 2015. http://www.transplantliving.org/before-the-transplant/financing-a-transplant/the-costs/ Date of access: 10 Aug. 2015.

Van den Heever, A. 2013. Strategic health reform and “National Health Insurance”. http://www.hsf.org.za/siteworkspace/cms-news-march-2013-nhi-final-website-1.pdf Date of access: 15 Aug. 2013.

Van der Plas, S.M., Hansen, B.E., De Boer, J.B., Stijnen, T., Passchier, J., De Man, R.A. & Schalm, S.W. 2007. Generic and disease-specific health related quality of life of liver patients with various aetiologies: a survey. *Quality of life research*, 16(3):375-388.

Van Voris L.P. & Newell, P.M. 1992. Antivirals for the chemoprophylaxis and treatment of influenza. *Seminars in respiratory infections,* 7(1):61-70.

Verbeeck, J., Maes, P., Lemey, P., Pybus, O.G., Wollants, E., Song, E., Nevens, F., Fevery, J., Delport, W., Van der Merwe, S. & Van Ranst, M. 2006. Investigating the origin and spread of hepatitis C virus genotype 5a. *Journal of virology*, 80(9):4220-4226.

Verbeeck, J., Peigue-Lafeuille, H., Ross, R.S., Abergel, A., Nevens, F., Van der Merwe, S., Van Ranst, M. & Henquell, C. 2008. HCV genotype 5: epidemiology and spread of an uncommon genotype. *Journal of clinical virology,* 41(2):170-171.

Villa, L.A. & Skrepnek, G.H. 2011. Pharmacoeconomics and developing nations. *Pharmaceuticals policy and law,* 14(1):17-25.

Villena, E.Z. 2006. Transmission routes of hepatitis C virus infection. *Annals of hepatology,* 5(Suppl. 1):S12-S14.

Walkom, E., Robertson, J., Newby, D. & Pillay, T. 2006. The role of pharmacoeconomics in formulary decision-making: considerations for hospital and managed care pharmacy and therapeutics committees. *Formulary,* 41:374-386.

Walley, T. 2004. Pharmacoeconomics and economic evaluation of drug therapies. (*In* Walley, T., Haycox, A. & Boland, A., *eds.* Pharmacoeconomics. London: Churchill Livingstone. p. 67-75).

Weinstein, M.C., O'Brien, B., Hornberger, J., Jackson, J., Johannesson, M., McCabe, C. & Luce, B.R. 2003. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices — Modeling Studies. *Value in health,* 6(1):9-17.

Weinstein, M.C., Torrance, G. & McGuire, A. 2009. QALYs: the Basics. *Value in health,* 12(1):S5-S9.

Weller, B.F., *ed*. 2005. Baillière's nurses' dictionary. 24th ed. London: Elsevier Limited.

Wendt, A. & Bourlière, M. 2013. An update on the treatment of genotype-1 chronic hepatitis C infection: lessons from recent clinical trials. *Therapeutic advances in infectious disease,* 1(6):191-208.

Whitehead, S.J. & Ali, S. 2010. Health outcomes in economic evaluation: the QALY and utilities. *British medical bulletin,* 96:5-21.

WHO (World Health Organization). 1997. WHOQOL. Measuring quality of life. The World Health Organization quality of life instruments. http://www.who.int/mental_health/media/68.pdf Date of access: 16 Sep. 2014.

WHO (World Health Organization). 2002. Hepatitis C. http://www.who.int/csr/disease/hepatitis/Hepc.pdf Date of access: 3 Oct. 2014.

WHO (World Health Organization). 2003. Introduction to drug utilisation research. http://apps.who.int/medicinedocs/pdf/s4876e/s4876e.pdf Date of access: 3 Oct. 2014.

WHO (World Health Organization). 2013. Hepatitis C fact sheet N˚164. http://www.who.int/mediacentre/factsheets/fs164/en/ Date of access: 9 Dec. 2013.

WHO (World Health Organization). 2015. Cost effectiveness and strategic planning: cost-effectiveness thresholds. http://www.who.int/choice/costs/CER_thresholds/en/ Date of access: 19 May 2015.

WHO (World Health Organization). 2016. Public health. http://www.who.int/trade/glossary/story076/en/ Date of access: 15 Mar. 2016.

Wiese, M., Berr, F., Lafrenz, M., Porst, H & Oesen, U. 2000. Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in germany: a 20-year multicenter study. *Hepatology,* 32(1):91-96.

Wiley, T.E., McCarthy, M., Breidi, L., McCarthy, M. & Layden, T.J. 1998. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology,* 28(3):805-809.

Williams, R. 2006. Global challenges in liver disease. *Hepatology,* 44(3):521-526.

Williams, S. 2013. This FDA approval is exciting news for hepatitis-C patients. *Daily finance,* 22 Jun. http://www.dailyfinance.com/2013/06/22/this-fda-approval-is-exciting-news-for-hepatitis-c/ Date of access: 8 Oct. 2013.

Wilkie, J.B. 2013. Identifying and managing hepatitis C in the community. *Primary health care,* 23(4):22-25.

XE Currency Converter. 2014. Convert USD to ZAR. http://www.xe.com/currencyconverter/ Date of access: 21 Jan. 2014.

Yee, H.S., Chang, M.F., Pocha, C., Lim, J., Ross, D. & Morgan, T.R. 2012. Update on the management and treatment of hepatitis C virus infection: recommendations from the department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. *American journal of gastroenterology*, 104(30):1-21.

Yee, L.J., Weiss, H.L., Langner, R.G., Herrera, J., Kaslow, R.A. & Van Leeuwen, D.J. 2001. Risk factors for acquisition of hepatitis C virus infection: a case series and potential implications for disease surveillance. *BMC infectious diseases,* 1(8). http://www.biomedcentral.com/1471-2334/1/8 Date of access: 11 May. 2014.

Younossi, Z.M., Boparai N., McCormick, M., Price, L.L. & Guyatt, G. 2001. Assessment of utilities and health-related quality of life in patients with chronic liver disease. *American journal of gastroenterology*, 96(2):579-583.

Zarski, J., Hutchison, J.M., Bronowicki, J., Sturm, N., Garcia-Kennedy, R., Hodaj, E., Trusta, B., Wright, T. & Gish, R. 2003. Rate of natural disease progression in patients with chronic hepatitis C. *Journal of hepatology,* 38(Suppl. 1):307-314.

Zein, N.N. & Edwards, K.M. 2009. The amazing liver. (*In* Zein, N.N. & Edwards, K.M., *eds.* The Cleveland Clinic guide to liver disorders. New York, NY: Kaplan. p. 1-10).

Zeuzem, S., Dusheiko, G.M., Salupere, R., Mangia, A., Flisiak, R., Hyland, R.H., Illeperuma, A., Svarovskaia, E., Brainard, D.M., Symonds, W.T., Subramanian, M., McHutchison, J.G., Weiland, O., Reesink, H.W., Ferenci, P., Hézode, C. & Esteban, R., for the VALENCE Investigators. 2014. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *The New England journal of medicine,* 370(21):1993-2001.

ANNEXURES

ANNEXURE A.1: SUPPLEMENT TO CHAPTER 1

A.1.1 EXPERT OPINION

The opinion of clinical hepatologists were sought to i) help identify the relevant disease states in the natural history model of chronic hepatitis C virus (HCV) genotype 5 infection; ii) help set the context of the economic evaluation by defining the place of the medicine treatment, i.e. what is the current standard of care for treating chronic hepatitis C virus (HCV) genotype 5 infection in South Africa and what the role of the new direct-acting antivirals are in this country; iii) to help identify the patterns of research use in the treatment of chronic HCV genotype 5 in a South African setting, and iv) to help predict which resources will be used and how often they will be used to manage the reported outcomes.

Hepatologists were identified by contacting the division of hepatology of the University of Cape Town (UCT). The UCT division of hepatology incorporates the Liver and Porphyria clinics associated with Groote Schuur hospital, as well as the Liver Research Centre, a research institution established within UCT by the South African Medical Research Council. It is a unique institution, offering highly specialised services not available elsewhere in South Africa, including dedicated hepatological expertise, liver transplantation services and a distinctive porphyria diagnostic and clinical service, together with clinical and laboratory-based research on liver disease and porphyria (UCT, 2016).

I was directed to the head of the hepatology division, Prof. Wendy Spearman and Dr. Mark W Sonderup, a senior specialist at the Groote Schuur hospital and a senior lecturer in the department of medicine at UCT. Both experts were approached (by e-mail) to see if they would be interested in assisting with this study. Dr. Sonderup agreed and also offered to become a co-promoter for this study.

Information was initially sought through a face-to-face meeting, in which Dr. Sonderup was presented with the study proposal to gain a background of the study and the proposed study objectives. In this meeting, he was informed that we would require his expert opinion on the four points listed above. He agreed to approach Dr. Spearman and that their joint opinion would be conveyed on the listed topics. The rest of the communication between me and Dr. Sonderup was over a large number of e-mails and telephonic conversations. Information was recorded in the form of track changes and comments made to this thesis *via* e-mail.

Personal Information of Clinical Experts:

Full Name: Mark Wayne Sonderup

Institution: University of Cape Town Faculty of Health Sciences

Department/Division: Department of Medicine – University of Cape Town

Division of Hepatology - University of Cape Town

E-mail Address: msonderup@samedical.co.za

Present positions: Senior Specialist (Groote Schuur Hospital)

Senior Lecturer (Department of Medicine, UCT)

Head of Medical Firm

Qualifications:

i. Bachelor of Pharmacy (cum laude), University of Port Elizabeth 1990

ii. Bachelor of Medicine and Bachelor of Surgery (first class honours), UCT 1995

iii. Fellowship of the College of Physicians of South Africa [FCP (SA)] 2002

iv. Masters in Medicine, University of Cape Town

Full Name: Catherine Wendy Spearman

Institution: University of Cape Town Faculty of Health Sciences

Department/Division: Department of Medicine – University of Cape Town

Division of Hepatology - University of Cape Town

E-mail Address: wendy.spearman@uct.ac.za

Present position: Head of Division of Hepatology (Department of Medicine, UCT)

A.1.2.1 CRITICAL APPRAISAL OF NEUTRINO TRIAL

Title and abstract		**NEUTRINO TRIAL (ClinicalTrials.gov Identifier: NCT01641640)**
	Identification as a randomised trial in the title	Phase 3, multicenter, open-label study to investigate the efficacy and safety of GS-7977 with peginterferon alfa 2a and ribavirin for 12 weeks in treatment-naive subjects with chronic genotype 1, 4, 5, or 6 HCV infection.
	Structured summary of trial design, methods, results, and conclusions	In a single-group, open-label, phase 3 study, researchers administered a 12-week regimen of sofosbuvir plus peginterferon alfa-2a and ribavirin in 327 patients with HCV genotype 1, 4, 5, or 6 (of whom 98% had genotype 1 or 4). A sustained virologic response was reported in >90% of patients (95% CI: 87-93).
Introduction		
Background and objectives	Scientific background and explanation of rationale	In phase 2 trials, the nucleotide polymerase inhibitor sofosbuvir was effective in previously untreated patients with chronic hepatitis C virus (HCV) genotype 1, 2, or 3 infection.
	Specific objectives or hypotheses	This study was to assess whether sofosbuvir in combination with ribavirin RBV and PEG administered for 12 weeks is safe and effective in patients with HCV genotypes 1, 4, 5, or 6 as assessed by the rate of SVR 12 weeks after discontinuation of therapy (SVR12).
Methods		
Trial design	Study design	Study type and phase: Interventional, Phase 3 Endpoint classification: Safety/Efficacy Study Intervention model: Single Group Assignment Masking: Open Label Primary purpose: Treatment
Participants	Eligibility criteria for participants	Ages Eligible for Study: 18 Years and older Genders Eligible for Study: Both Accepts Healthy Volunteers: No ***Inclusion Criteria:*** • Infection with HCV genotype 1, 4, 5, or 6; Cirrhosis determination • Subject met the following classifications: treatment-naïve, screening laboratory values within defined thresholds, not treated with any investigational drug or device within 30 days of screening • Use of highly effective contraception methods if female of childbearing potential or sexually active male ***Exclusion Criteria:*** • Prior exposure to an direct-acting antiviral targeting the HCV nonstructural protein (NS)5B polymerase • Pregnant or nursing female, or male with pregnant female partner • Current or prior history of clinical hepatic decompensation • History of clinically-significant illness or any other major medical disorder that may have interfered with subject treatment, assessment, or compliance with the protocol • Excessive alcohol ingestion or significant drug abuse
	Settings and locations	56 locations listed, including USA and Puerto Rico
Interventions	The interventions for each group	***Drug: Sofosbuvir*** (Sovaldi®; GS-7977; PSI-7977) Sofosbuvir 400 mg tablet administered orally once daily ***Drug: RBV*** (Ribasphere®) Ribavirin (RBV) tablets administered orally in a divided daily dose according to package insert weight-based dosing recommendations (< 75kg = 1000 mg and ≥ 75 kg = 1200 mg) ***Drug: PEG*** (PEGASYS®) Pegylated interferon alfa-2a (PEG) 180 µg administered once weekly by subcutaneous injection
Outcomes	Completely defined pre-specified primary and secondary outcome measures	***Primary Outcome Measures:*** • Percentage of participants achieving sustained virologic response (SVR)12; [Time frame: Post-treatment week 12]. SVR12 was defined as HCV RNA < the lower limit of quantitation (LLOQ; ie, 25 IU/mL) 12 weeks after cessation of therapy. • Number of participants experiencing adverse events leading to permanent discontinuation of study drug; [Time frame: Baseline to week 12]. The number of participants experiencing adverse events leading to permanent discontinuation of study drug was summarized.

		Secondary Outcome Measures: • Percentage of participants achieving SVR4; [Time frame: Post-treatment week 4]. SVR4 was defined as HCV RNA < LLOQ 4 weeks after cessation of therapy. • Percentage of participants achieving SVR24; [Time Frame: Post-treatment Week 24]. SVR24 was defined as HCV RNA < LLOQ 24 weeks after cessation of therapy. • Percentage of participants with viral breakthrough; [Time frame: baseline to week 12]. Viral breakthrough was defined as HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ while receiving treatment, confirmed with 2 consecutive values (second confirmation value could be post-treatment), or last available on-treatment measurement with no subsequent follow-up values. • Percentage of participants with viral relapse; [Time frame: End of treatment to post-treatment week 24]. Viral relapse was defined as HCV RNA ≥ LLOQ during the post-treatment period having achieved HCV RNA < LLOQ at end of treatment, confirmed with 2 consecutive values or last available post-treatment measurement.
Sample size	How sample size was determined	• Sample size: 328 • Study participants were volunteers who met the eligibility criteria
Randomisation		Not applicable. Single arm study.
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes	• Statistical Analysis for percentage of participants achieving sustained virologic response (SVR)12: Superiority would be demonstrated if the SVR12 rate was higher than the 60% null SVR rate based on historical control data • Method: BINOMICAL EXACT TEST • p-value: <0.001
	Additional analyses	No applicable
Results		
Participant flow	For each group, the numbers of participants	456 participants were screened and 328 were enrolled; 327 participants were treated, and comprise the Safety Analysis Set and the Full Analysis Set.
	For each group, losses and exclusions after randomisation, together with reasons	• STARTED = 328 → Enrolled and treated = 327 • COMPLETED = 292; NOT COMPLETED = 36 • Enrolled but not treated = 1; Efficacy failure = 29; Lost to follow-up = 3; Withdrawal by subject = 2; Adverse event = 1
Recruitment	Dates defining the periods of recruitment and follow-up	• Subjects were enrolled in a total of 55 study sites in the United States. The first participant was screened on 18 June 2012. The last participant observation was on 16 April 2013.
Baseline data	Table showing baseline demographic & clinical characteristics	Chapter 1, Table 1.7
Numbers	Number of participants	327
Outcomes and estimation		Percentage of participants achieving sustained virologic response (SVR)12: 91 (95% CI = 87-93)
Harms	All important harms or unintended effects	Total, serious adverse events: participants affected / at risk = 4/327 (1.22%). (All adverse events with percentages listed in trial document).
Discussion		
Limitations		None discussed
Generalisability	Generalisability (external validity, applicability) of the trial findings	As the intervention was implemented for both sexes of all ages (over 18 years), different ethnic groups, with or without cirrhosis, the results indicate that >90% of patients infected with HCV genotypes 1, 4, 5 or 6 could benefit from using SOF + PEG + RBV for 12 weeks
Other information		
Registration		ClinicalTrials.gov, NCT01641640
Funding		Gilead Sciences

A.1.2.2 CRITICAL APPRAISAL OF ABERGEL STUDY

Title and abstract		**ABERGEL STUDY (ClinicalTrials.gov Identifier: NCT02081079)**
	Identification as a trial in the title	A Phase 2, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination in Treatment-Naive and Treatment-Experienced Subjects With Chronic Genotype 4 or 5 HCV Infection
	Structured summary of trial design, methods, results, and conclusions	Open-label, multicentre, single-arm, phase 2 trial at five hospitals in France. Eligible patients were at least 18 years old and had chronic infection with HCV genotype 5, with plasma HCV RNA of at least 10 000 IU/mL. BLAST analyses of NS5B partial sequences were used to establish the genotype and subtype at screening. Patients were given a fixed-dose combination tablet of 90 mg ledipasvir and 400 mg sofosbuvir orally once per day for 12 weeks. The primary endpoint was the proportion of patients with a sustained viral response, defined as HCV RNA concentration less than 15 IU/mL at 12 weeks after the end of treatment (SVR12). SVR12 was achieved by 20 (95%, 76–100) of the 21 patients who were treatment naive and 19 (95%, 75–100) of the 20 patients who were treatment experienced. The oral regimen of ledipasvir-sofosbuvir is an effective and well-tolerated treatment for patients with HCV genotype 5 infection who are treatment naive or treatment experienced.
Introduction		
Background and objectives	Scientific background and explanation of rationale	Data about the response of hepatitis C virus (HCV) genotype 5 to approved and experimental treatment regimens are scarce. We assessed the efficacy and safety of combination therapy with the NS5A inhibitor ledipasvir and the NS5B polymerase inhibitor sofosbuvir in patients with HCV genotype 5.
	Specific objectives or hypotheses	This study is to evaluate the efficacy, safety, and tolerability of ledipasvir/sofosbuvir (LDV/SOF) fixed-dose combination (FDC) in participants with chronic genotype 4 or 5 hepatitis C virus (HCV) infection as measured by the proportion of subjects with sustained virologic response (SVR12), defined as HCV RNA < lower limit of quantification (LLOQ) 12 weeks after discontinuation of therapy.
Methods		
Trial design	Study design	Study Type: Interventional Study Design: Allocation: Non-Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment
Participants	Eligibility criteria for participants	Ages Eligible for Study: 18 Years and older Genders Eligible for Study: Both Accepts Healthy Volunteers: No ***Inclusion Criteria:*** • HCV RNA ≥ 10^4 IU/mL at screening • Chronic genotype 4 or 5 HCV Infection • Individuals may be treatment naive or treatment experienced • Presence or absence of cirrhosis, a liver biopsy may be required • Healthy according to medical history and physical examination with the exception of HCV diagnosis • Use two forms of highly effective contraception for duration of the study ***Exclusion Criteria:*** • History or current evidence of any condition, therapy, laboratory abnormality or other circumstance that might confound the results of the study, or interfere with the individual's participation for the full duration of the study or not be in the best interest of the individual in the opinion of the investigator • Prior exposure to approved or experimental HCV specific direct acting antiviral(s) (DAA) other than NS3/4A protease inhibitors • History of any other clinically significant chronic liver disease • Evidence of or history of decompensated liver disease • HIV or chronic hepatitis B (HBV) infection • Hepatocellular carcinoma (HCC) or other malignancy (with exception of certain resolved skin cancers) • Chronic use of immunosuppressive agents or immunomodulatory agents
	Settings and locations	Clermont Ferrand, France, 63003; Clichy, France, 92110; Limoges, France, 87042; Toulouse, France, 31059; Villejuif, France, 94800

Interventions	The interventions for each group	***Experimental: Genotype 5*** *LDV/SOF for up to 12 weeks in treatment-naive and treatment-experienced participants with genotype 5 hepatitis C virus (HCV) infection* ***Drug: LDV/SOF*** *LDV/SOF (90/400 mg) FDC tablet administered orally once daily* ***Other Names:*** *Harvoni®; GS-5885/GS-7977*
Outcomes	Completely defined pre-specified primary and secondary outcome measures	***Primary Outcome Measures:*** • Percentage of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR12) [Time Frame: Post-treatment week 12] • Percentage of participants who permanently discontinued LDV/SOF due to an adverse event [Time Frame: Up to 12 weeks] ***Secondary Outcome Measures:*** • Percentage of participants with SVR at 4 and 24 weeks after discontinuation of therapy (SVR4 and SVR24) [Time Frame: Post-treatment Weeks 4 and 24] • Percentage of patients with virologic failure [Time Frame: Up to 12 weeks] • Change from baseline in HCV RNA at weeks 2, 4, 8, and 12 [Time Frame: Baseline; Weeks 2, 4, 8, and 12]
Sample size	How sample size was determined	• Sample size: 41 (HCV-G5) + 44 (HCV-G4) • Study participants were volunteers who met the eligibility criteria
Randomisation		Not applicable. Single arm study.
Statistical methods	Statistical methods used to compare groups outcomes	None
	Additional analyses	No applicable
Results		
Participant flow	For each group, the numbers of participants	91 participants were screened
	For each group, losses and exclusions after randomisation, together with reasons	Genotype 5 • STARTED = 41 • COMPLETED = 39 • NOT COMPLETED = 2 • Lack of Efficacy = 2 • Lost to Follow-up = 0
Recruitment	Dates defining the periods of recruitment and follow-up	Participants were enrolled at study sites in France. The first participant was screened on 07 March 2014. The last study visit occurred on 17 February 2015.
Baseline data	A table showing baseline demographic and clinical characteristics	Chapter 1, Table 1.9.
Numbers	Number of participants	Genotype 5 = 41 (plus 44 with genotype 4)
Outcomes and estimation		In the overall study population, 39 (95%, 95% CI 83–99) of 41 patients achieved SVR12. SVR12 was achieved by 20 (95%, 76–100) of the 21 patients who were treatment naive and 19 (95%, 75–100) of the 20 patients who were treatment experienced. Eight (89%) of nine patients with cirrhosis achieved SVR12, whereas 31 (97%) of the 32 patients without cirrhosis achieved SVR12. The two patients who did not reach SVR12 both had IL28B TT genotype and had viral relapse within 4 weeks of the end of treatment.
Harms	All important harms or unintended effects	The most common adverse events were asthenia (16 [39%] patients), headache (11 [27%] patients), and fatigue (four [10%] patients). One patient had a serious adverse event, worsening depression, which we judged to be unrelated to study treatment.
Discussion		
Limitations		There were no limitations affecting the analysis or results
Generalisability	Generalisability (external validity, applicability) of the trial findings	The oral regimen of ledipasvir-sofosbuvir is an effective and well-tolerated treatment for patients with HCV genotype 5 infection who are treatment naive or treatment experienced.
Other information		
Registration		ClinicalTrials.gov, NCT02081079
Funding		Gilead Sciences

ANNEXURE A.2: SUPPLEMENT TO CHAPTER 3

This supplement contains information, tables and figures relevant to the empirical investigation of the study (refer to chapter 3).

A.2.1 Model structures

All three models started with an initial decision tree (below) with a branch (or arm) for each treatment strategy, followed by a Markov model (M). The public health impact model combined SOF/LDV and SOF-TT into one arm (figure a.1.2). For the cost-effectiveness model and the budget impact models, the Markov structures for SOF/LDV and SOF-TT were the same.

Figure A.1.1 Decision tree for cost-effectiveness and budget impact models

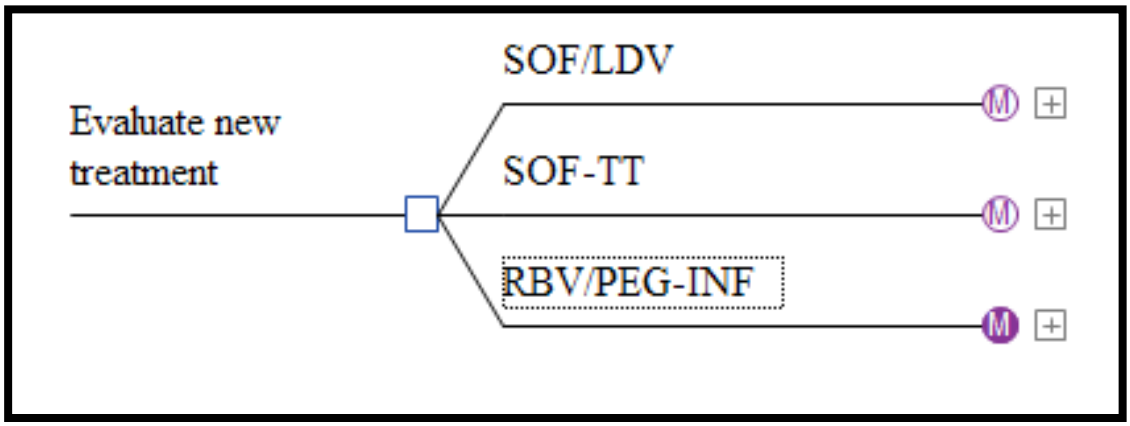


Figure A.1.2 Decision tree for public health impact model

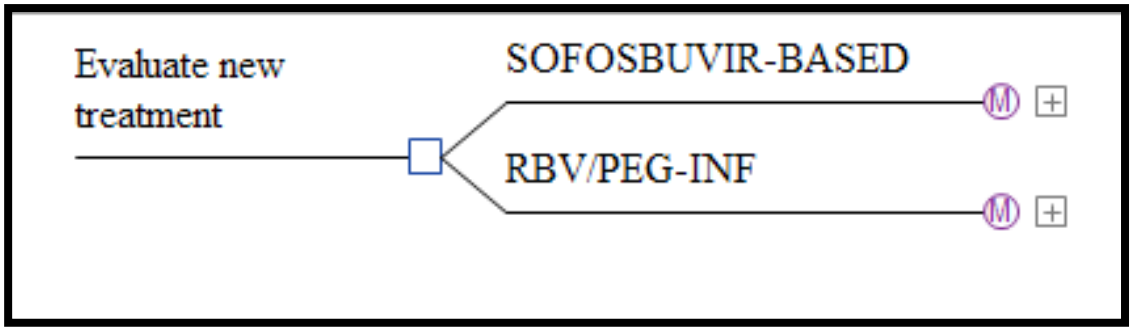


Figure A.1.3 Model structure: Cost-effectiveness model (SOF/LDV / SOF-TT arm)

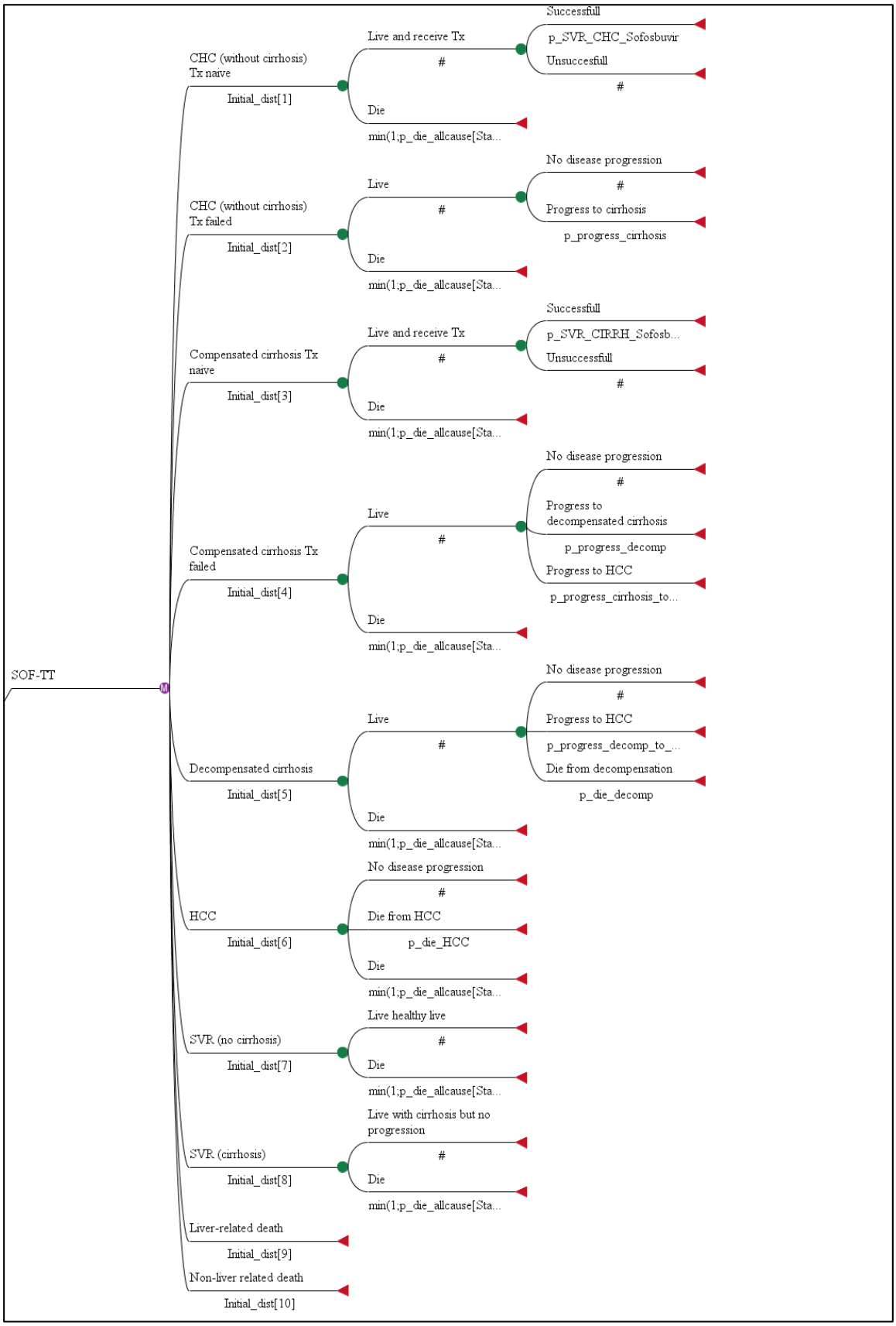


Figure A.1.4 Model structure: Cost-effectiveness model (SOC arm)

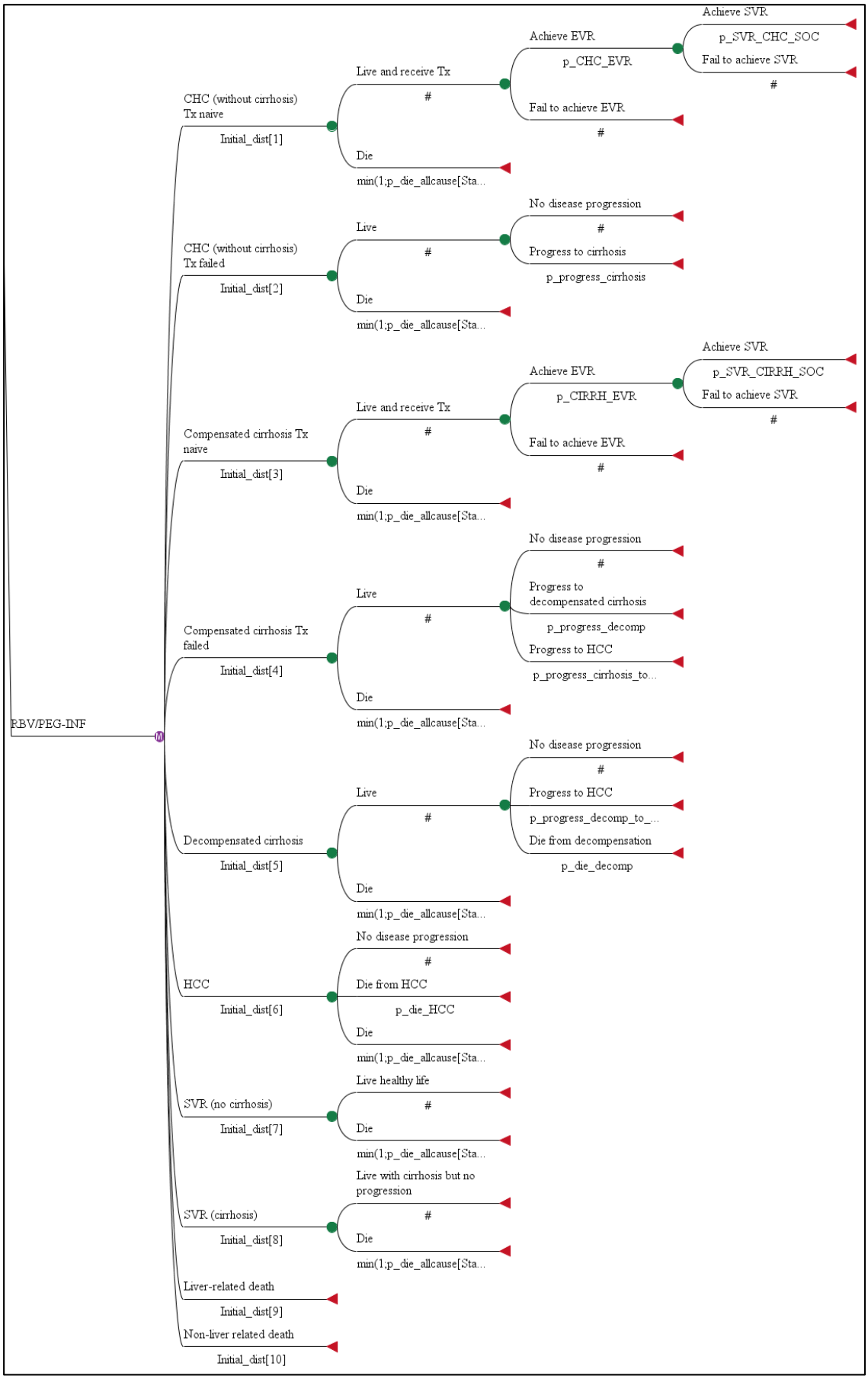


Figure A.1.5 Model structure: Public health impact model (SOF-based arm)

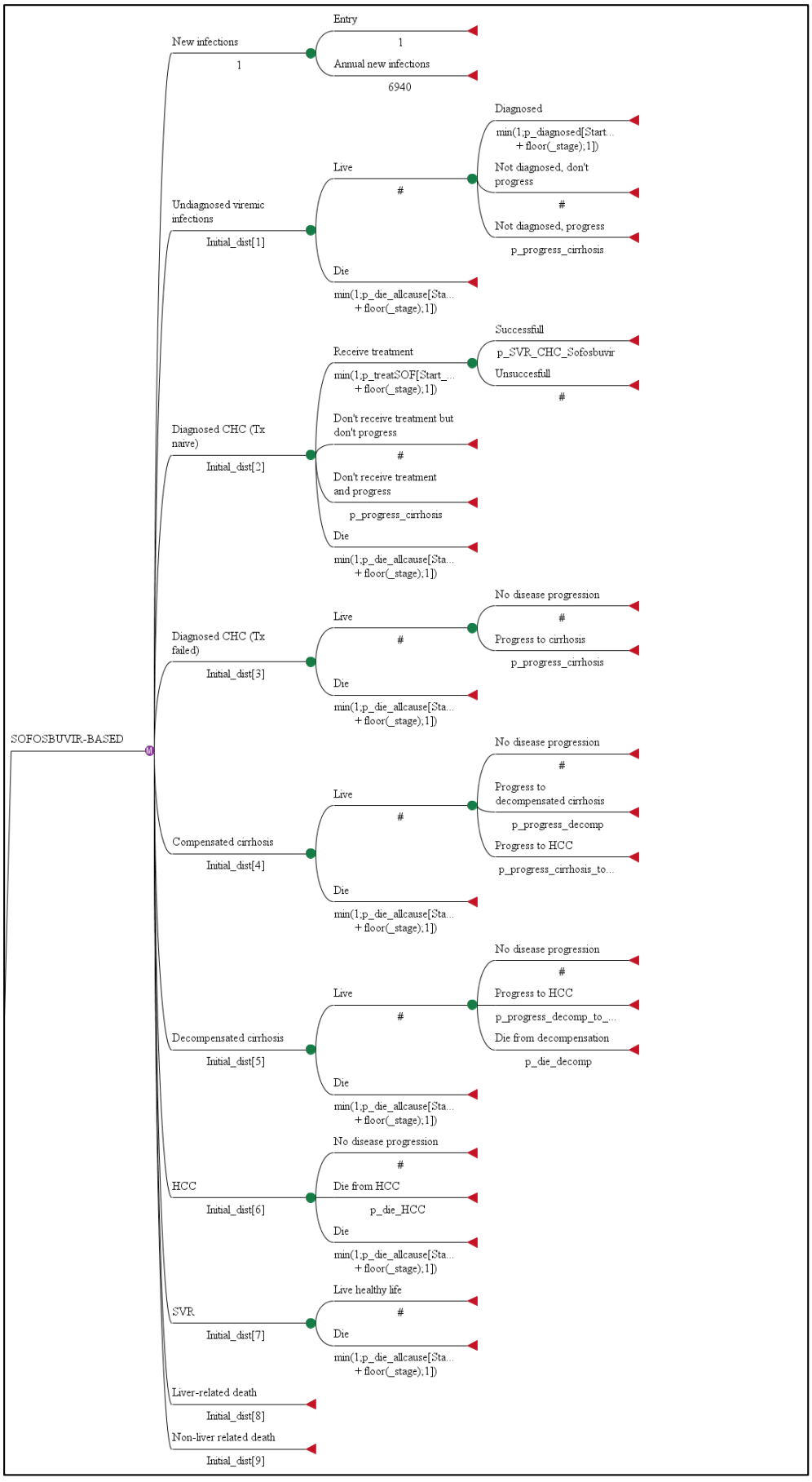


Figure A.1.6 Model structure: Public health impact model (SOC arm)

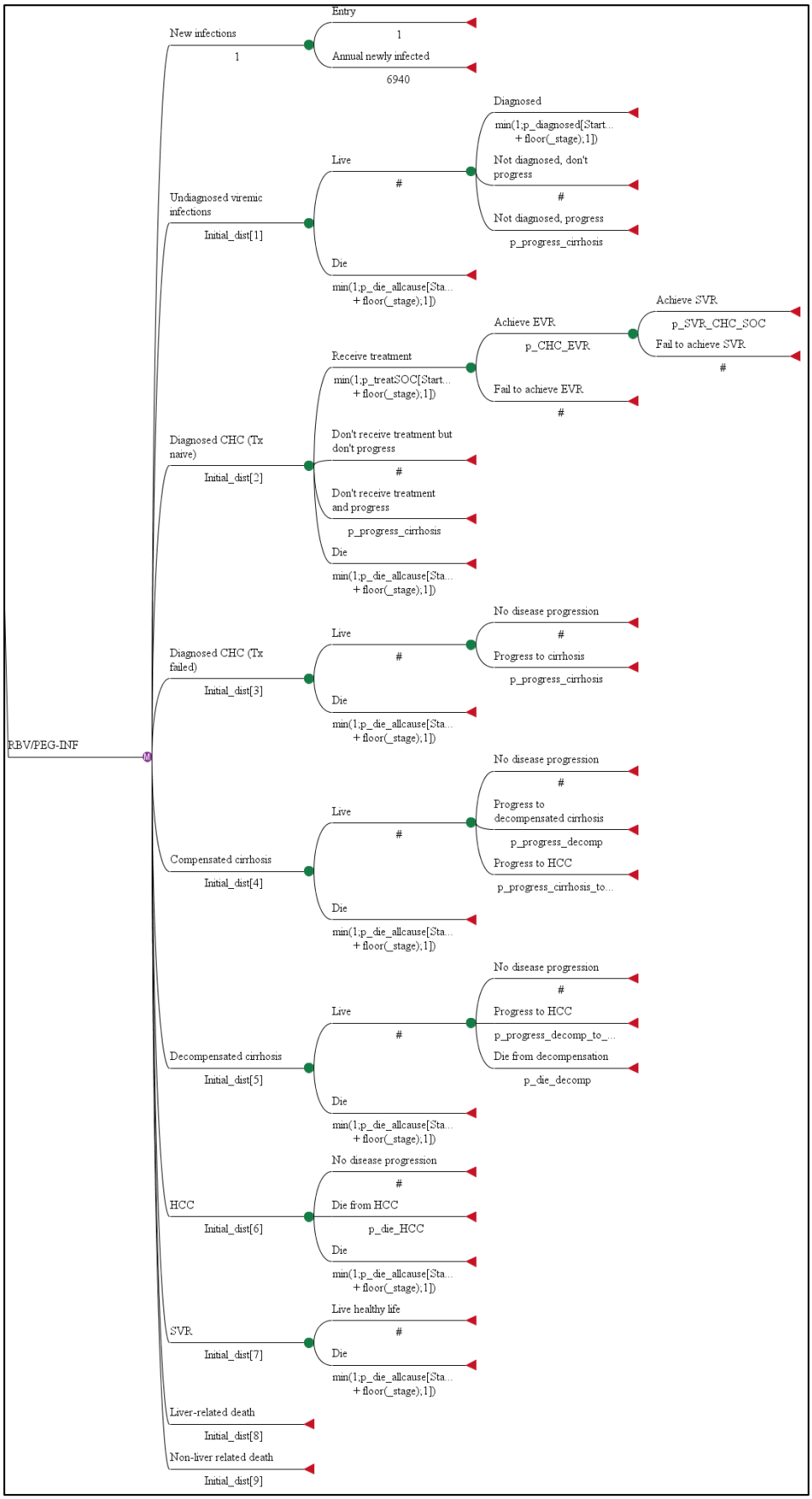


Figure A.1.7 Model structure: Budget impact model (SOF/LDV / SOF-TT arm)

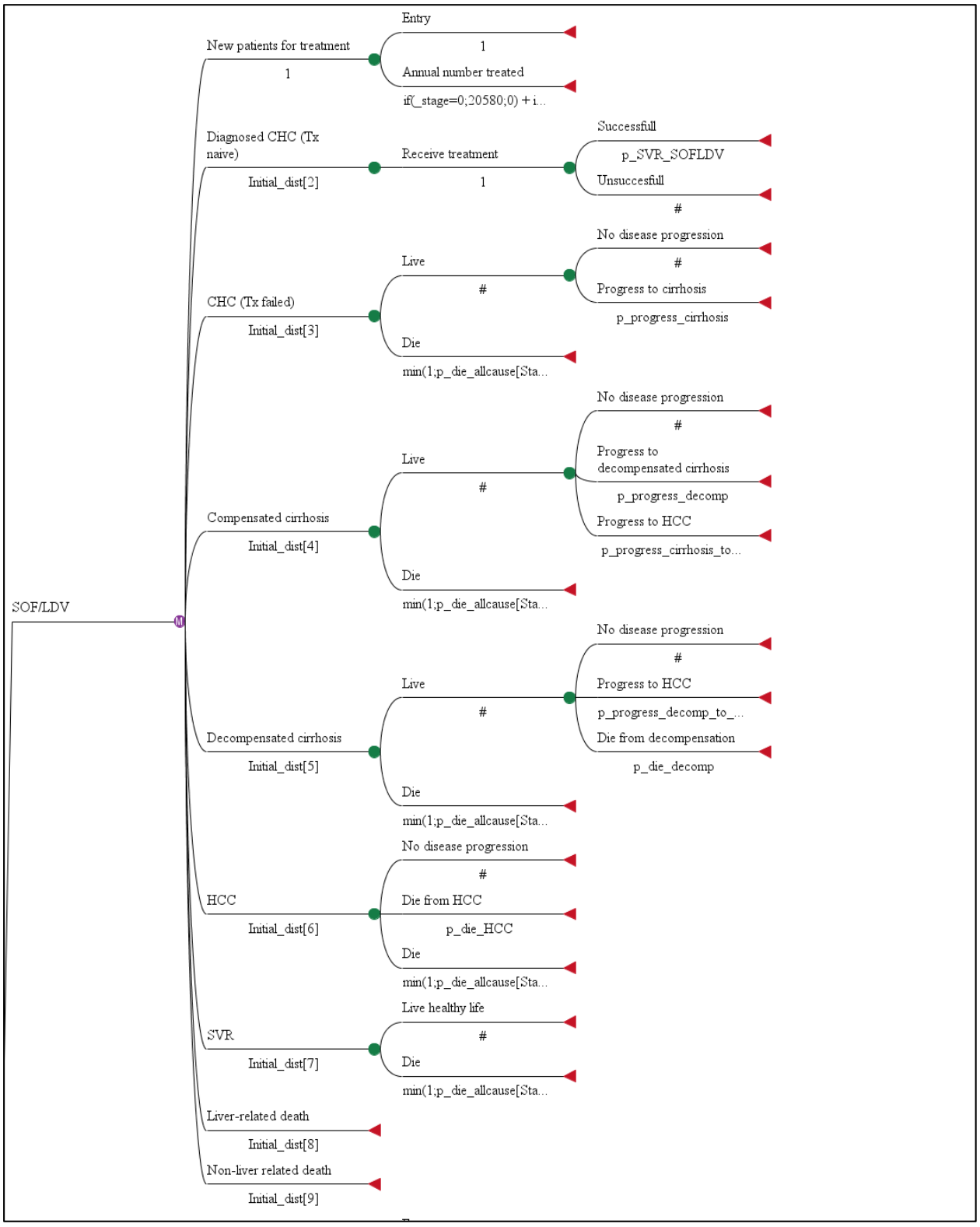
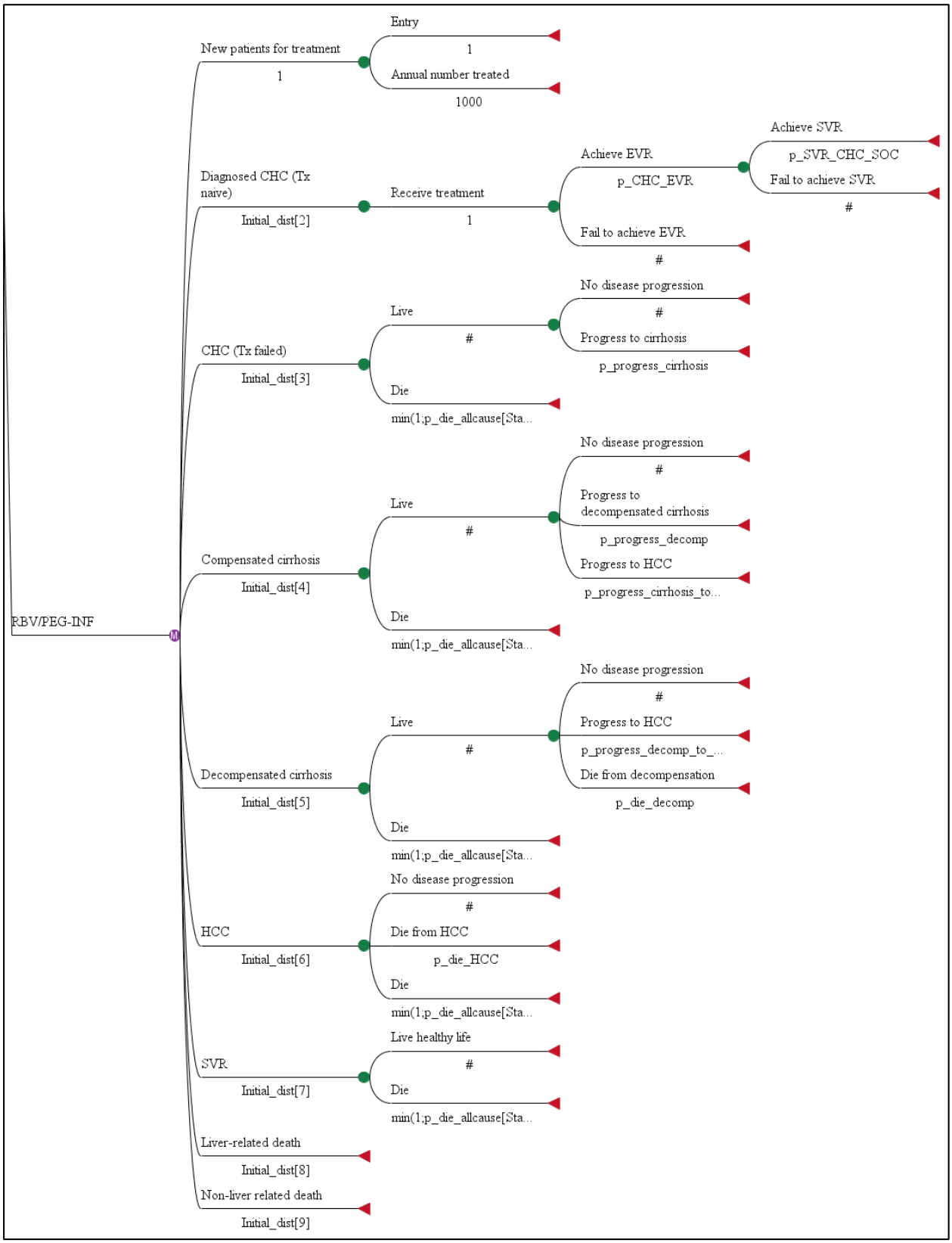


Figure A.1.8 Model structure: Budget impact model (SOC arm)


RBV/PEG-INF
New patients for treatment
1
Entry
1
Annual number treated
1000
Diagnosed CHC (Tx naive)
Initial_dist[2]
Receive treatment
1
Achieve EVR
p_CHC_EVR
Achieve SVR
p_SVR_CHC_SOC
Fail to achieve SVR
#
Fail to achieve EVR
#
CHC (Tx failed)
Initial_dist[3]
Live
#
No disease progression
#
Progress to cirrhosis
p_progress_cirrhosis
Die
min(1;p_die_allcause[Sta...
Compensated cirrhosis
Initial_dist[4]
Live
#
No disease progression
#
Progress to decompensated cirrhosis
p_progress_decomp
Progress to HCC
p_progress_cirrhosis_to...
Die
min(1;p_die_allcause[Sta...
Decompensated cirrhosis
Initial_dist[5]
Live
#
No disease progression
#
Progress to HCC
p_progress_decomp_to_...
Die from decompensation
p_die_decomp
Die
min(1;p_die_allcause[Sta...
HCC
Initial_dist[6]
No disease progression
#
Die from HCC
p_die_HCC
Die
min(1;p_die_allcause[Sta...
SVR
Initial_dist[7]
Live healthy life
#
Die
min(1;p_die_allcause[Sta...
Liver-related death
Initial_dist[8]
Non-liver related death
Initial_dist[9]

A.2.2 Background mortality rates

For all three manuscripts, sex- and age-specific mortality rates from causes other than HCV were taken from the Actuarial Society of South Africa (ASSA) HIV demographic model: 2008 version, run for 2014. For our model, background mortality rates were weighted for HIV-negative males and females, based on the assumption that 55% of the cohort was male and 45% was female (**Table A.2**).

Formula for calculating weighted average:

$$Weighted\ background\ mortality\ rate\ per\ age = rate\ per\ age\ males\ x\ (1 - 45\%) + rate\ per\ age\ females\ x\ 45\%$$

Table A.2: Background mortality rates calculated from STATSSA

All-cause mortality per age	Male	Female	Combined rate used in model
50	0.013571	0.006911	0.010574
51	0.014762	0.007475	0.011483
52	0.015944	0.008053	0.012393
53	0.017103	0.008633	0.013292
54	0.018218	0.009256	0.014185
55	0.019367	0.009998	0.015151
56	0.020537	0.010900	0.016200
57	0.021796	0.011964	0.017372
58	0.023189	0.013063	0.018632
59	0.024775	0.014066	0.019956
60	0.026404	0.015046	0.021293
61	0.028045	0.016081	0.022661
62	0.029669	0.017049	0.023990
63	0.031933	0.018424	0.025854
64	0.034418	0.019800	0.027840
65	0.037262	0.021323	0.030089
66	0.040307	0.022843	0.032448
67	0.043580	0.024512	0.034999
68	0.046933	0.026390	0.037689
69	0.050593	0.028384	0.040599
70	0.057733	0.032571	0.046410
71	0.061930	0.035178	0.049892
72	0.066472	0.037968	0.053645
73	0.071541	0.041103	0.057844
74	0.077030	0.044438	0.062364
75	0.082878	0.051333	0.068683
76	0.088884	0.054935	0.073607
77	0.094955	0.058912	0.078736
78	0.101136	0.063528	0.084212
79	0.107553	0.068609	0.090028
80	0.114197	0.074282	0.096235
81	0.120985	0.080014	0.102548
82	0.128372	0.086607	0.109578
83	0.137611	0.093920	0.117950
84	0.148468	0.102568	0.127813
85	0.160873	0.112476	0.139094
86	0.173896	0.121967	0.150528
87	0.189282	0.133294	0.164087
88	0.203802	0.145343	0.177495

A.3 Additional results and calculations

A.3.1 Manuscript 1 model output

Table A.3.1: Cost-effectiveness rankings

	Life-years	QALY	Total cost	Incremental life-years	Incremental QALY	Incremental cost / QALY gained
BASE CASE: discounted						
SOF/LEDIPASVIR	12.82	12.32	R241,560.54 ($20,588.55)	-	-	-
SOF+PEG-INF/RBV	12.67	12.07	R263,132.38 ($22,427.15)	-0.15	-0.25	DOMINATED
PEG-INF/RBV	12.18	10.40	R392,126.64 ($33,421.52)	-0.49	-1.92	DOMINATED
BASE CASE: undiscounted						
SOF/LEDIPASVIR	22.26	21.44	R252,139.66 ($23,497.25)	-	-	-
SOF+PEG-INF/RBV	21.89	20.94	R282,539.53 ($24,081.25)	-0.37	-0.50	DOMINATED
PEG-INF/RBV	20.66	18.02	R476,964.81 ($40,652.40)	-1.60	-3.42	DOMINATED
SUB-GROUP ANALYSIS A: 12 week stopping rule not applied						
SOF/LEDIPASVIR	12.82	12.32	R241,560.54 ($20,588.55)	-	-	-
SOF+PEG-INF/RBV	12.67	12.07	R263,132.38 ($22,427.15)	-0.15	-0.25	DOMINATED
PEG-INF/RBV	12.18	10.38	R419,372.12 ($35,743.69)	-0.64	-1.94	DOMINATED
SUB-GROUP ANALYSIS B: SOF/LDV for 24 weeks in cirrhotic patients						
SOF+PEG-INF/RBV	12.67	12.07	R263,132.38 ($22,427.15)	-	-	-
SOF/LEDIPASVIR	12.82	12.31	R265,108.46 ($22,595.58	+0.15	+0.25	R7,991.67
PEG-INF/RBV	12.18	10.40	R392,126.64 ($33,421.52)	-0.49	-1.67	DOMINATED

peg-INF = pegylated-interferon; QALY = quality-adjusted life-years; RBV = ribavirin; SOF = sofosbuvir

A.3.2 Manuscript 2 model output

Table A.3.2.1: Annual number of new infections, newly diagnosed cases and number of patients receiving treatment – sofosbuvir-based base case

Cycle	Disease state	Node name	Cases	Cycle	Disease state	Node name	Cases
0	New infections	Annual new infections	6940	**11**	New infections	Annual new infections	6940
0	Undiagnosed viremic infections	Diagnosed	2600	**11**	Undiagnosed viremic infections	Diagnosed	2604
0	Diagnosed CHC (Treatment naive)	Receive treatment	100	**11**	Diagnosed CHC (Treatment naive)	Receive treatment	112
0	Diagnosed CHC (Treatment naive)	Treatment successful	92	**11**	Diagnosed CHC (Treatment naive)	Treatment successful	103
0	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	8	**11**	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	9
1	New infections	Annual new infections	6940	**12**	New infections	Annual new infections	6940
1	Undiagnosed viremic infections	Diagnosed	2600	**12**	Undiagnosed viremic infections	Diagnosed	2604
1	Diagnosed CHC (Treatment naive)	Receive treatment	102	**12**	Diagnosed CHC (Treatment naive)	Receive treatment	113
1	Diagnosed CHC (Treatment naive)	Treatment successful	94	**12**	Diagnosed CHC (Treatment naive)	Treatment successful	104
1	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	8	**12**	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	9
2	New infections	Annual new infections	6940	**13**	New infections	Annual new infections	6940
2	Undiagnosed viremic infections	Diagnosed	2601	**13**	Undiagnosed viremic infections	Diagnosed	2605
2	Diagnosed CHC (Treatment naive)	Receive treatment	104	**13**	Diagnosed CHC (Treatment naive)	Receive treatment	114
2	Diagnosed CHC (Treatment naive)	Treatment successful	96	**13**	Diagnosed CHC (Treatment naive)	Treatment successful	105
2	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	8	**13**	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	9
3	New infections	Annual new infections	6940	**14**	New infections	Annual new infections	6940
3	Undiagnosed viremic infections	Diagnosed	2601	**14**	Undiagnosed viremic infections	Diagnosed	2605
3	Diagnosed CHC (Treatment naive)	Receive treatment	105	**14**	Diagnosed CHC (Treatment naive)	Receive treatment	115
3	Diagnosed CHC (Treatment naive)	Treatment successful	97	**14**	Diagnosed CHC (Treatment naive)	Treatment successful	106
3	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	8	**14**	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	9
4	New infections	Annual new infections	6940	**15**	New infections	Annual new infections	6940
4	Undiagnosed viremic infections	Diagnosed	2602	**15**	Undiagnosed viremic infections	Diagnosed	2605
4	Diagnosed CHC (Treatment naive)	Receive treatment	107	**15**	Diagnosed CHC (Treatment naive)	Receive treatment	117
4	Diagnosed CHC (Treatment naive)	Treatment successful	98	**15**	Diagnosed CHC (Treatment naive)	Treatment successful	107
4	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	9	**15**	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	9

Cycle	Disease state	Node name	Cases	Cycle	Disease state	Node name	Cases
5	New infections	Annual new infections	6940	**16**	New infections	Annual new infections	6940
5	Undiagnosed viremic infections	Diagnosed	2602	**16**	Undiagnosed viremic infections	Diagnosed	2606
5	Diagnosed CHC (Treatment naive)	Receive treatment	108	**16**	Diagnosed CHC (Treatment naive)	Receive treatment	118
5	Diagnosed CHC (Treatment naive)	Treatment successful	99	**16**	Diagnosed CHC (Treatment naive)	Treatment successful	108
5	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	9	**16**	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	9
6	New infections	Annual new infections	6940	**17**	New infections	Annual new infections	6940
6	Undiagnosed viremic infections	Diagnosed	2602	**17**	Undiagnosed viremic infections	Diagnosed	2606
6	Diagnosed CHC (Treatment naive)	Receive treatment	109	**17**	Diagnosed CHC (Treatment naive)	Receive treatment	119
6	Diagnosed CHC (Treatment naive)	Treatment successful	100	**17**	Diagnosed CHC (Treatment naive)	Treatment successful	110
6	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	9	**17**	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	10
7	New infections	Annual new infections	6940	**18**	New infections	Annual new infections	6940
7	Undiagnosed viremic infections	Diagnosed	2603	**18**	Undiagnosed viremic infections	Diagnosed	2606
7	Diagnosed CHC (Treatment naive)	Receive treatment	109	**18**	Diagnosed CHC (Treatment naive)	Receive treatment	121
7	Diagnosed CHC (Treatment naive)	Treatment successful	101	**18**	Diagnosed CHC (Treatment naive)	Treatment successful	111
7	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	9	**18**	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	10
8	New infections	Annual new infections	6940	**19**	New infections	Annual new infections	6940
8	Undiagnosed viremic infections	Diagnosed	2603	**19**	Undiagnosed viremic infections	Diagnosed	2606
8	Diagnosed CHC (Treatment naive)	Receive treatment	110	**19**	Diagnosed CHC (Treatment naive)	Receive treatment	123
8	Diagnosed CHC (Treatment naive)	Treatment successful	101	**19**	Diagnosed CHC (Treatment naive)	Treatment successful	113
8	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	9	**19**	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	10
9	New infections	Annual new infections	6940	**20**	New infections	Annual new infections	6940
9	Undiagnosed viremic infections	Diagnosed	2604	**20**	Undiagnosed viremic infections	Diagnosed	2607
9	Diagnosed CHC (Treatment naive)	Receive treatment	111	**20**	Diagnosed CHC (Treatment naive)	Receive treatment	124
9	Diagnosed CHC (Treatment naive)	Treatment successful	102	**20**	Diagnosed CHC (Treatment naive)	Treatment successful	114
9	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	9	**20**	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	10
10	New infections	Annual new infections	6940				
10	Undiagnosed viremic infections	Diagnosed	2604				
10	Diagnosed CHC (Treatment naive)	Receive treatment	112				
10	Diagnosed CHC (Treatment naive)	Treatment successful	103				
10	Diagnosed CHC (Treatment naive)	Treatment unsuccessful	9				

Table A.3.2.2: Annual number of new infections, newly diagnosed cases and number of patients receiving treatment – standard of care base case

Cycle	Disease state	Nodename	Cases	Cycle	Disease state	Nodename	Cases
0	New infections	Annual new infections	6940	**11**	New infections	Annual newly infected	6940
0	Undiagnosed viremic infections	Diagnosed	2600	**11**	Undiagnosed viremic infections	Diagnosed	2641
0	Diagnosed CHC (Treatment naive)	Receive treatment	100	**11**	Diagnosed CHC (Treatment naive)	Receive treatment	113
0	Diagnosed CHC (Treatment naive)	Achieve EVR	86	**11**	Diagnosed CHC (Treatment naive)	Achieve EVR	97
0	Diagnosed CHC (Treatment naive)	Achieve SVR	56	**11**	Diagnosed CHC (Treatment naive)	Achieve SVR	64
0	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	30	**11**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	34
0	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	14	**11**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	16
1	New infections	Annual newly infected	6940	**12**	New infections	Annual newly infected	6940
1	Undiagnosed viremic infections	Diagnosed	2600	**12**	Undiagnosed viremic infections	Diagnosed	2641
1	Diagnosed CHC (Treatment naive)	Receive treatment	102	**12**	Diagnosed CHC (Treatment naive)	Receive treatment	115
1	Diagnosed CHC (Treatment naive)	Achieve EVR	87	**12**	Diagnosed CHC (Treatment naive)	Achieve EVR	98
1	Diagnosed CHC (Treatment naive)	Achieve SVR	57	**12**	Diagnosed CHC (Treatment naive)	Achieve SVR	64
1	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	30	**12**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	34
1	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	14	**12**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	16
2	New infections	Annual newly infected	6940	**13**	New infections	Annual newly infected	6940
2	Undiagnosed viremic infections	Diagnosed	2601	**13**	Undiagnosed viremic infections	Diagnosed	2641
2	Diagnosed CHC (Treatment naive)	Receive treatment	103	**13**	Diagnosed CHC (Treatment naive)	Receive treatment	116
2	Diagnosed CHC (Treatment naive)	Achieve EVR	88	**13**	Diagnosed CHC (Treatment naive)	Achieve EVR	99
2	Diagnosed CHC (Treatment naive)	Achieve SVR	58	**13**	Diagnosed CHC (Treatment naive)	Achieve SVR	65
2	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	30	**13**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	34
2	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	15	**13**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	16
3	New infections	Annual newly infected	6940	**14**	New infections	Annual newly infected	6940
3	Undiagnosed viremic infections	Diagnosed	2601	**14**	Undiagnosed viremic infections	Diagnosed	2641
3	Diagnosed CHC (Treatment naive)	Receive treatment	104	**14**	Diagnosed CHC (Treatment naive)	Receive treatment	117
3	Diagnosed CHC (Treatment naive)	Achieve EVR	89	**14**	Diagnosed CHC (Treatment naive)	Achieve EVR	101
3	Diagnosed CHC (Treatment naive)	Achieve SVR	58	**14**	Diagnosed CHC (Treatment naive)	Achieve SVR	66
3	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	31	**14**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	35
3	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	15	**14**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	17
4	New infections	Annual newly infected	6940	**15**	New infections	Annual newly infected	6940
4	Undiagnosed viremic infections	Diagnosed	2602	**15**	Undiagnosed viremic infections	Diagnosed	2641

Cycle	Disease state	Nodename	Cases	Cycle	Disease state	Nodename	Cases
4	Diagnosed CHC (Treatment naive)	Receive treatment	105	**15**	Diagnosed CHC (Treatment naive)	Receive treatment	119
4	Diagnosed CHC (Treatment naive)	Achieve EVR	90	**15**	Diagnosed CHC (Treatment naive)	Achieve EVR	102
4	Diagnosed CHC (Treatment naive)	Achieve SVR	59	**15**	Diagnosed CHC (Treatment naive)	Achieve SVR	67
4	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	31	**15**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	35
4	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	15	**15**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	17
5	New infections	Annual newly infected	6940	**16**	New infections	Annual newly infected	6940
5	Undiagnosed viremic infections	Diagnosed	2602	**16**	Undiagnosed viremic infections	Diagnosed	2641
5	Diagnosed CHC (Treatment naive)	Receive treatment	106	**16**	Diagnosed CHC (Treatment naive)	Receive treatment	120
5	Diagnosed CHC (Treatment naive)	Achieve EVR	91	**16**	Diagnosed CHC (Treatment naive)	Achieve EVR	103
5	Diagnosed CHC (Treatment naive)	Achieve SVR	60	**16**	Diagnosed CHC (Treatment naive)	Achieve SVR	67
5	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	31	**16**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	36
5	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	15	**16**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	17
6	New infections	Annual newly infected	6940	**17**	New infections	Annual newly infected	6940
6	Undiagnosed viremic infections	Diagnosed	2602	**17**	Undiagnosed viremic infections	Diagnosed	2641
6	Diagnosed CHC (Treatment naive)	Receive treatment	107	**17**	Diagnosed CHC (Treatment naive)	Receive treatment	122
6	Diagnosed CHC (Treatment naive)	Achieve EVR	92	**17**	Diagnosed CHC (Treatment naive)	Achieve EVR	104
6	Diagnosed CHC (Treatment naive)	Achieve SVR	60	**17**	Diagnosed CHC (Treatment naive)	Achieve SVR	68
6	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	32	**17**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	36
6	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	15	**17**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	17
7	New infections	Annual newly infected	6940	**18**	New infections	Annual newly infected	6940
7	Undiagnosed viremic infections	Diagnosed	2603	**18**	Undiagnosed viremic infections	Diagnosed	2641
7	Diagnosed CHC (Treatment naive)	Receive treatment	108	**18**	Diagnosed CHC (Treatment naive)	Receive treatment	123
7	Diagnosed CHC (Treatment naive)	Achieve EVR	93	**18**	Diagnosed CHC (Treatment naive)	Achieve EVR	106
7	Diagnosed CHC (Treatment naive)	Achieve SVR	61	**18**	Diagnosed CHC (Treatment naive)	Achieve SVR	69
7	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	32	**18**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	37
7	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	15	**18**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	18
8	New infections	Annual newly infected	6940	**19**	New infections	Annual newly infected	6940
8	Undiagnosed viremic infections	Diagnosed	2603	**19**	Undiagnosed viremic infections	Diagnosed	2641
8	Diagnosed CHC (Treatment naive)	Receive treatment	109	**19**	Diagnosed CHC (Treatment naive)	Receive treatment	125
8	Diagnosed CHC (Treatment naive)	Achieve EVR	93	**19**	Diagnosed CHC (Treatment naive)	Achieve EVR	107
8	Diagnosed CHC (Treatment naive)	Achieve SVR	61	**19**	Diagnosed CHC (Treatment naive)	Achieve SVR	70
8	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	32	**19**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	37
8	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	15	**19**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	18

Cycle	Disease state	Nodename	Cases	Cycle	Disease state	Nodename	Cases
9	New infections	Annual newly infected	6940	**20**	New infections	Annual newly infected	6940
9	Undiagnosed viremic infections	Diagnosed	2604	**20**	Undiagnosed viremic infections	Diagnosed	2641
9	Diagnosed CHC (Treatment naive)	Receive treatment	110	**20**	Diagnosed CHC (Treatment naive)	Receive treatment	127
9	Diagnosed CHC (Treatment naive)	Achieve EVR	94	**20**	Diagnosed CHC (Treatment naive)	Achieve EVR	109
9	Diagnosed CHC (Treatment naive)	Achieve SVR	62	**20**	Diagnosed CHC (Treatment naive)	Achieve SVR	72
9	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	33	**20**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	38
9	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	16	**20**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	18
10	New infections	Annual newly infected	6940				
10	Undiagnosed viremic infections	Diagnosed	2604				
10	Diagnosed CHC (Treatment naive)	Receive treatment	111				
10	Diagnosed CHC (Treatment naive)	Achieve EVR	95				
10	Diagnosed CHC (Treatment naive)	Achieve SVR	62				
10	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	33				
10	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	16				

Table A.3.2.3: Total number of cases per disease state per cycle – SOF-based (base case)

Cycle	Disease state	Cases	Stage	Disease state	Cases	Cycle	Disease state	Cases
0	Undiagnosed VI	338300	**7**	Undiagnosed VI	308996	**14**	Undiagnosed VI	267477
0	Diagnosed CHC	9380	**7**	Diagnosed CHC	23868	**14**	Diagnosed CHC	34113
0	Cirrhosis	39700	**7**	Cirrhosis	35534	**14**	Cirrhosis	30964
0	Decomp. cirrhosis	4810	**7**	Decomp. cirrhosis	8803	**14**	Decomp. cirrhosis	8118
0	HCC	1610	**7**	HCC	2986	**14**	HCC	2644
0	SVR	0	**7**	SVR	643	**14**	SVR	1205
0	Liver-related death	0	**7**	Liver-related death	19652	**14**	Liver-related death	41703
1	Undiagnosed VI	334772	**8**	Undiagnosed VI	303836	**15**	Undiagnosed VI	260286
1	Diagnosed CHC	11661	**8**	Diagnosed CHC	25622	**15**	Diagnosed CHC	35120
1	Cirrhosis	39066	**8**	Cirrhosis	34937	**15**	Cirrhosis	30186
1	Decomp. cirrhosis	6139	**8**	Decomp. cirrhosis	8820	**15**	Decomp. cirrhosis	7918
1	HCC	2351	**8**	HCC	2960	**15**	HCC	2571
1	SVR	92	**8**	SVR	731	**15**	SVR	1272
1	Liver-related death	1772	**8**	Liver-related death	22908	**15**	Liver-related death	44622
2	Undiagnosed VI	331029	**9**	Undiagnosed VI	298432	**16**	Undiagnosed VI	252748
2	Diagnosed CHC	13876	**9**	Diagnosed CHC	27288	**16**	Diagnosed CHC	35993
2	Cirrhosis	38454	**9**	Cirrhosis	34327	**16**	Cirrhosis	29367
2	Decomp. cirrhosis	7095	**9**	Decomp. cirrhosis	8783	**16**	Decomp. cirrhosis	7702
2	HCC	2697	**9**	HCC	2924	**16**	HCC	2494
2	SVR	185	**9**	SVR	817	**16**	SVR	1335
2	Liver-related death	4212	**9**	Liver-related death	26149	**16**	Liver-related death	47461
3	Undiagnosed VI	327082	**10**	Undiagnosed VI	292798	**17**	Undiagnosed VI	244881
3	Diagnosed CHC	16023	**10**	Diagnosed CHC	28862	**17**	Diagnosed CHC	36729
3	Cirrhosis	37860	**10**	Cirrhosis	33704	**17**	Cirrhosis	28507
3	Decomp. cirrhosis	7769	**10**	Decomp. cirrhosis	8706	**17**	Decomp. cirrhosis	7471
3	HCC	2867	**10**	HCC	2880	**17**	HCC	2412
3	SVR	278	**10**	SVR	900	**17**	SVR	1393
3	Liver-related death	7018	**10**	Liver-related death	29361	**17**	Liver-related death	50215
4	Undiagnosed VI	322922	**11**	Undiagnosed VI	286966	**18**	Undiagnosed VI	236689
4	Diagnosed CHC	18100	**11**	Diagnosed CHC	30345	**18**	Diagnosed CHC	37320
4	Cirrhosis	37277	**11**	Cirrhosis	33068	**18**	Cirrhosis	27604
4	Decomp. cirrhosis	8232	**11**	Decomp. cirrhosis	8597	**18**	Decomp. cirrhosis	7227
4	HCC	2952	**11**	HCC	2831	**18**	HCC	2327
4	SVR	371	**11**	SVR	981	**18**	SVR	1446
4	Liver-related death	10038	**11**	Liver-related death	32531	**18**	Liver-related death	52879
5	Undiagnosed VI	318534	**12**	Undiagnosed VI	280808	**19**	Undiagnosed VI	227555
5	Diagnosed CHC	20103	**12**	Diagnosed CHC	31718	**19**	Diagnosed CHC	37663
5	Cirrhosis	36700	**12**	Cirrhosis	32401	**19**	Cirrhosis	26585
5	Decomp. cirrhosis	8535	**12**	Decomp. cirrhosis	8460	**19**	Decomp. cirrhosis	6950
5	HCC	2989	**12**	HCC	2774	**19**	HCC	2227
5	SVR	463	**12**	SVR	1059	**19**	SVR	1490
5	Liver-related death	13185	**12**	Liver-related death	35650	**19**	Liver-related death	55445
6	Undiagnosed VI	313896	**13**	Undiagnosed VI	274323	**20**	Undiagnosed VI	218157
6	Diagnosed CHC	22027	**13**	Diagnosed CHC	32977	**20**	Diagnosed CHC	37853
6	Cirrhosis	36121	**13**	Cirrhosis	31702	**20**	Cirrhosis	25527
6	Decomp. cirrhosis	8715	**13**	Decomp. cirrhosis	8299	**20**	Decomp. cirrhosis	6661
6	HCC	2997	**13**	HCC	2712	**20**	HCC	2127
6	SVR	554	**13**	SVR	1134	**20**	SVR	1529
6	Liver-related death	16402	**13**	Liver-related death	38710	**20**	Liver-related death	57901

CHC = chronic hepatitis C; HCC = hepatocellular carcinoma; SVR = sustained virologic response; VI = viremic infections
**Diagnosed CHC = treatment naïve*

Table A.3.2.4: Total number of cases per disease state per cycle – SOC (base case)

Cycle	Disease state	Cases	Stage	Disease state	Cases	Cycle	Disease state	Cases
0	Undiagnosed VI	338300	**7**	Undiagnosed VI	308996	**14**	Undiagnosed VI	267477
0	Diagnosed CHC	9380	**7**	Diagnosed CHC	23876	**14**	Diagnosed CHC	34123
0	Cirrhosis	39700	**7**	Cirrhosis	35541	**14**	Cirrhosis	30985
0	Decomp. cirrhosis	4810	**7**	Decomp. cirrhosis	8804	**14**	Decomp. cirrhosis	8121
0	HCC	1610	**7**	HCC	2986	**14**	HCC	2645
0	SVR	0	**7**	SVR	388	**14**	SVR	730
0	Liver-related death	0	**7**	Liver-related death	19653	**14**	Liver-related death	41708
1	Undiagnosed VI	334772	**8**	Undiagnosed VI	303836	**15**	Undiagnosed VI	260286
1	Diagnosed CHC	11661	**8**	Diagnosed CHC	25631	**15**	Diagnosed CHC	35129
1	Cirrhosis	39066	**8**	Cirrhosis	34946	**15**	Cirrhosis	30209
1	Decomp. cirrhosis	6139	**8**	Decomp. cirrhosis	8821	**15**	Decomp. cirrhosis	7922
1	HCC	2351	**8**	HCC	2961	**15**	HCC	2573
1	SVR	56	**8**	SVR	441	**15**	SVR	771
1	Liver-related death	1772	**8**	Liver-related death	22909	**15**	Liver-related death	44628
2	Undiagnosed VI	331029	**9**	Undiagnosed VI	298432	**16**	Undiagnosed VI	252748
2	Diagnosed CHC	13876	**9**	Diagnosed CHC	27298	**16**	Diagnosed CHC	36002
2	Cirrhosis	38454	**9**	Cirrhosis	34338	**16**	Cirrhosis	29392
2	Decomp. cirrhosis	7095	**9**	Decomp. cirrhosis	8785	**16**	Decomp. cirrhosis	7706
2	HCC	2697	**9**	HCC	2925	**16**	HCC	2495
2	SVR	113	**9**	SVR	493	**16**	SVR	810
2	Liver-related death	4212	**9**	Liver-related death	26150	**16**	Liver-related death	47469
3	Undiagnosed VI	327082	**10**	Undiagnosed VI	292798	**17**	Undiagnosed VI	244881
3	Diagnosed CHC	16025	**10**	Diagnosed CHC	28873	**17**	Diagnosed CHC	36736
3	Cirrhosis	37861	**10**	Cirrhosis	33716	**17**	Cirrhosis	28533
3	Decomp. cirrhosis	7769	**10**	Decomp. cirrhosis	8707	**17**	Decomp. cirrhosis	7476
3	HCC	2867	**10**	HCC	2881	**17**	HCC	2414
3	SVR	169	**10**	SVR	544	**17**	SVR	846
3	Liver-related death	7018	**10**	Liver-related death	29362	**17**	Liver-related death	50225
4	Undiagnosed VI	322922	**11**	Undiagnosed VI	286966	**18**	Undiagnosed VI	236689
4	Diagnosed CHC	18103	**11**	Diagnosed CHC	30355	**18**	Diagnosed CHC	37326
4	Cirrhosis	37280	**11**	Cirrhosis	33082	**18**	Cirrhosis	27632
4	Decomp. cirrhosis	8232	**11**	Decomp. cirrhosis	8599	**18**	Decomp. cirrhosis	7232
4	HCC	2952	**11**	HCC	2831	**18**	HCC	2329
4	SVR	225	**11**	SVR	593	**18**	SVR	879
4	Liver-related death	10038	**11**	Liver-related death	32533	**18**	Liver-related death	52890
5	Undiagnosed VI	318534	**12**	Undiagnosed VI	280808	**19**	Undiagnosed VI	227555
5	Diagnosed CHC	20107	**12**	Diagnosed CHC	31729	**19**	Diagnosed CHC	37668
5	Cirrhosis	36704	**12**	Cirrhosis	32418	**19**	Cirrhosis	26615
5	Decomp. cirrhosis	8535	**12**	Decomp. cirrhosis	8462	**19**	Decomp. cirrhosis	6955
5	HCC	2989	**12**	HCC	2775	**19**	HCC	2229
5	SVR	280	**12**	SVR	641	**19**	SVR	907
5	Liver-related death	13185	**12**	Liver-related death	35653	**19**	Liver-related death	55458
6	Undiagnosed VI	313896	**13**	Undiagnosed VI	274323	**20**	Undiagnosed VI	218157
6	Diagnosed CHC	22033	**13**	Diagnosed CHC	32988	**20**	Diagnosed CHC	37857
6	Cirrhosis	36126	**13**	Cirrhosis	31721	**20**	Cirrhosis	25558
6	Decomp. cirrhosis	8716	**13**	Decomp. cirrhosis	8302	**20**	Decomp. cirrhosis	6667
6	HCC	2997	**13**	HCC	2713	**20**	HCC	2129
6	SVR	335	**13**	SVR	686	**20**	SVR	931
6	Liver-related death	16402	**13**	Liver-related death	38714	**20**	Liver-related death	57916

CHC = chronic hepatitis C; HCC = hepatocellular carcinoma; SVR = sustained virologic response; VI = viremic infections
**Diagnosed CHC = treatment naïve*

Table A.3.2.5: Model output: total number of cases of advance liver-disease and liver-related deaths per cycle – SOF-based (base case)

Cycle	Decompensated cirrhosis			HCC			Liver-related death		
		Cases	Calculate new cases		Cases	Calculate new cases		Cases	Calculate new cases
0	Start cycle in decomp. cirrhosis state	4810		Start cycle in HCC state	1610			0	
0	No disease progression	3629		No disease progression	616				
1	Total cases of decomp. cirrhosis in cycle	6139	2509	Total cases of HCC in cycle	2351	1735	Total cases of liver-related death	1772	1772
1	No disease progression	4628		No disease progression	897				
2	Total cases of decomp. cirrhosis in cycle	7095	2467	Total cases of HCC in cycle	2697	1800	Total cases of liver-related death	4212	2440
2	No disease progression	5343		No disease progression	1027				
3	Total cases of decomp. cirrhosis in cycle	7769	2426	Total cases of HCC in cycle	2867	1840	Total cases of liver-related death	7018	2807
3	No disease progression	5846		No disease progression	1089				
4	Total cases of decomp. cirrhosis in cycle	8232	2386	Total cases of HCC in cycle	2952	1863	Total cases of liver-related death	10038	3020
4	No disease progression	6188		No disease progression	1118				
5	Total cases of decomp. cirrhosis in cycle	8535	2347	Total cases of HCC in cycle	2989	1871	Total cases of liver-related death	13185	3146
5	No disease progression	6407		No disease progression	1129				
6	Total cases of decomp. cirrhosis in cycle	8715	2308	Total cases of HCC in cycle	2997	1869	Total cases of liver-related death	16402	3217
6	No disease progression	6534		No disease progression	1128				
7	Total cases of decomp. cirrhosis in cycle	8803	2269	Total cases of HCC in cycle	2986	1858	Total cases of liver-related death	19652	3250
7	No disease progression	6591		No disease progression	1120				
8	Total cases of decomp. cirrhosis in cycle	8820	2229	Total cases of HCC in cycle	2960	1840	Total cases of liver-related death	22908	3256
8	No disease progression	6595		No disease progression	1106				
9	Total cases of decomp. cirrhosis in cycle	8783	2188	Total cases of HCC in cycle	2924	1818	Total cases of liver-related death	26149	3241
9	No disease progression	6558		No disease progression	1089				
10	Total cases of decomp. cirrhosis in cycle	8706	2147	Total cases of HCC in cycle	2880	1792	Total cases of liver-related death	29361	3211
10	No disease progression	6492		No disease progression	1069				
11	Total cases of decomp. cirrhosis in cycle	8597	2105	Total cases of HCC in cycle	2831	1762	Total cases of liver-related death	32531	3170
11	No disease progression	6398		No disease progression	1045				
12	Total cases of decomp. cirrhosis in cycle	8460	2062	Total cases of HCC in cycle	2774	1729	Total cases of liver-related death	35650	3119
12	No disease progression	6283		No disease progression	1019				
13	Total cases of decomp. cirrhosis in cycle	8299	2016	Total cases of HCC in cycle	2712	1693	Total cases of liver-related death	38710	3060
13	No disease progression	6150		No disease progression	990				

	Decompensated cirrhosis			HCC			Liver-related death		
14	Total cases of decomp. cirrhosis in cycle	8118	1968	Total cases of HCC in cycle	2644	1654	Total cases of liver-related death	41703	2993
14	No disease progression	6001		No disease progression	959				
15	Total cases of decomp. cirrhosis in cycle	7918	1917	Total cases of HCC in cycle	2571	1613	Total cases of liver-related death	44622	2919
15	No disease progression	5838		No disease progression	926				
16	Total cases of decomp. cirrhosis in cycle	7702	1864	Total cases of HCC in cycle	2494	1568	Total cases of liver-related death	47461	2839
16	No disease progression	5663		No disease progression	891				
17	Total cases of decomp. cirrhosis in cycle	7471	1809	Total cases of HCC in cycle	2412	1521	Total cases of liver-related death	50215	2754
17	No disease progression	5476		No disease progression	855				
18	Total cases of decomp. cirrhosis in cycle	7227	1750	Total cases of HCC in cycle	2327	1472	Total cases of liver-related death	52879	2664
18	No disease progression	5265		No disease progression	811				0
19	Total cases of decomp. cirrhosis in cycle	6950	1685	Total cases of HCC in cycle	2227	1416	Total cases of liver-related death	55445	2566
19	No disease progression	5045		No disease progression	769				0
20	Total cases of decomp. cirrhosis in cycle	6661	1617	Total cases of HCC in cycle	2127	1358	Total cases of liver-related death	57901	2457
20	No disease progression	4816		No disease progression	726				0

$$\textit{New cases per cycle} = \textit{total cases in cycle} - \textit{cases of no disease progression from previous cycle}$$

Table A.3.2.6: Model output: total number of cases of advance liver-disease and liver-related deaths per cycle – SOC (base case)

Cycle	Decompensated cirrhosis			HCC			Liver-related deaths		
		Cases	Calculate new cases		Cases	Calculate new cases		Cases	Calculate new cases
0	Start cycle in decomp. cirrhosis state	4810		Start cycle in HCC state	1610		Total cases of liver-related death	0	
0	No disease progression	3629		No disease progression	616				
1	Total cases of decomp. cirrhosis in cycle	6139	2509	Total cases of HCC in cycle	2351	1735	Total cases of liver-related death	1772	1772
1	No disease progression	4628		No disease progression	897				
2	Total cases of decomp. cirrhosis in cycle	7095	2467	Total cases of HCC in cycle	2697	1800	Total cases of liver-related death	4212	2440
2	No disease progression	5343		No disease progression	1027				
3	Total cases of decomp. cirrhosis in cycle	7769	2426	Total cases of HCC in cycle	2867	1840	Total cases of liver-related death	7018	2806
3	No disease progression	5846		No disease progression	1089				
4	Total cases of decomp. cirrhosis in cycle	8232	2386	Total cases of HCC in cycle	2952	1863	Total cases of liver-related death	10038	3020
4	No disease progression	6188		No disease progression	1118				
5	Total cases of decomp. cirrhosis in cycle	8535	2347	Total cases of HCC in cycle	2989	1871	Total cases of liver-related death	13185	3146
5	No disease progression	6407		No disease progression	1129				
6	Total cases of decomp. cirrhosis in cycle	8716	2308	Total cases of HCC in cycle	2997	1869	Total cases of liver-related death	16402	3217
6	No disease progression	6535		No disease progression	1128				
7	Total cases of decomp. cirrhosis in cycle	8804	2269	Total cases of HCC in cycle	2986	1858	Total cases of liver-related death	19653	3250
7	No disease progression	6592		No disease progression	1120				
8	Total cases of decomp. cirrhosis in cycle	8821	2229	Total cases of HCC in cycle	2961	1841	Total cases of liver-related death	22909	3256
8	No disease progression	6596		No disease progression	1106				
9	Total cases of decomp. cirrhosis in cycle	8785	2189	Total cases of HCC in cycle	2925	1818	Total cases of liver-related death	26150	3242
9	No disease progression	6559		No disease progression	1089				
10	Total cases of decomp. cirrhosis in cycle	8707	2148	Total cases of HCC in cycle	2881	1792	Total cases of liver-related death	29362	3212
10	No disease progression	6493		No disease progression	1069				
11	Total cases of decomp. cirrhosis in cycle	8599	2106	Total cases of HCC in cycle	2831	1763	Total cases of liver-related death	32533	3171
11	No disease progression	6400		No disease progression	1045				
12	Total cases of decomp. cirrhosis in cycle	8462	2063	Total cases of HCC in cycle	2775	1730	Total cases of liver-related death	35653	3120
12	No disease progression	6285		No disease progression	1019				
13	Total cases of decomp. cirrhosis in cycle	8302	2017	Total cases of HCC in cycle	2713	1694	Total cases of liver-related death	38714	3061
13	No disease progression	6152		No disease progression	990				
14	Total cases of decomp. cirrhosis in cycle	8121	1969	Total cases of HCC in cycle	2645	1655	Total cases of liver-related death	41708	2994

	Decompensated cirrhosis			HCC			Liver-related death		
14	No disease progression	6003		No disease progression	959				
15	Total cases of decomp. cirrhosis in cycle	7922	1919	Total cases of HCC in cycle	2573	1614	Total cases of liver-related death	44628	2920
15	No disease progression	5840		No disease progression	926				
16	Total cases of decomp. cirrhosis in cycle	7706	1866	Total cases of HCC in cycle	2495	1569	Total cases of liver-related death	47469	2841
16	No disease progression	5666		No disease progression	892				
17	Total cases of decomp. cirrhosis in cycle	7476	1810	Total cases of HCC in cycle	2414	1523	Total cases of liver-related death	50225	2756
17	No disease progression	5480		No disease progression	856				
18	Total cases of decomp. cirrhosis in cycle	7232	1752	Total cases of HCC in cycle	2329	1473	Total cases of liver-related death	52890	2666
18	No disease progression	5269		No disease progression	812				
19	Total cases of decomp. cirrhosis in cycle	6955	1686	Total cases of HCC in cycle	2229	1418	Total cases of liver-related death	55458	2567
19	No disease progression	5049		No disease progression	769				
20	Total cases of decomp. cirrhosis in cycle	6667	1618	Total cases of HCC in cycle	2129	1360	Total cases of liver-related death	57917	2459
20	No disease progression	4820		No disease progression	727				

$$\textit{New cases per cycle} = \textit{total cases in cycle} - \textit{cases of no disease progression from previous cycle}$$

Table A.3.2.7: Annual number of new infections, newly diagnosed cases and number of patients receiving treatment – SOF-based (treatment scale-up)

Cycle	Disease state	Nodename	Cases	Cycle	Disease state	Nodename	Cases
0	New infections	Annual new infections	6940	**11**	New infections	Annual new infections	6940
0	Undiagnosed viremic infections	Diagnosed	2600	**11**	Undiagnosed viremic infections	Diagnosed	2604
0	Diagnosed CHC (Treatment naive)	Receive treatment	938	**11**	Diagnosed CHC (Treatment naive)	Receive treatment	1764
0	Diagnosed CHC (Treatment naive)	Successful	863	**11**	Diagnosed CHC (Treatment naive)	Successful	1623
0	Diagnosed CHC (Treatment naive)	Unsuccessful	75	**11**	Diagnosed CHC (Treatment naive)	Unsuccessful	141
1	New infections	Annual new infections	6940	**12**	New infections	Annual new infections	6940
1	Undiagnosed viremic infections	Diagnosed	2600	**12**	Undiagnosed viremic infections	Diagnosed	2604
1	Diagnosed CHC (Treatment naive)	Receive treatment	1082	**12**	Diagnosed CHC (Treatment naive)	Receive treatment	1783
1	Diagnosed CHC (Treatment naive)	Successful	996	**12**	Diagnosed CHC (Treatment naive)	Successful	1641
1	Diagnosed CHC (Treatment naive)	Unsuccessful	87	**12**	Diagnosed CHC (Treatment naive)	Unsuccessful	143
2	New infections	Annual new infections	6940	**13**	New infections	Annual new infections	6940
2	Undiagnosed viremic infections	Diagnosed	2601	**13**	Undiagnosed viremic infections	Diagnosed	2605
2	Diagnosed CHC (Treatment naive)	Receive treatment	1208	**13**	Diagnosed CHC (Treatment naive)	Receive treatment	1796
2	Diagnosed CHC (Treatment naive)	Successful	1111	**13**	Diagnosed CHC (Treatment naive)	Successful	1652
2	Diagnosed CHC (Treatment naive)	Unsuccessful	97	**13**	Diagnosed CHC (Treatment naive)	Unsuccessful	144
3	New infections	Annual new infections	6940	**14**	New infections	Annual new infections	6940
3	Undiagnosed viremic infections	Diagnosed	2601	**14**	Undiagnosed viremic infections	Diagnosed	2605
3	Diagnosed CHC (Treatment naive)	Receive treatment	1317	**14**	Diagnosed CHC (Treatment naive)	Receive treatment	1803
3	Diagnosed CHC (Treatment naive)	Successful	1211	**14**	Diagnosed CHC (Treatment naive)	Successful	1659
3	Diagnosed CHC (Treatment naive)	Unsuccessful	105	**14**	Diagnosed CHC (Treatment naive)	Unsuccessful	144
4	New infections	Annual new infections	6940	**15**	New infections	Annual new infections	6940
4	Undiagnosed viremic infections	Diagnosed	2602	**15**	Undiagnosed viremic infections	Diagnosed	2605
4	Diagnosed CHC (Treatment naive)	Receive treatment	1411	**15**	Diagnosed CHC (Treatment naive)	Receive treatment	1805
4	Diagnosed CHC (Treatment naive)	Successful	1298	**15**	Diagnosed CHC (Treatment naive)	Successful	1661
4	Diagnosed CHC (Treatment naive)	Unsuccessful	113	**15**	Diagnosed CHC (Treatment naive)	Unsuccessful	144
5	New infections	Annual new infections	6940	**16**	New infections	Annual new infections	6940
5	Undiagnosed viremic infections	Diagnosed	2602	**16**	Undiagnosed viremic infections	Diagnosed	2606
5	Diagnosed CHC (Treatment naive)	Receive treatment	1491	**16**	Diagnosed CHC (Treatment naive)	Receive treatment	1802
5	Diagnosed CHC (Treatment naive)	Successful	1372	**16**	Diagnosed CHC (Treatment naive)	Successful	1658
5	Diagnosed CHC (Treatment naive)	Unsuccessful	119	**16**	Diagnosed CHC (Treatment naive)	Unsuccessful	144

Cycle	Disease state	Nodename	Cases	Cycle	Disease state	Nodename	Cases
6	New infections	Annual new infections	6940	**17**	New infections	Annual new infections	6940
6	Undiagnosed viremic infections	Diagnosed	2602	**17**	Undiagnosed viremic infections	Diagnosed	2606
6	Diagnosed CHC (Treatment naive)	Receive treatment	1560	**17**	Diagnosed CHC (Treatment naive)	Receive treatment	1795
6	Diagnosed CHC (Treatment naive)	Successful	1435	**17**	Diagnosed CHC (Treatment naive)	Successful	1651
6	Diagnosed CHC (Treatment naive)	Unsuccessful	125	**17**	Diagnosed CHC (Treatment naive)	Unsuccessful	144
7	New infections	Annual new infections	6940	**18**	New infections	Annual new infections	6940
7	Undiagnosed viremic infections	Diagnosed	2603	**18**	Undiagnosed viremic infections	Diagnosed	2606
7	Diagnosed CHC (Treatment naive)	Receive treatment	1618	**18**	Diagnosed CHC (Treatment naive)	Receive treatment	1783
7	Diagnosed CHC (Treatment naive)	Successful	1489	**18**	Diagnosed CHC (Treatment naive)	Successful	1641
7	Diagnosed CHC (Treatment naive)	Unsuccessful	129	**18**	Diagnosed CHC (Treatment naive)	Unsuccessful	143
8	New infections	Annual new infections	6940	**19**	New infections	Annual new infections	6940
8	Undiagnosed viremic infections	Diagnosed	2603	**19**	Undiagnosed viremic infections	Diagnosed	2606
8	Diagnosed CHC (Treatment naive)	Receive treatment	1667	**19**	Diagnosed CHC (Treatment naive)	Receive treatment	1763
8	Diagnosed CHC (Treatment naive)	Successful	1533	**19**	Diagnosed CHC (Treatment naive)	Successful	1622
8	Diagnosed CHC (Treatment naive)	Unsuccessful	133	**19**	Diagnosed CHC (Treatment naive)	Unsuccessful	141
9	New infections	Annual new infections	6940	**20**	New infections	Annual new infections	6940
9	Undiagnosed viremic infections	Diagnosed	2604	**20**	Undiagnosed viremic infections	Diagnosed	2607
9	Diagnosed CHC (Treatment naive)	Receive treatment	1706	**20**	Diagnosed CHC (Treatment naive)	Receive treatment	1740
9	Diagnosed CHC (Treatment naive)	Successful	1570	**20**	Diagnosed CHC (Treatment naive)	Successful	1601
9	Diagnosed CHC (Treatment naive)	Unsuccessful	137	**20**	Diagnosed CHC (Treatment naive)	Unsuccessful	139
10	New infections	Annual new infections	6940				
10	Undiagnosed viremic infections	Diagnosed	2604				
10	Diagnosed CHC (Treatment naive)	Receive treatment	1739				
10	Diagnosed CHC (Treatment naive)	Successful	1600				
10	Diagnosed CHC (Treatment naive)	Unsuccessful	139				

Table A.3.2.8: Annual number of new infections, newly diagnosed cases and number of patients receiving treatment – SOC (treatment scale-up)

Cycle	Disease state	Node name	Cases	Cycle	Disease state	Node name	Cases
0	New infections	Annual newly infected	6940	**11**	New infections	Annual newly infected	6940
0	Undiagnosed viremic infections	Diagnosed	2600	**11**	Undiagnosed viremic infections	Diagnosed	2604
0	Diagnosed CHC (Treatment naive)	Receive treatment	938	**11**	Diagnosed CHC (Treatment naive)	Receive treatment	1764
0	Diagnosed CHC (Treatment naive)	Achieve EVR	805	**11**	Diagnosed CHC (Treatment naive)	Achieve EVR	1514
0	Diagnosed CHC (Treatment naive)	Achieve SVR	527	**11**	Diagnosed CHC (Treatment naive)	Achieve SVR	992
0	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	278	**11**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	522
0	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	133	**11**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	251
1	New infections	Annual newly infected	6940	**12**	New infections	Annual newly infected	6940
1	Undiagnosed viremic infections	Diagnosed	2600	**12**	Undiagnosed viremic infections	Diagnosed	2604
1	Diagnosed CHC (Treatment naive)	Receive treatment	1082	**12**	Diagnosed CHC (Treatment naive)	Receive treatment	1783
1	Diagnosed CHC (Treatment naive)	Achieve EVR	929	**12**	Diagnosed CHC (Treatment naive)	Achieve EVR	1530
1	Diagnosed CHC (Treatment naive)	Achieve SVR	608	**12**	Diagnosed CHC (Treatment naive)	Achieve SVR	1002
1	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	320	**12**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	528
1	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	154	**12**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	253
2	New infections	Annual newly infected	6940	**13**	New infections	Annual newly infected	6940
2	Undiagnosed viremic infections	Diagnosed	2601	**13**	Undiagnosed viremic infections	Diagnosed	2605
2	Diagnosed CHC (Treatment naive)	Receive treatment	1208	**13**	Diagnosed CHC (Treatment naive)	Receive treatment	1796
2	Diagnosed CHC (Treatment naive)	Achieve EVR	1036	**13**	Diagnosed CHC (Treatment naive)	Achieve EVR	1541
2	Diagnosed CHC (Treatment naive)	Achieve SVR	679	**13**	Diagnosed CHC (Treatment naive)	Achieve SVR	1009
2	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	358	**13**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	532
2	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	172	**13**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	255
3	New infections	Annual newly infected	6940	**14**	New infections	Annual newly infected	6940
3	Undiagnosed viremic infections	Diagnosed	2601	**14**	Undiagnosed viremic infections	Diagnosed	2605
3	Diagnosed CHC (Treatment naive)	Receive treatment	1317	**14**	Diagnosed CHC (Treatment naive)	Receive treatment	1803
3	Diagnosed CHC (Treatment naive)	Achieve EVR	1130	**14**	Diagnosed CHC (Treatment naive)	Achieve EVR	1547
3	Diagnosed CHC (Treatment naive)	Achieve SVR	740	**14**	Diagnosed CHC (Treatment naive)	Achieve SVR	1013
3	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	390	**14**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	534
3	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	187	**14**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	256

Cycle	Disease state	Node name	Cases	Cycle	Disease state	Node name	Cases
4	New infections	Annual newly infected	6940	**15**	New infections	Annual newly infected	6940
4	Undiagnosed viremic infections	Diagnosed	2602	**15**	Undiagnosed viremic infections	Diagnosed	2605
4	Diagnosed CHC (Treatment naive)	Receive treatment	1411	**15**	Diagnosed CHC (Treatment naive)	Receive treatment	1805
4	Diagnosed CHC (Treatment naive)	Achieve EVR	1210	**15**	Diagnosed CHC (Treatment naive)	Achieve EVR	1549
4	Diagnosed CHC (Treatment naive)	Achieve SVR	793	**15**	Diagnosed CHC (Treatment naive)	Achieve SVR	1014
4	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	418	**15**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	534
4	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	200	**15**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	256
5	New infections	Annual newly infected	6940	**16**	New infections	Annual newly infected	6940
5	Undiagnosed viremic infections	Diagnosed	2602	**16**	Undiagnosed viremic infections	Diagnosed	2606
5	Diagnosed CHC (Treatment naive)	Receive treatment	1491	**16**	Diagnosed CHC (Treatment naive)	Receive treatment	1802
5	Diagnosed CHC (Treatment naive)	Achieve EVR	1280	**16**	Diagnosed CHC (Treatment naive)	Achieve EVR	1546
5	Diagnosed CHC (Treatment naive)	Achieve SVR	838	**16**	Diagnosed CHC (Treatment naive)	Achieve SVR	1013
5	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	441	**16**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	533
5	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	212	**16**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	256
6	New infections	Annual newly infected	6940	**17**	New infections	Annual newly infected	6940
6	Undiagnosed viremic infections	Diagnosed	2602	**17**	Undiagnosed viremic infections	Diagnosed	2606
6	Diagnosed CHC (Treatment naive)	Receive treatment	1560	**17**	Diagnosed CHC (Treatment naive)	Receive treatment	1795
6	Diagnosed CHC (Treatment naive)	Achieve EVR	1339	**17**	Diagnosed CHC (Treatment naive)	Achieve EVR	1540
6	Diagnosed CHC (Treatment naive)	Achieve SVR	877	**17**	Diagnosed CHC (Treatment naive)	Achieve SVR	1009
6	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	462	**17**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	531
6	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	222	**17**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	255
7	New infections	Annual newly infected	6940	**18**	New infections	Annual newly infected	6940
7	Undiagnosed viremic infections	Diagnosed	2603	**18**	Undiagnosed viremic infections	Diagnosed	2606
7	Diagnosed CHC (Treatment naive)	Receive treatment	1618	**18**	Diagnosed CHC (Treatment naive)	Receive treatment	1783
7	Diagnosed CHC (Treatment naive)	Achieve EVR	1388	**18**	Diagnosed CHC (Treatment naive)	Achieve EVR	1530
7	Diagnosed CHC (Treatment naive)	Achieve SVR	909	**18**	Diagnosed CHC (Treatment naive)	Achieve SVR	1002
7	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	479	**18**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	528
7	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	230	**18**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	253

Cycle	Disease state	Node name	Cases	Cycle	Disease state	Node name	Cases
8	New infections	Annual newly infected	6940	**19**	New infections	Annual newly infected	6940
8	Undiagnosed viremic infections	Diagnosed	2603	**19**	Undiagnosed viremic infections	Diagnosed	2606
8	Diagnosed CHC (Treatment naive)	Receive treatment	1667	**19**	Diagnosed CHC (Treatment naive)	Receive treatment	1763
8	Diagnosed CHC (Treatment naive)	Achieve EVR	1430	**19**	Diagnosed CHC (Treatment naive)	Achieve EVR	1513
8	Diagnosed CHC (Treatment naive)	Achieve SVR	937	**19**	Diagnosed CHC (Treatment naive)	Achieve SVR	991
8	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	493	**19**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	522
8	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	237	**19**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	250
9	New infections	Annual newly infected	6940	**20**	New infections	Annual newly infected	6940
9	Undiagnosed viremic infections	Diagnosed	2604	**20**	Undiagnosed viremic infections	Diagnosed	2607
9	Diagnosed CHC (Treatment naive)	Receive treatment	1706	**20**	Diagnosed CHC (Treatment naive)	Receive treatment	1740
9	Diagnosed CHC (Treatment naive)	Achieve EVR	1464	**20**	Diagnosed CHC (Treatment naive)	Achieve EVR	1493
9	Diagnosed CHC (Treatment naive)	Achieve SVR	959	**20**	Diagnosed CHC (Treatment naive)	Achieve SVR	978
9	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	505	**20**	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	515
9	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	242	**20**	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	247
10	New infections	Annual newly infected	6940				
10	Undiagnosed viremic infections	Diagnosed	2604				
10	Diagnosed CHC (Treatment naive)	Receive treatment	1739				
10	Diagnosed CHC (Treatment naive)	Achieve EVR	1492				
10	Diagnosed CHC (Treatment naive)	Achieve SVR	977				
10	Diagnosed CHC (Treatment naive)	Fail to achieve SVR	515				
10	Diagnosed CHC (Treatment naive)	Fail to achieve EVR	247				

Table A.3.2.9: Number of cases per disease state — SOF-based(treatment scale-up)

Stage	Disease state	Cases	Stage	Disease state	Cases	Stage	Disease state	Cases
0	Undiagnosed VI	338300	7	Undiagnosed VI	308996	14	Undiagnosed VI	267477
0	Diagnosed CHC	9380	7	Diagnosed CHC	16182	14	Diagnosed CHC	18032
0	Cirrhosis	39700	7	Cirrhosis	35356	14	Cirrhosis	30297
0	Decomp. cirrhosis	4810	7	Decomp. cirrhosis	8788	14	Decomp. cirrhosis	8020
0	HCC	1610	7	HCC	2979	14	HCC	2606
0	SVR	0	7	SVR	7922	14	SVR	16929
0	Liver-related death	0	7	Liver-related death	19645	14	Liver-related death	41566
1	Undiagnosed VI	334772	8	Undiagnosed VI	303836	15	Undiagnosed VI	260286
1	Diagnosed CHC	10823	8	Diagnosed CHC	16665	15	Diagnosed CHC	18051
1	Cirrhosis	39066	8	Cirrhosis	34701	15	Cirrhosis	29442
1	Decomp. cirrhosis	6139	8	Decomp. cirrhosis	8798	15	Decomp. cirrhosis	7805
1	HCC	2351	8	HCC	2950	15	HCC	2528
1	SVR	863	8	SVR	9253	15	SVR	18038
1	Liver-related death	1772	8	Liver-related death	22894	15	Liver-related death	44446
2	Undiagnosed VI	331029	9	Undiagnosed VI	298432	16	Undiagnosed VI	252748
2	Diagnosed CHC	12078	9	Diagnosed CHC	17064	16	Diagnosed CHC	18021
2	Cirrhosis	38445	9	Cirrhosis	34029	16	Cirrhosis	28548
2	Decomp. cirrhosis	7095	9	Decomp. cirrhosis	8752	16	Decomp. cirrhosis	7572
2	HCC	2697	9	HCC	2911	16	HCC	2445
2	SVR	1847	9	SVR	10589	16	SVR	19068
2	Liver-related death	4212	9	Liver-related death	26126	16	Liver-related death	47241
3	Undiagnosed VI	327082	10	Undiagnosed VI	292798	17	Undiagnosed VI	244881
3	Diagnosed CHC	13167	10	Diagnosed CHC	17387	17	Diagnosed CHC	17947
3	Cirrhosis	37834	10	Cirrhosis	33338	17	Cirrhosis	27615
3	Decomp. cirrhosis	7769	10	Decomp. cirrhosis	8663	17	Decomp. cirrhosis	7325
3	HCC	2867	10	HCC	2863	17	HCC	2358
3	SVR	2932	10	SVR	11919	17	SVR	20007
3	Liver-related death	7018	10	Liver-related death	29324	17	Liver-related death	49944
4	Undiagnosed VI	322922	11	Undiagnosed VI	286966	18	Undiagnosed VI	236689
4	Diagnosed CHC	14107	11	Diagnosed CHC	17643	18	Diagnosed CHC	17832
4	Cirrhosis	37226	11	Cirrhosis	32629	18	Cirrhosis	26643
4	Decomp. cirrhosis	8230	11	Decomp. cirrhosis	8543	18	Decomp. cirrhosis	7065
4	HCC	2951	11	HCC	2808	18	HCC	2267
4	SVR	4099	11	SVR	13233	18	SVR	20846
4	Liver-related death	10038	11	Liver-related death	32476	18	Liver-related death	52551
5	Undiagnosed VI	318534	12	Undiagnosed VI	280808	19	Undiagnosed VI	227555
5	Diagnosed CHC	14914	12	Diagnosed CHC	17833	19	Diagnosed CHC	17631
5	Cirrhosis	36614	12	Cirrhosis	31888	19	Cirrhosis	25562
5	Decomp. cirrhosis	8530	12	Decomp. cirrhosis	8392	19	Decomp. cirrhosis	6773
5	HCC	2987	12	HCC	2747	19	HCC	2163
5	SVR	5330	12	SVR	14514	19	SVR	21519
5	Liver-related death	13184	12	Liver-related death	35573	19	Liver-related death	55055
6	Undiagnosed VI	313896	13	Undiagnosed VI	274323	20	Undiagnosed VI	218157
6	Diagnosed CHC	15602	13	Diagnosed CHC	17962	20	Diagnosed CHC	17401
6	Cirrhosis	35992	13	Cirrhosis	31112	20	Cirrhosis	24448
6	Decomp. cirrhosis	8706	13	Decomp. cirrhosis	8217	20	Decomp. cirrhosis	6471
6	HCC	2993	13	HCC	2679	20	HCC	2058
6	SVR	6610	13	SVR	15750	20	SVR	22067
6	Liver-related death	16399	13	Liver-related death	38606	20	Liver-related death	57445

CHC = chronic hepatitis C; HCC = hepatocellular carcinoma; SVR = sustained virologic response; VI = viremic infections

Table A.3.2.10: Number of cases per disease state — SOC (treatment scale-up)

Cycle	Disease state	Cases	Cycle	Disease state	Cases	Cycle	Disease state	Cases
0	Undiagnosed VI	338300	7	Undiagnosed VI	308996	14	Undiagnosed VI	267477
0	Diagnosed CHC	9380	7	Diagnosed CHC	16182	14	Diagnosed CHC	18032
0	Cirrhosis	39700	7	Cirrhosis	35431	14	Cirrhosis	30570
0	Decomp. cirrhosis	4810	7	Decomp. cirrhosis	8794	14	Decomp. cirrhosis	8060
0	HCC	1610	7	HCC	2982	14	HCC	2622
0	SVR	0	7	SVR	4839	14	SVR	10341
0	Liver-related death	0	7	Liver-related death	19648	14	Liver-related death	41623
1	Undiagnosed VI	334772	8	Undiagnosed VI	303836	15	Undiagnosed VI	260286
1	Diagnosed CHC	10823	8	Diagnosed CHC	16665	15	Diagnosed CHC	18051
1	Cirrhosis	39066	8	Cirrhosis	34800	15	Cirrhosis	29746
1	Decomp. cirrhosis	6139	8	Decomp. cirrhosis	8807	15	Decomp. cirrhosis	7851
1	HCC	2351	8	HCC	2954	15	HCC	2546
1	SVR	527	8	SVR	5652	15	SVR	11019
1	Liver-related death	1772	8	Liver-related death	22900	15	Liver-related death	44519
2	Undiagnosed VI	331029	9	Undiagnosed VI	298432	16	Undiagnosed VI	252748
2	Diagnosed CHC	12078	9	Diagnosed CHC	17064	16	Diagnosed CHC	18021
2	Cirrhosis	38449	9	Cirrhosis	34153	16	Cirrhosis	28882
2	Decomp. cirrhosis	7095	9	Decomp. cirrhosis	8765	16	Decomp. cirrhosis	7626
2	HCC	2697	9	HCC	2916	16	HCC	2465
2	SVR	1128	9	SVR	6468	16	SVR	11648
2	Liver-related death	4212	9	Liver-related death	26136	16	Liver-related death	47332
3	Undiagnosed VI	327082	10	Undiagnosed VI	292798	17	Undiagnosed VI	244881
3	Diagnosed CHC	13167	10	Diagnosed CHC	17387	17	Diagnosed CHC	17947
3	Cirrhosis	37845	10	Cirrhosis	33490	17	Cirrhosis	27977
3	Decomp. cirrhosis	7769	10	Decomp. cirrhosis	8681	17	Decomp. cirrhosis	7385
3	HCC	2867	10	HCC	2870	17	HCC	2380
3	SVR	1791	10	SVR	7281	17	SVR	12221
3	Liver-related death	7018	10	Liver-related death	29339	17	Liver-related death	50056
4	Undiagnosed VI	322922	11	Undiagnosed VI	286966	18	Undiagnosed VI	236689
4	Diagnosed CHC	14107	11	Diagnosed CHC	17643	18	Diagnosed CHC	17832
4	Cirrhosis	37248	11	Cirrhosis	32811	18	Cirrhosis	27032
4	Decomp. cirrhosis	8231	11	Decomp. cirrhosis	8565	18	Decomp. cirrhosis	7131
4	HCC	2951	11	HCC	2818	18	HCC	2292
4	SVR	2504	11	SVR	8083	18	SVR	12734
4	Liver-related death	10038	11	Liver-related death	32499	18	Liver-related death	52687
5	Undiagnosed VI	318534	12	Undiagnosed VI	280808	19	Undiagnosed VI	227555
5	Diagnosed CHC	14914	12	Diagnosed CHC	17833	19	Diagnosed CHC	17631
5	Cirrhosis	36650	12	Cirrhosis	32100	19	Cirrhosis	25975
5	Decomp. cirrhosis	8532	12	Decomp. cirrhosis	8420	19	Decomp. cirrhosis	6845
5	HCC	2988	12	HCC	2758	19	HCC	2189
5	SVR	3256	12	SVR	8866	19	SVR	13145
5	Liver-related death	13184	12	Liver-related death	35605	19	Liver-related death	55216
6	Undiagnosed VI	313896	13	Undiagnosed VI	274323	20	Undiagnosed VI	218157
6	Diagnosed CHC	15602	13	Diagnosed CHC	17962	20	Diagnosed CHC	17401
6	Cirrhosis	36046	13	Cirrhosis	31355	20	Cirrhosis	24882
6	Decomp. cirrhosis	8710	13	Decomp. cirrhosis	8251	20	Decomp. cirrhosis	6548
6	HCC	2995	13	HCC	2693	20	HCC	2086
6	SVR	4038	13	SVR	9621	20	SVR	13480
6	Liver-related death	16400	13	Liver-related death	38649	20	Liver-related death	57633

CHC = chronic hepatitis C; HCC = hepatocellular carcinoma; SVR = sustained virologic response; VI = viremic infections

Table A.3.2.11: Model output: total number of cases of advance liver-disease and liver-related deaths per cycle – SOF-based (treatment scale-up)

	Decompensated cirrhosis			HCC			Liver-related death		
Cycle		Cases	Calculate new cases		Cases	Calculate new cases		Cases	Calculate new cases
0	Start cycle in decomp. cirrhosis state	4810		Start cycle in HCC state	1610			0	0
0	No disease progression	3629		No disease progression	616				
1	Total cases of decomp. cirrhosis in cycle	6139	2509	Total cases of HCC in cycle	2351	1735	Total cases of liver-related death	1772	1772
1	No disease progression	4628		No disease progression	897				
2	Total cases of decomp. cirrhosis in cycle	7095	2467	Total cases of HCC in cycle	2697	1800	Total cases of liver-related death	4212	2440
2	No disease progression	5343		No disease progression	1027				
3	Total cases of decomp. cirrhosis in cycle	7769	2426	Total cases of HCC in cycle	2867	1840	Total cases of liver-related death	7018	2807
3	No disease progression	5846		No disease progression	1089				
4	Total cases of decomp. cirrhosis in cycle	8230	2385	Total cases of HCC in cycle	2951	1862	Total cases of liver-related death	10038	3020
4	No disease progression	6186		No disease progression	1118				
5	Total cases of decomp. cirrhosis in cycle	8530	2344	Total cases of HCC in cycle	2987	1869	Total cases of liver-related death	13184	3145
5	No disease progression	6404		No disease progression	1128				
6	Total cases of decomp. cirrhosis in cycle	8706	2303	Total cases of HCC in cycle	2993	1865	Total cases of liver-related death	16399	3215
6	No disease progression	6528		No disease progression	1126				
7	Total cases of decomp. cirrhosis in cycle	8788	2261	Total cases of HCC in cycle	2979	1853	Total cases of liver-related death	19645	3246
7	No disease progression	6580		No disease progression	1117				
8	Total cases of decomp. cirrhosis in cycle	8798	2218	Total cases of HCC in cycle	2950	1833	Total cases of liver-related death	22894	3249
8	No disease progression	6578		No disease progression	1103				
9	Total cases of decomp. cirrhosis in cycle	8752	2174	Total cases of HCC in cycle	2911	1808	Total cases of liver-related death	26126	3232
9	No disease progression	6535		No disease progression	1084				
10	Total cases of decomp. cirrhosis in cycle	8663	2128	Total cases of HCC in cycle	2863	1779	Total cases of liver-related death	29324	3198
10	No disease progression	6460		No disease progression	1062				
11	Total cases of decomp. cirrhosis in cycle	8543	2082	Total cases of HCC in cycle	2808	1746	Total cases of liver-related death	32476	3152
11	No disease progression	6358		No disease progression	1037				
12	Total cases of decomp. cirrhosis in cycle	8392	2034	Total cases of HCC in cycle	2747	1710	Total cases of liver-related death	35573	3097
12	No disease progression	6233		No disease progression	1009				

	Decompensated cirrhosis			HCC			Liver-related death		
13	Total cases of decomp. cirrhosis in cycle	8217	1984	Total cases of HCC in cycle	2679	1671	Total cases of liver-related death	38606	3032
13	No disease progression	6089		No disease progression	978				
14	Total cases of decomp. cirrhosis in cycle	8020	1931	Total cases of HCC in cycle	2606	1628	Total cases of liver-related death	41566	2960
14	No disease progression	5929		No disease progression	945				
15	Total cases of decomp. cirrhosis in cycle	7805	1876	Total cases of HCC in cycle	2528	1583	Total cases of liver-related death	44446	2880
15	No disease progression	5754		No disease progression	910				
16	Total cases of decomp. cirrhosis in cycle	7572	1818	Total cases of HCC in cycle	2445	1535	Total cases of liver-related death	47241	2795
16	No disease progression	5567		No disease progression	874				
17	Total cases of decomp. cirrhosis in cycle	7325	1758	Total cases of HCC in cycle	2358	1484	Total cases of liver-related death	49944	2703
17	No disease progression	5369		No disease progression	836				
18	Total cases of decomp. cirrhosis in cycle	7065	1696	Total cases of HCC in cycle	2267	1432	Total cases of liver-related death	52551	2607
18	No disease progression	5147		No disease progression	790				
19	Total cases of decomp. cirrhosis in cycle	6773	1626	Total cases of HCC in cycle	2163	1373	Total cases of liver-related death	55055	2504
19	No disease progression	4917		No disease progression	747				
20	Total cases of decomp. cirrhosis in cycle	6471	1554	Total cases of HCC in cycle	2058	1312	Total cases of liver-related death	57445	2390
20	No disease progression	4679		No disease progression	703				

Table A.3.2.12: Model output: total number of cases of advance liver-disease and liver-related deaths per cycle – SOC (treatment scale-up)

Cycle	Decompensated cirrhosis		HCC				Liver-related death		
		Cases	Calculate new cases		Cases	Calculate new cases		Cases	Calculate new cases
0	Start cycle in decomp. cirrhosis state	4810		Start cycle in HCC state	1610			0	
0	No disease progression	3629		No disease progression	616				
1	Total cases of decomp. cirrhosis in cycle	6139	2509	Total cases of HCC in cycle	2351	1735	Total cases of liver-related death	1772	1772
1	No disease progression	4628		No disease progression	897				
2	Total cases of decomp. cirrhosis in cycle	7095	2467	Total cases of HCC in cycle	2697	1800	Total cases of liver-related death	4212	2440
2	No disease progression	5343		No disease progression	1027				
3	Total cases of decomp. cirrhosis in cycle	7769	2426	Total cases of HCC in cycle	2867	1840	Total cases of liver-related death	7018	2807
3	No disease progression	5846		No disease progression	1089				
4	Total cases of decomp. cirrhosis in cycle	8231	2385	Total cases of HCC in cycle	2951	1862	Total cases of liver-related death	10038	3020
4	No disease progression	6187		No disease progression	1118				
5	Total cases of decomp. cirrhosis in cycle	8532	2345	Total cases of HCC in cycle	2988	1870	Total cases of liver-related death	13184	3146
5	No disease progression	6405		No disease progression	1128				
6	Total cases of decomp. cirrhosis in cycle	8710	2305	Total cases of HCC in cycle	2995	1867	Total cases of liver-related death	16400	3216
6	No disease progression	6530		No disease progression	1127				
7	Total cases of decomp. cirrhosis in cycle	8794	2264	Total cases of HCC in cycle	2982	1855	Total cases of liver-related death	19648	3248
7	No disease progression	6585		No disease progression	1118				
8	Total cases of decomp. cirrhosis in cycle	8807	2222	Total cases of HCC in cycle	2954	1836	Total cases of liver-related death	22900	3252
8	No disease progression	6585		No disease progression	1104				
9	Total cases of decomp. cirrhosis in cycle	8765	2180	Total cases of HCC in cycle	2916	1812	Total cases of liver-related death	26136	3236
9	No disease progression	6545		No disease progression	1086				
10	Total cases of decomp. cirrhosis in cycle	8681	2136	Total cases of HCC in cycle	2870	1784	Total cases of liver-related death	29339	3204
10	No disease progression	6473		No disease progression	1065				
11	Total cases of decomp. cirrhosis in cycle	8565	2092	Total cases of HCC in cycle	2818	1753	Total cases of liver-related death	32499	3160
11	No disease progression	6375		No disease progression	1040				
12	Total cases of decomp. cirrhosis in cycle	8420	2046	Total cases of HCC in cycle	2758	1718	Total cases of liver-related death	35605	3106
12	No disease progression	6254		No disease progression	1013				

	Decompensated cirrhosis			HCC			Liver-related death		
13	Total cases of decomp. cirrhosis in cycle	8251	1997	Total cases of HCC in cycle	2693	1680	Total cases of liver-related death	38649	3044
13	No disease progression	6114		No disease progression	983				
14	Total cases of decomp. cirrhosis in cycle	8060	1946	Total cases of HCC in cycle	2622	1639	Total cases of liver-related death	41623	2974
14	No disease progression	5958		No disease progression	950				
15	Total cases of decomp. cirrhosis in cycle	7851	1893	Total cases of HCC in cycle	2546	1595	Total cases of liver-related death	44519	2896
15	No disease progression	5789		No disease progression	916				
16	Total cases of decomp. cirrhosis in cycle	7626	1837	Total cases of HCC in cycle	2465	1549	Total cases of liver-related death	47332	2813
16	No disease progression	5606		No disease progression	881				
17	Total cases of decomp. cirrhosis in cycle	7385	1779	Total cases of HCC in cycle	2380	1500	Total cases of liver-related death	50056	2724
17	No disease progression	5413		No disease progression	844				
18	Total cases of decomp. cirrhosis in cycle	7131	1718	Total cases of HCC in cycle	2292	1448	Total cases of liver-related death	52687	2630
18	No disease progression	5195		No disease progression	799				
19	Total cases of decomp. cirrhosis in cycle	6845	1650	Total cases of HCC in cycle	2189	1390	Total cases of liver-related death	55216	2529
19	No disease progression	4969		No disease progression	756				
20	Total cases of decomp. cirrhosis in cycle	6548	1579	Total cases of HCC in cycle	2086	1331	Total cases of liver-related death	57633	2417
20	No disease progression	4734		No disease progression	712				

A.3.3 Manuscript 2 analyses and calculations

Table A.3.1: Estimated number of cases of HCV infection in South Africa

	Current estimated cases	Estimated number of cases in 2035	
		SOC	SOF-based regimens
Undiagnosed viremic infections		218157	218157
Diagnosed CHC (Treatment naive)		37857	37853
Compensated cirrhosis		25558	25527
Decompensated cirrhosis	4 810	6667	6661
Hepatocellular carcinoma	1 610	2129	2127
Total viremic infections	393 800	290368	290325
Total diagnosed cases	55 500	72211	72168
SOC = standard of care; SOF = sofosbuvir			

Table A.3.2: HCV treatment cascade with current treatment protocol

	Current	% of TVI	SOC 2035	% of TVI	SOF-based 2035	% of TVI
Total viremic infections (TVI)	393800	1	290368	100	290325	100
Diagnosed and aware	55500	14	72211	24.869	72168	24.858
Prescribed HCV treatment	100	0.025	127	0.044	124	0.043
Achieved sustained virologic response (SVR)	56	0.014	72	0.025	114	0.039
SOC = standard of care; SOF = sofosbuvir						

Table A.3.3: HCV treatment cascade with proposed treatment scale-up

	Current	% of TVI	SOC 2035	% of TVI	SOF-based 2035	% of TVI
Total viremic infections (TVI)	393800	1	269075	100	268536	100
Diagnosed and aware	55500	14	50918	18.92	50379	18.76
Prescribed HCV treatment	100	0.025	1740	0.647	1740	0.647
Achieved sustained virologic response	56	0.014	978	0.363	1601	0.596
SOC = standard of care; SOF = sofosbuvir						

Table A.3.4: Incidence of new cases of advanced liver-disease and liver-related deaths

Year	Treat 0.18% of diagnosed patients per year with sofosbuvir-based regimens			Treat 10% new patients per year with sofosbuvir-based regimens		
	Decompensated cirrhosis	Hepatocellular carcinoma	Liver-related death	Decompensated cirrhosis	Hepatocellular carcinoma	Liver-related death
2015/2016	2509	1735	1772	2509	1735	1772
2016/2017	2467	1800	2440	2467	1800	2440
2017/2018	2426	1840	2807	2426	1840	2807
2018/2019	2386	1863	3020	2385	1862	3020
2019/2020	2347	1871	3146	2344	1869	3145
2020/2021	2308	1869	3217	2303	1865	3215
2021/2022	2269	1858	3250	2261	1853	3246
2022/2023	2229	1840	3256	2218	1833	3249
2023/2024	2188	1818	3241	2174	1808	3232
2024/2025	2147	1792	3211	2128	1779	3198
2025/2026	2105	1762	3170	2082	1746	3152
2026/2027	2062	1729	3119	2034	1710	3097
2027/2028	2016	1693	3060	1984	1671	3032
2028/2029	1968	1654	2993	1931	1628	2960
2029/2030	1917	1613	2919	1876	1583	2880
2030/2031	1864	1568	2839	1818	1535	2795
2031/2032	1809	1521	2754	1758	1484	2703
2032/2033	1750	1472	2664	1696	1432	2607
2033/2034	1685	1416	2566	1626	1373	2504
2034/2035	1617	1358	2457	1554	1312	2390
	42070	**34071**	**57901**	**41574**	**33717**	**57445**

Model outputs and calculations for manuscript 3 are as represented in the manuscript and associated tables.

ANNEXURE B: AUTHOR GUIDELINES

ANNEXURE B.1 Author guidelines: PharmacoEconomics

Available at:
http://www.springer.com/adis/journal/40273?print_view=true&detailsPage=pltci_2295304 Date of access: 1 Nov. 2015

For authors and editors

2014 Impact Factor: 2.450

Types of papers

Please note: The word counts given below do not include the abstract, references, figure legends or table captions.

Review Article: Word count up to 6000. Provides an authoritative, balanced, comprehensive, fully referenced and critical review of the literature.

Current Opinion: Word count 1500 to 3000. Places an area in perspective given that it is of current international interest and a consensus has not yet been reached; therefore, the arguments presented may be controversial, but at the same time must be balanced and rational.

Leading Article: Word count up to 3000. Provides a short, balanced overview of the current state of development of an emerging area.

Practical Application: Word count up to 3000. Reviews and explores the practicalities of implementing/using particular economic methodologies to address healthcare decision problems. The paper should either focus on one particular method and review its advantages and disadvantages, or focus more on a particular decision problem and review the various methods that might help inform the problem.

Systematic Review: Word count up to 10,000. Collates all empirical evidence that fits pre-specified eligibility criteria to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing reliable findings from which conclusions can be drawn and decisions made. Please follow the reporting guidelines of PRISMA.

Original Research: This can be submitted as either a full length report, entitled an Original Research Article (word count up to 4000 plus any Electronic Supplementary Material) or a short report describing preliminary research, entitled a Short Communication (word count up to 2000).

Letter to the Editor: Word count up to 1000. Comment on an article published recently in the journal; a response to the comments would normally be sought from the authors of the original article and published in the same issue, where possible.

Editorial/Commentary: Word count up to 1500. A brief opinion piece on a current topic of high interest.

Editorial procedure

Internal Review by Editorial Staff: The journal editor will perform an initial appraisal of each manuscript. If your paper has been peer reviewed by another journal as part of a prior submission, the journal editor will also assess any previous editorial/referee comments and how these have been dealt with as part of the appraisal process. If your manuscript is considered unsuitable for the journal to which it has been submitted, it may be assessed for suitability for publication in other Adis journals by appropriate editors. However, it will not be progressed to external peer review for an alternative journal without your permission.

External Peer Review: Peer reviewer identities are kept confidential, but author identities are known to the reviewers. Peer reviewers are asked to disclose potential conflicts of interests that may affect their ability to provide an unbiased review of an article. The majority of manuscripts will require some degree of revision following peer review before they can be accepted for publication. The final decision on acceptability for publication lies with the journal editor.

Copy Editing: All accepted manuscripts are copy edited. This process addresses general publishing considerations, such as layout of tables and figures, house-style and clarity of expression. Authors will receive proofs following editing for their approval and sign off. It should be noted that the responsibility for checking the technical accuracy and consistency of data within the article rests with the authors.

Manuscript Submission

Submission of a manuscript implies: that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out. The publisher will not be held legally responsible should there be any claims for compensation.

Permissions

Authors wishing to include figures, tables, or text passages that have already been published elsewhere are required to obtain permission from the copyright owner(s) for both the print and online format and to include evidence that such permission has been granted when submitting their papers. Any material received without such evidence will be assumed to originate from the authors.

Online Submission

Please follow the hyperlink “Submit online” on the right and upload all of your manuscript files following the instructions given on the screen.

Title Page

The title page should include: The name(s) of the author(s), a concise and informative title, the affiliation(s) and address (es) of the author(s), the e-mail address, telephone and fax numbers of the corresponding author.

Abstract

Please provide an abstract of 150 to 250 words. The abstract should not contain any undefined abbreviations or unspecified references.

Text Formatting

Manuscripts should be submitted in Word. Use a normal, plain font (e.g., 10-point Times Roman) for text. Use italics for emphasis. Use the automatic page numbering function to number the pages. Do not use field functions. Use tab stops or other commands for indents, not the space bar. Use the table function, not spreadsheets, to make tables. Use the equation editor or MathType for equations. Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Headings

Please use the decimal system of headings with no more than three levels.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables. Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols. Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

References

Citation: Reference citations in the text should be identified by numbers in square brackets. For example: This result was later contradicted by Becker and Seligman [5]. This effect has been widely studied [1-3, 7].

Reference list

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text. Do not use footnotes or endnotes as a substitute for a reference list. The entries in the list should be numbered consecutively.

Journal article: Smith JJ. The world of science. Am J Sci. 1999;36:234–5.

Article by DOI: Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. J Mol Med. 2000; doi:10.1007/s001090000086

Book: Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

Book chapter: Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. International review of cytology. London: Academic; 1980. pp. 251–306.

Online document: Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

Always use the standard abbreviation of a journal's name according to the ISSN List of Title Word Abbreviations, see ISSN.org LTWA. If you are unsure, please use the full journal title. For authors using EndNote, Springer provides an output style that supports the formatting of in-text citations and reference list. EndNote style (zip, 3 kB)

Tables

All tables are to be numbered using Arabic numerals. Tables should always be cited in text in consecutive numerical order. For each table, please supply a table caption (title) explaining the components of the table. Identify any previously published material by giving the original source in the form of a reference at the end of the table caption. Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

Artwork

For the best quality final product, it is highly recommended that you submit all of your artwork – photographs, line drawings, etc. – in an electronic format. Your art will then be produced to the highest standards with the greatest accuracy to detail. The published work will directly reflect the quality of the artwork provided.

Electronic Figure Submission

Supply all figures electronically. Indicate what graphics program was used to create the artwork. For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MS Office files are also acceptable. Vector graphics containing fonts must have the fonts embedded in the files. Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

Line Art: Definition: Black and white graphic with no shading. Do not use faint lines and/or lettering and check that all lines and lettering within the figures are legible at final size. All lines should be at least 0.1 mm (0.3 pt) wide. Scanned line drawings and line drawings in bitmap format should have a minimum resolution of 1200 dpi. Vector graphics containing fonts must have the fonts embedded in the files.

Halftone Art: Definition: Photographs, drawings, or paintings with fine shading, etc. If any magnification is used in the photographs, indicate this by using scale bars within the figures themselves. Halftones should have a minimum resolution of 300 dpi.

Combination Art: Definition: a combination of halftone and line art, e.g., halftones containing line drawing, extensive lettering, color diagrams, etc. Combination artwork should have a minimum resolution of 600 dpi.

Color Art: Color art is free of charge for print and online publication. Color illustrations should be submitted as RGB.

Figure Lettering

To add lettering, it is best to use Helvetica or Arial (sans serif fonts). Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt). Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label. Avoid effects such as shading, outline letters, etc. Do not include titles or captions within your illustrations.

Figure Numbering

All figures are to be numbered using Arabic numerals. Figures should always be cited in text in consecutive numerical order. Figure parts should be denoted by lowercase letters (a, b, c, etc.). If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures, "A1, A2, A3, etc." Figures in online appendices (Electronic Supplementary Material) should, however, be numbered separately.

Figure Captions

Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file. Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type. No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption. Identify all elements found in the figure in the figure caption; and use boxes, circles, etc., as coordinate points in graphs. Identify previously published material by giving the original source in the form of a reference citation at the end of the figure caption.

Figure Placement and Size

When preparing your figures, size figures to fit in the column width. For most journals the figures should be 39 mm, 84 mm, 129 mm, or 174 mm wide and not higher than 234 mm. For books and book-sized journals, the figures should be 80 mm or 122 mm wide and not higher than 198 mm.

Permissions

If you include figures that have already been published elsewhere, you must obtain permission from the copyright owner(s) for both the print and online format. Please be aware that some publishers do not grant electronic rights for free and that Springer will not be able to refund any costs that may have occurred to receive these permissions. In such cases, material from other sources should be used.

Accessibility

In order to give people of all abilities and disabilities access to the content of your figures, please make sure that all figures have descriptive captions (blind users could then use a text-to-speech software or a text-to-Braille hardware). Patterns are used instead of or in addition to colors for conveying information (color-blind users would then be able to distinguish the visual elements). Any figure lettering has a contrast ratio of at least 4.5:1

Electronic supplementary material

Springer accepts electronic multimedia files (animations, movies, audio, etc.) and other supplementary files to be published online along with an article or a book chapter. This feature can add dimension to the author's article, as certain information cannot be printed or is more convenient in electronic form.

Submission

Supply all supplementary material in standard file formats. Please include in each file the following information: article title, journal name, author names; affiliation and e-mail address of the corresponding author. To accommodate user downloads, please keep in mind that larger-sized files may require very long download times and that some users may experience other problems during downloading.

Audio, Video, and Animations

Resolution: 16:9 or 4:3. Maximum file size: 25 GB. Minimum video duration: 1 sec. Supported file formats: avi, wmv, mp4, mov, m2p, mp2, mpg, mpeg, flv, mxf, mts, m4v, 3gp

Text and Presentations

Submit your material in PDF format; .doc or .ppt files are not suitable for long-term viability. A collection of figures may also be combined in a PDF file.

Spreadsheets

Spreadsheets should be converted to PDF if no interaction with the data is intended. If the readers should be encouraged to make their own calculations, spreadsheets should be submitted as .xls files (MS Excel).

Specialized Formats

Specialized format such as .pdb (chemical), .wrl (VRML), .nb (Mathematica notebook), and .tex can also be supplied.

Collecting Multiple Files

It is possible to collect multiple files in a .zip or .gz file.

Numbering

If supplying any supplementary material, the text must make specific mention of the material as a citation, similar to that of figures and tables. Refer to the supplementary files as “Online Resource”, e.g., "... as shown in the animation (Online Resource 3)", “... additional data are given in Online Resource 4”. Name the files consecutively, e.g. “ESM_3.mpg”, “ESM_4.pdf”.

Captions

For each supplementary material, please supply a concise caption describing the content of the file.

Processing of supplementary files

Electronic supplementary material will be published as received from the author without any conversion, editing, or reformatting.

Accessibility

In order to give people of all abilities and disabilities access to the content of your supplementary files, please make sure that the manuscript contains a descriptive caption for each supplementary material. Video files do not contain anything that flashes more than three times per second (so that users prone to seizures caused by such effects are not put at risk)

Scientific style

Please always use internationally accepted signs and symbols for units (SI units). Nomenclature: Insofar as possible, authors should use systematic names similar to those used by Chemical Abstract Service or IUPAC. Genus and species names should be in italics. Generic names of drugs and pesticides are preferred; if trade names are used, the generic name should be given at first mention. Please use the standard mathematical notation for formulae, symbols, etc.: Italic for single letters that denote mathematical constants, variables, and unknown quantities. Roman/upright for numerals, operators, and punctuation, and commonly defined functions or abbreviations, e.g., cos, det, e or exp, lim, log, max, min, sin, tan, d (for derivative). Bold for vectors, tensors, and matrices.

Ethical responsibilities of authors

This journal is committed to upholding the integrity of the scientific record. As a member of the Committee on Publication Ethics (COPE) the journal will follow the COPE guidelines on how to deal with potential acts of misconduct. Authors should refrain from misrepresenting research results which could damage the trust in the journal, the professionalism of scientific authorship, and ultimately the entire scientific endeavour. Maintaining integrity of the research and its presentation can be achieved by following the rules of good scientific practice, which include:

The manuscript has not been submitted to more than one journal for simultaneous consideration; the manuscript has not been published previously (partly or in full), unless the new work concerns an expansion of previous work (please provide transparency on the re-use of material to avoid the hint of text-recycling (“self-plagiarism”)); a single study is not split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time (e.g. “salami-publishing”); no data have been fabricated or manipulated (including images) to support your conclusions; no data, text, or theories by others are presented as if they were the author’s own (“plagiarism”). Proper acknowledgements to other works must be given (this includes material that is closely copied (near verbatim), summarized and/or paraphrased), quotation marks are used for verbatim copying of material, and permissions are secured for material that is copyrighted.

Important note: the journal may use software to screen for plagiarism. Consent to submit has been received explicitly from all co-authors, as well as from the responsible authorities - tacitly or explicitly - at the institute/organization where the work has been carried out, before the work is submitted. Authors whose names appear on the submission have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results. In addition: Changes of authorship or in the order of authors are not accepted after acceptance of a manuscript.

Requesting to add or delete authors at revision stage, proof stage, or after publication is a serious matter and may be considered when justifiably warranted. Justification for changes in authorship must be compelling and may be considered only after receipt of written approval from all authors and a convincing, detailed explanation about the role/deletion of the new/deleted author. In case of changes at revision stage, a letter must accompany the revised manuscript. In case of changes after acceptance or publication, the request and documentation must be sent via the Publisher to the Editor-in-Chief. In all cases, further documentation may be required to support your request. The decision on accepting the change rests with the Editor-in-Chief of the journal and may be turned down. Therefore authors are strongly advised to ensure the correct author group, corresponding author, and order of authors at submission. Upon request authors should be prepared to send relevant documentation or data in order to verify the validity of the results. This could be in the form of raw data, samples, records, etc.

If there is a suspicion of misconduct, the journal will carry out an investigation following the COPE guidelines. If, after investigation, the allegation seems to raise valid concerns, the accused author will be contacted and given an opportunity to address the issue. If misconduct has been established beyond reasonable doubt, this may result in the Editor-in-Chief's implementation of the following measures, including, but not limited to:

If the article is still under consideration, it may be rejected and returned to the author. If the article has already been published online, depending on the nature and severity of the infraction, either an erratum will be placed with the article or in severe cases complete retraction of the article will occur. The reason must be given in the published erratum or retraction note. The author's institution may be informed.

Compliance with ethical standards

To ensure objectivity and transparency in research and to ensure that accepted principles of ethical and professional conduct have been followed, authors should include information regarding sources of funding, potential conflicts of interest (financial or non-financial), informed consent if the research involved human participants, and a statement on welfare of animals if

the research involved animals. Authors should include the following statements (if applicable) in a separate section entitled “Compliance with Ethical Standards” when submitting a paper: Disclosure of potential conflicts of interest; Research involving Human Participants and/or Animals; Informed consent.

Please note that standards could vary slightly per journal dependent on their peer review policies (i.e. single or double blind peer review) as well as per journal subject discipline. Before submitting your article check the instructions following this section carefully. The corresponding author should be prepared to collect documentation of compliance with ethical standards and send if requested during peer review or after publication. The Editors reserve the right to reject manuscripts that do not comply with the above-mentioned guidelines. The author will be held responsible for false statements or failure to fulfill the above-mentioned guidelines.

Disclosure of potential conflicts of interest

Authors must disclose all relationships or interests that could influence or bias the work. Although an author may not feel there are conflicts, disclosure of relationships and interests affords a more transparent process, leading to an accurate and objective assessment of the work. Awareness of real or perceived conflicts of interests is a perspective to which the readers are entitled and is not meant to imply that a financial relationship with an organization that sponsored the research or compensation for consultancy work is inappropriate. Examples of potential conflicts of interests that are directly or indirectly related to the research may include but are not limited to the following: Research grants from funding agencies (please give the research funder and the grant number); Honoraria for speaking at symposia; Financial support for attending symposia; Financial support for educational programs; Employment or consultation; Support from a project sponsor; Position on advisory board or board of directors or other type of management relationships; Multiple affiliations; Financial relationships, for example equity ownership or investment interest; Intellectual property rights (e.g. patents, copyrights and royalties from such rights) and Holdings of spouse and/or children that may have financial interest in the work.

In addition, interests that go beyond financial interests and compensation (non-financial interests) that may be important to readers should be disclosed. These may include but are not limited to personal relationships or competing interests directly or indirectly tied to this research, or professional interests or personal beliefs that may influence your research. The corresponding author collects the conflict of interest disclosure forms from all authors. (Please note that each author should complete a disclosure form.) Please make sure to submit all Conflict of Interest disclosure forms together with the manuscript. Examples of disclosures:

Funding: This study was funded by X (grant number X). Conflict of Interest: Author A has received research grants from Company A. Author B has received a speaker honorarium from Company X and owns stock in Company Y. Author C is a member of committee Z. If no conflict exists, the authors should state: Conflict of Interest: Author A, Author B, and Author C declare that they have no conflict of interest.

Language

Manuscripts that are accepted for publication will be checked by our copyeditors for spelling and formal style. This may not be sufficient if English is not your native language and substantial editing would be required. In that case, you may want to ask a native speaker to help you or arrange for your manuscript to be checked by a professional language editor prior to submission. A clear and concise language will help editors and reviewers concentrate on the scientific content of your paper and thus smooth the peer review process.

ANNEXURE. B.2 Author guidelines: Public Health

Available at:
http://www.elsevier.com/wps/find/journaldescription.cws_home/645727?generatepdf=true

Impact factor

2014: 1.434 © Thomson Reuters Journal Citation Reports 2015

Guide for authors

INTRODUCTION

Aims

Public Health is an international, multidisciplinary peer-reviewed journal. It publishes original papers, reviews and short communications on all aspects of the science, philosophy and practice of public health.

It is aimed at all public health practitioners and researchers and those who manage and deliver public health services and systems. It will also be of interest to anyone involved in provision of public health programmes, the care of populations or communities and those who contribute to public health systems in any way.

Scope

Public Health considers submissions on any aspect of public health across age groups and settings.

These include:

• Public health practice and impact

• Applied epidemiology

• Need or impact assessments

• Health service effectiveness, management and re-design

• Health protection including control of communicable diseases

• Health promotion and disease prevention

• Evaluation of public health programmes or interventions

• Public health governance, audit and quality

• Public health law and ethics

• Public health policy and comparisons

• Capacity in public health systems and workforce

This is not an exhaustive list and the Editors will consider articles on any issue relating to the health of populations or the public.

Reviews and Supplements

Public Health publishes invited articles, reviews and supplements from leading experts on topical issues. Organizations or individuals who wish to present proposals for supplements should contact the Editors at public.health@rsph.org.uk for a copy of the specific guidance on the publication of supplements.

Impact on Practice

Papers describing original research impacting on public health practice are particularly encouraged. Those describing a particular event (e.g. an outbreak of infectious disease) should be submitted as soon as possible. Fast track publication of suitable articles is possible; please contact the Editorial Office regarding this.

Papers are invited from anywhere in the world, and so authors are asked to ensure that sufficient context is provided for all readers to appreciate their contribution.

Types of paper

The types of papers that may be considered for inclusion are:

1) Original research, including evaluations of public health interventions or programmes, and public health practice original work on audit, workforce or resource development;

2) Short communications and;

3) Review papers, which include meta-analysis and systematic review.

We also consider the following papers:

1) Book reviews (normally by invitation);

2) Letters;

3) Celebrating Public Health Lives: biographical articles about named individuals, living or deceased, who have made a special contribution to public health.

We welcome student papers and encourage students to publish their work, e.g. originating from practice-based research, which will be subject to constructive peer review process.

On submission, authors should indicate in which category their contribution is to be considered. If authors are uncertain of the category to which their paper is best suited, they should make this clear in their covering letter to the Editors.

Submission process

Papers submitted to Public Health are carefully reviewed in the first instance by one of the Editors. Papers that do not meet editorial needs; are methodically flawed; or lack originality will be rejected. We will also reject papers that fail to provide sufficient ethical approval where required (see section 9.3) and we shall refer papers back for revision prior to any review if they do not comply with Journal style.

Papers which pass the Editorial review will be sent out to peer-review and will be reviewed by at least two external reviewers (short communications will only be sent to one reviewer). Reviewers are asked to consider whether the paper: contains new research findings or information; is relevant to public health practice, is technically sound; and is suitably presented.

1. How to submit your manuscript

All manuscripts should be submitted online at http://ees.elsevier.com/puhe/ by clicking on the 'submit paper' link. Authors will first need to register their details, and can then submit their paper. Any author unable to submit online should contact the Editorial Office at public.health@rsph.org.uk

2. Correspondence

The official language of Public Health is British English. Support may be made available to overseas authors whose first language is not English. Any correspondence (including books for review) should be sent to the Editorial Office as follows:

The Editors
Public Health Editorial Office
The Royal Society for Public Health
John Snow House
59 Mansell Street
London
E1 8AN
Tel: +44 (0)20 3177 1632
Fax: +44 (0)20 3177 1601
E-mail: public.health@rsph.org.uk

BEFORE YOU BEGIN

Ethics in publishing

For information on Ethics in publishing and Ethical guidelines for journal publication see http://www.elsevier.com/publishingethics and http://www.elsevier.com/journal-authors/ethics.

Human and animal rights

Public Health is a member of the Committee on Publication Ethics (COPE), for more information please visit http://publicationethics.org

Papers describing research including human subjects will not be considered if ethical approval has not been sought. Work on human beings that is submitted to Public Health should comply with the principles laid down in the Declaration of Helsinki; Recommendations guiding physicians in biomedical research involving human subjects. Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983, and the 41st World Medical Assembly, Hong Kong, September 1989.

The manuscript should contain a statement that the work has been approved by the appropriate ethical committees related to the institution(s) in which it was performed and that subjects gave informed consent to the work. Studies involving experiments with animals must state that their care was in accordance with institution guidelines. Studies on patients or volunteers require ethics committee approval and informed consent which should be documented in your paper. Patients have a right to privacy. Therefore identifying information, including patients images, names, initials, or hospital numbers, should not be included in videos, recordings, written descriptions, photographs, and pedigrees unless the information is essential for scientific

purposes and you have obtained written informed consent for publication in print and electronic form from the patient (or parent, guardian or next of kin where applicable). If such consent is made subject to any conditions, Elsevier must be made aware of all such conditions. Written consents must be provided to Elsevier on request. Even where consent has been given, identifying details should be omitted if they are not essential. If identifying characteristics are altered to protect anonymity, such as in genetic pedigrees, authors should provide assurance that alterations do not distort scientific meaning and editors should so note. If such consent has not been obtained, personal details of patients included in any part of the paper and in any supplementary materials (including all illustrations and videos) must be removed before submission.

Conflict of interest

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. See also http://www.elsevier.com/conflictsofinterest. Further information and an example of a Conflict of Interest form can be found at:
http://service.elsevier.com/app/answers/detail/a_id/286/supporthub/publishing.

Upon submission authors will be required to declare funding, competing interests and to indicate whether ethical approval was sought. This information must also be inserted into the manuscript under the 'Acknowledgements' section with the headings below. If there are no declarations to make, the following statements should be inserted into the manuscript:

Funding: None
Competing interests: None declared
Ethical approval: Not required (please add a brief explanation as to why ethical approval was not needed for this study).

Submission declaration and verification

Submission of an article implies that the work described has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis or as an electronic preprint, see http://www.elsevier.com/sharingpolicy), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. To verify originality, your article

may be checked by the originality detection service CrossCheck:
http://www.elsevier.com/editors/plagdetect.

Contributors

Each author is required to declare his or her individual contribution to the article: all authors must have materially participated in the research and/or article preparation, so roles for all authors should be described. The statement that all authors have approved the final article should be true and included in the disclosure.

Authorship

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Changes to authorship

This policy concerns the addition, deletion, or rearrangement of author names in the authorship of accepted manuscripts: Before the accepted manuscript is published in an online issue: Requests to add or remove an author, or to rearrange the author names, must be sent to the Journal Manager from the corresponding author of the accepted manuscript and must include: (a) the reason the name should be added or removed, or the author names rearranged and (b) written confirmation (e-mail, fax, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed. Requests that are not sent by the corresponding author will be forwarded by the Journal Manager to the corresponding author, who must follow the procedure as described above. Note that: (1) Journal Managers will inform the Journal Editors of any such requests and (2) publication of the accepted manuscript in an online issue is suspended until authorship has been agreed.

After the accepted manuscript is published in an online issue: Any requests to add, delete, or rearrange author names in an article published in an online issue will follow the same policies as noted above and result in a corrigendum.

Reporting clinical trials

Randomized controlled trials should be presented according to the CONSORT guidelines. At manuscript submission, authors must provide the CONSORT checklist accompanied by a flow

diagram that illustrates the progress of patients through the trial, including recruitment, enrollment, randomization, withdrawal and completion, and a detailed description of the randomization procedure. The CONSORT checklist and template flow diagram can be found on http://www.consort-statement.org.

Registration of clinical trials

Registration in a public trials registry is a condition for publication of clinical trials in this journal in accordance with International Committee of Medical Journal Editors (ICMJE, http://www.icmje.org) recommendations. Trials must register at or before the onset of patient enrolment. The clinical trial registration number should be included at the end of the abstract of the article. A clinical trial is defined as any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects of health outcomes. Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example drugs, surgical procedures, devices, behavioural treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration.

Copyright

Upon acceptance of an article, authors will be asked to complete a 'Journal Publishing Agreement' (for more information on this and copyright, see http://www.elsevier.com/copyright). An e-mail will be sent to the corresponding author confirming receipt of the manuscript together with a 'Journal Publishing Agreement' form or a link to the online version of this agreement.

Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. Permission of the Publisher is required for resale or distribution outside the institution and for all other derivative works, including compilations and translations (please consult http://www.elsevier.com/permissions). If excerpts from other copyrighted works are included, the author(s) must obtain written permission from the copyright owners and credit the source(s) in the article. Elsevier has preprinted forms for use by authors in these cases: please consult http://www.elsevier.com/permissions.

For open access articles: Upon acceptance of an article, authors will be asked to complete an 'Exclusive License Agreement' (for more information see http://www.elsevier.com/OAauthoragreement).

Role of the funding source

You are requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor(s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. If the funding source(s) had no such involvement then this should be stated.

Funding body agreements and policies

Elsevier has established a number of agreements with funding bodies which allow authors to comply with their funder's open access policies. Some authors may also be reimbursed for associated publication fees. To learn more about existing agreements please visit http://www.elsevier.com/fundingbodies.

After acceptance, open access papers will be published under a noncommercial license. For authors requiring a commercial CC BY license, you can apply after your manuscript is accepted for publication.

Open access

This journal offers authors a choice in publishing their research:

Open access

• Articles are freely available to both subscribers and the wider public with permitted reuse

• An open access publication fee is payable by authors or on their behalf e.g. by their research funder or institution

Subscription

• Articles are made available to subscribers as well as developing countries and patient groups through our universal access programs (http://www.elsevier.com/access).

• No open access publication fee payable by authors.

Regardless of how you choose to publish your article, the journal will apply the same peer review criteria and acceptance standards.

For open access articles, permitted third party (re)use is defined by the following Creative Commons user licenses: Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND). For non-commercial purposes, lets others distribute and copy the article, and to include in a collective work (such as an anthology), as long as they credit the author(s) and provided they do not alter or modify the article.

The open access publication fee for this journal is USD 2500, excluding taxes. Learn more about Elsevier's pricing policy: http://www.elsevier.com/openaccesspricing.

Green open access

Authors can share their research in a variety of different ways and Elsevier has a number of green open access options available. We recommend authors see our green open access page for further information (http://elsevier.com/greenopenaccess). Authors can also self-archive their manuscripts immediately and enable public access from their institution's repository after an embargo period. This is the version that has been accepted for publication and which typically includes author-incorporated changes suggested during submission, peer review and in editor-author communications. Embargo period: For subscription articles, an appropriate amount of time is needed for journals to deliver value to subscribing customers before an article becomes freely available to the public. This is the embargo period and begins from the publication date of the issue your article appears in. This journal has an embargo period of 12 months.

Language (usage and editing services)

Please write your text in good English (American or British usage is accepted, but not a mixture of these). Authors who feel their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English may wish to use the English Language Editing service available from Elsevier's WebShop (http://webshop.elsevier.com/languageediting/) or visit our customer support site (http://support.elsevier.com) for more information.

Submission

Our online submission system guides you stepwise through the process of entering your article details and uploading your files. The system converts your article files to a single PDF file used

in the peer-review process. Editable files (e.g., Word, LaTeX) are required to typeset your article for final publication. All correspondence, including notification of the Editor's decision and requests for revision, is sent by e-mail.

PREPARATION

Use of word processing software

It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns.

The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier: http://www.elsevier.com/guidepublication). Note that source files of figures, tables and text graphics will be required whether or not you embed your figures in the text. See also the section on Electronic artwork. To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Article structure

4.2 Original research, including evaluation papers

Papers should be clear, precise and logical and should not normally exceed 3,000 words. Original research papers should be set out as follows:

• Covering letter-the letter must contain: why the submission is appropriate for publication in Public Health; what is known about the topic discussed; what your study adds; and confirmation that the paper has not been published elsewhere

• Title page- bearing title, all authors' initials, surname, main degrees (two only) and the name and location of the institution(s) where the work was done. The author to whom proofs and correspondence should be sent should be clearly indicated with correct address, e-mail, telephone and fax details.

• Abstract. This should be structured under the following headings:

Objectives
Study design
Methods
Results
Conclusions

• Keywords. 3-6 keywords should follow the abstract

• Introduction

• Methods

• Results

• Discussion

• Acknowledgements including declarations: Statements of ethical approval, funding and competing interests (see section 9)

• References (see section 10)

Please note that any costs for reproducing material whose copyright is not held by the authors or the RSPH is to be met by the authors.

Tables and figures

Tables and figures should be kept to a minimum. Tables must be comprehensible without reference to the text if possible. References can be cited in the tables if needed. Authors should indicate at approximately what point in the text the table should appear. Figures, graphs, drawings etc. should not be over complex and must be intelligible when reduced in size for printing. They should be on separate sheets, numbered and with legends.

Tables

Number tables consecutively in accordance with their appearance in the text. Place footnotes to tables below the table body and indicate them with superscript lowercase letters. Avoid vertical rules. Be sparing in the use of tables and ensure that the data presented in tables do not duplicate results described elsewhere in the article.

4.3 Short communications

A short communication is preferred for the submission of important preliminary observations or data that does not warrant publication as a full paper. Short communications should be approximately 500-1500 words in length and provide adequate information to allow for the same peer review given to other submissions.

• An abstract will be requested during the online submission process in order to facilitate peer-review, but should not be included within the manuscript.

• Keywords are not required. Specific sections, such as Methods, should not be used.

• A short communication can include one table or figure and up to 10 references. Preliminary data published as a short communication will not preclude subsequent publication of more complete results if the work is significantly expanded.

4.4 Review papers

Systematic Review papers presenting exhaustive, critical assessments of the published literature on relevant public health topics or questions will be considered. Such reviews should be prepared in strict compliance with MOOSE or PRISMA guidelines or with Cochrane's complementary guidelines for systematic reviews of health promotion and public health interventions, as appropriate. Public Health encourages authors to use alternative databases covering scientific literature from low- and middle-income countries not indexed in the traditional international databases (i.e. Medline, Web of Science).

All systematic reviews need to be submitted with a supporting statement of which guideline has been used in the preparation of the review. Narrative Review papers will be considered by Public Health. Whilst no formal guidelines for such reviews exist, authors should be very clear in what criteria they have used for the selection of studies and describe the methods used to undertake the review in the body of the paper. Generally speaking, narrative reviews will only be considered where the author(s) are clearly experts in the research field under consideration or the public health issue under consideration is not amenable to systematic review. The reviews needs to be submitted with a supporting statement justifying the appropriateness of undertaking a narrative review.

Review papers should not exceed 3000 words. They should include a Structured Abstract: Tables/Illustrations can be included up to a maximum of 5, though larger tables may be included only on the electronic version of the paper. References: up to a maximum of 100.

4.5 Letters

Readers are encouraged to submit Letters to the Editors and these can include responses to previously published papers or original data. Authors will be given the opportunity to comment and respond to any correspondence we intend to include in the `Letters to the Editors' regarding their previously published manuscript.

4.6 Celebrating Public Health Lives

Papers should be clear, precise and logical and should not normally exceed 1,500 words in length. An abstract is not required and specific sections, such as methods, discussion etc, should not be used. Keywords are not required.

Essential title page information

• Title. Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.

• Author names and affiliations. Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lowercase superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.

• Corresponding author. Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.

• Present/permanent address. If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Highlights

Highlights are mandatory for this journal. They consist of a short collection of bullet points that convey the core findings of the article and should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

Acknowledgements

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

Artwork

Electronic artwork

- Make sure you use uniform lettering and sizing of your original artwork.
- Embed the used fonts if the application provides that option.
- Aim to use the following fonts in your illustrations: Arial, Courier, Times New Roman, Symbol, or use fonts that look similar.
- Number the illustrations according to their sequence in the text.
- Use a logical naming convention for your artwork files.
- Provide captions to illustrations separately.
- Size the illustrations close to the desired dimensions of the published version.
- Submit each illustration as a separate file.

A detailed guide on electronic artwork is available on our website: http://www.elsevier.com/artworkinstructions. You are urged to visit this site; some excerpts from the detailed information are given here.

Formats

If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply 'as is' in the native document format. Regardless of the application used other than Microsoft Office, when your electronic artwork is finalized, please 'Save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

EPS (or PDF): Vector drawings, embed all used fonts.
TIFF (or JPEG): Color or grayscale photographs (halftones), keep to a minimum of 300 dpi.

TIFF (or JPEG): Bitmapped (pure black & white pixels) line drawings, keep to a minimum of 1000 dpi.
TIFF (or JPEG): Combinations bitmapped line/half-tone (color or grayscale), keep to a minimum of 500 dpi.

Please do not:

- Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); these typically have a
- low number of pixels and limited set of colors;
- Supply files that are too low in resolution;
- Submit graphics that are disproportionately large for the content.

Color artwork

Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF), or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color online (e.g., ScienceDirect and other sites) regardless of whether or not these illustrations are reproduced in color in the printed version. For color reproduction in print, you will receive information regarding the costs from Elsevier after receipt of your accepted article. Please indicate your preference for color: in print or online only. For further information on the preparation of electronic artwork, please see http://www.elsevier.com/artworkinstructions.

References

Citation in text

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

Reference management software

Most Elsevier journals have a standard template available in key reference management packages. This covers packages using the Citation Style Language, such as Mendeley (http://www.mendeley.com/features/reference-manager) and also others like EndNote (http://www.endnote.com/support/enstyles.asp) and Reference Manager (http://refman.com/downloads/styles). Using plug-ins to word processing packages which are available from the above sites, authors only need to select the appropriate journal template when preparing their article and the list of references and citations to these will be formatted according to the journal style as described in this Guide. The process of including templates in these packages is constantly ongoing. If the journal you are looking for does not have a template available yet, please see the list of sample references and citations provided in this Guide to help you format these according to the journal style.

If you manage your research with Mendeley Desktop, you can easily install the reference style for this journal by clicking the link below: http://open.mendeley.com/use-citation-style/public-health. When preparing your manuscript, you will then be able to select this style using the Mendeley plugins for Microsoft Word or LibreOffice. For more information about the Citation Style Language, visit http://citationstyles.org.

Reference style

Text: Indicate references by superscript numbers in the text. The actual authors can be referred to, but the reference number(s) must always be given. List: Number the references in the list in the order in which they appear in the text.

Examples:

Reference to a journal publication:

1. Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. J Sci Commun 2010;163:51–9.

Reference to a book:

2. Strunk Jr W, White EB. The elements of style. 4th ed. New York: Longman; 2000.

Reference to a chapter in an edited book:

3. Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, editors. Introduction to the electronic age, New York: E-Publishing Inc; 2009, p. 281–304.

Note shortened form for last page number. e.g., 51–9, and that for more than 6 authors the first 6 should be listed followed by 'et al.' For further details you are referred to 'Uniform Requirements for Manuscripts submitted to Biomedical Journals' (J Am Med Assoc 1997;277:927–34) (see also http://www.nlm.nih.gov/bsd/uniform_requirements.html).

Submission checklist

The following list will be useful during the final checking of an article prior to sending it to the journal for review. Please consult this Guide for Authors for further details of any item.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:

- E-mail address
- Full postal address

All necessary files have been uploaded, and contain:

- Keywords
- All figure captions
- All tables (including title, description, footnotes)

Further considerations

- Manuscript has been 'spell-checked' and 'grammar-checked'
- References are in the correct format for this journal
- All references mentioned in the Reference list are cited in the text, and vice versa
- Permission has been obtained for use of copyrighted material from other sources (including the Internet)

Printed version of figures (if applicable) in color or black-and-white

- Indicate clearly whether or not color or black-and-white in print is required.

For any further information please visit our customer support site at http://support.elsevier.com.

AFTER ACCEPTANCE

Use of the Digital Object Identifier

The Digital Object Identifier (DOI) may be used to cite and link to electronic documents. The DOI consists of a unique alpha-numeric character string which is assigned to a document by the publisher upon the initial electronic publication. The assigned DOI never changes. Therefore, it is an ideal medium for citing a document, particularly 'Articles in press' because they have not yet received their full bibliographic information. Example of a correctly given DOI (in URL format; here an article in the journal Physics Letters B): http://dx.doi.org/10.1016/j.physletb.2010.09.059

When you use a DOI to create links to documents on the web, the DOIs are guaranteed never to change.

Proofs

One set of page proofs (as PDF files) will be sent by e-mail to the corresponding author (if we do not have an e-mail address then paper proofs will be sent by post) or, a link will be provided in the e-mail so that authors can download the files themselves. Elsevier now provides authors with PDF proofs which can be annotated; for this you will need to download Adobe Reader version 9 (or higher) available free from http://get.adobe.com/reader. Instructions on how to annotate PDF files will accompany the proofs (also given online). The exact system requirements are given at the Adobe site: http://www.adobe.com/products/reader/tech-specs.html.

If you do not wish to use the PDF annotations function, you may list the corrections (including replies to the Query Form) and return them to Elsevier in an e-mail. Please list your corrections quoting line number. If, for any reason, this is not possible, then mark the corrections and any other comments (including replies to the Query Form) on a printout of your proof and return by fax, or scan the pages and e-mail, or by post. Please use this proof only for checking the typesetting, editing, completeness and correctness of the text, tables and figures. Significant changes to the article as accepted for publication will only be considered at this stage with permission from the Editor. We will do everything possible to get your article published quickly and accurately. It is important to ensure that all corrections are sent back to us in one communication: please check carefully before replying, as inclusion of any subsequent corrections cannot be guaranteed. Proofreading is solely your responsibility.

ANNEXURE. B.3 Author guidelines: Medical Decision Making

Available at: http://mdm.uic.edu/manuscript-requirements/ Date of access: 1 Nov. 2015

Article categories

Original research articles (3,000-5,000 words).

Reviews (3,500 words). MDM considers systematic reviews as well as informal, narrative reviews.

Tutorials (5,000 words). Authors are encouraged to consult with the ***editor-in-chief*** before submitting a tutorial. Prospective authors should provide an outline of the tutorial with an estimated word count. MDM is interested in tutorials about techniques and software for advanced mathematical, statistical, and economic modeling. Authors are encouraged to include hyperlinks to online materials that can be used in the tutorial.

Brief reports, technical notes, and letters to the editor (1,500 words). Brief reports describe preliminary or limited results of original research—ideally illustrating a new methodologic approach or a new feature of an established methodology. Technical notes describe and propose an approach to a methodologic issue that is part of a larger model or analysis.

Editorials (1,500 words). The journal regularly publishes editorials, which are considered as a result of a presubmission inquiry or invitation only.

Rounds (5,000 words). MDM has an ongoing, occasional series in the areas of clinical and policy decision making rounds. Typically, clinical rounds illustrate the application of a decision model to an individual patient. Policy rounds describe the role of an actual decision model, cost-effectiveness analysis, or other type of mathematical model in actual policy decisions, including, for example, a clinical practice guideline or a national coverage policy decision. The ideal submission of this kind would include detailed information about the problem addressed, collaboration among modelers and decision makers in framing questions, the development and results of the model, and how the model influenced (or failed to influence) a decision. Rounds manuscripts can be a single submission or a pair of manuscripts that conform to the word-count restriction noted.

Manuscript Format and Style

MDM welcomes files submitted in Microsoft Office Word (*.doc, *.docx) format. Manuscripts submitted in TeX/LaTeX format are acceptable; however, MDM requires that a PDF version of the manuscript accompany these submissions as a supplementary file.

Although objects (i.e., tables, figures) are generally embedded in a single manuscript file throughout the review process, authors of accepted manuscripts will be required to submit all components in separate, editable files for production purposes. The following graphic formats are acceptable for production: *.eps, *png, *.ppt, *.psd, *.tif, and *.xls. ScholarOne Manuscripts provides helpful information to authors concerning uploading files and images for accepted manuscripts.

Authors should write for a sophisticated general medical readership and follow principles of clear scientific writing. Aim for clear, concise, and logically organized presentations. Avoid convoluted sentences and use the active voice whenever possible. MDM largely conforms to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (December 2014) developed by the International Committee of Medical Journal Editors. Authors are encouraged to consult *Scientific Style and Format: The CSE Manual for Authors, Editors, and Publishers* (2014) throughout manuscript preparation.

In addition, for randomized trials, adherence to the most recent CONSORT statement and checklists is encouraged. Other CONSORT statements, such as STARD or STROBE, may also be useful for structuring research manuscripts. For systematic reviews, MDM's editors recommend following the reporting guidelines in chapter 5, Standards for Reporting Systematic Reviews, in the 2011 Institute of Medicine report, Finding What Works in Health Care: Standards for Systematic Reviews.

Abbreviations. With the exception of units of measure (see also below), the use of abbreviations is strongly discouraged—especially in manuscript titles. The first time an abbreviation appears in a manuscript, unless it is a unit of measure (e.g., mL), it should be preceded by the words for which it stands.

Drug names. Although MDM encourages the use of nonproprietary (generic) names for all drugs noted in a manuscript, proprietary names may be added in parentheses on first mention at author discretion.

Units of measure. All units of measure should be expressed in conventional units with Système International units provided in parentheses throughout the text. Conventional units should also be used in figures and tables with conversion factors provided in legends or footnotes.

Currency may be presented in US dollars, Canadian dollars, British pounds, or Euros. If the study was not conducted in the United States, authors may wish, for the benefit of readers, to provide the rate of exchange to US dollars at the time the study was conducted in the Methods section (e.g., May 2015: 1 Euro = 1.12 US dollars).

Numbers and statistics. Equations should be typed exactly as they are to appear in the final manuscript. Authors are encouraged review recommendations from the Annals of Internal Medicine regarding the presentation of percentages and statistical measures such as error measures, *P* values, and trends. Likewise, authors are encouraged to consult guidelines from the American Psychological Association for information on presenting statistical results.

On manuscript acceptance, authors will be required to supply all in-line and full equations within the document in an editable format. Equations submitted as figures are not acceptable for production.

Manuscript components

For the convenience of editors, reviewers, and editorial staff, MDM encourages authors to submit one file that includes the complete manuscript with components in the following sequence: title page, abstract, text, acknowledgments (if any), references, tables, figure legends, figures, and appendices (if any). ScholarOne Manuscripts automatically generates a PDF proof for use by the journal during the peer review process. (Do not use line numbering in the manuscript; line numbering is automatically applied when the PDF proof is generated.) The submitting author is required to ensure the full legibility of this PDF proof.

Title page. Provide the manuscript's tentative title. If the study is a randomized trial, systematic review, or meta-analysis, that descriptor must be added as the subtitle (e.g., Effectiveness of a decision aid for patients with asthma: a randomized trial). Provide also a running head of no more than 50 letters and spaces.

Author names are not concealed from reviewers in MDM's peer-review process. All authors' full names should appear on the title page exactly as they are to appear in print, including highest academic degree(s) earned. Affiliation information and contact information must also be provided for each author. Specify which author will serve as corresponding author for the manuscript.

Please also provide the name of the department(s) and institution(s) where the work was done; meeting(s) at which the work was presented (if any); grant or other financial support (if any). Specify also the word-count total for the manuscript text, excluding the abstract, acknowledgments, references, and figure legends.

The statement that follows should be included (1) in the cover letter and (2) as a footnote on the title page:

Financial support for this study was provided [choose one: entirely or in part] by a [choose one: grant from or contract with] [insert name(s) of the funding source(s), whether a company, government agency, philanthropic foundation, institute, etc.]. The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report. [The following sentence should be inserted, if applicable:] The following author(s) is/are employed by the sponsor: [identify employees].

During the submission process, the author is asked to identify keywords from two lists: APPLICATION AREAS and DETAILED METHODOLOGY. The editors use these author-selected keywords to match the manuscript to reviewers who have pertinent expertise. Authors are encouraged to review these keyword lists carefully—and completely—before making selections to ensure that the best possible keywords are chosen for the manuscript.

Abstract. Word for word, the abstract is probably the most important part of a manuscript. Editors use the abstract to decide whether the article is of interest for MDM. Reviewers use it to decide whether to accept an invitation to review the manuscript. Once the manuscript is published, readers use the abstract to decide whether they want to read the article.

Authors are encouraged to take extra time to write a good, clear abstract that addresses all of these "audiences." Describe why readers will find the article interesting, address the critical points of the methods and results, and list your most important conclusions, including clinical or policy implications. Think about the words and phrases that will help readers and researchers locate your published article—and use them in the abstract.

Abstracts must accompany all submissions except editorials and brief reports. Structured abstracts (275 words) are required for cost-effectiveness studies and systematic reviews, including meta-analyses. Structured abstracts are preferred, but not required, for other original research manuscripts. For brief reports, abstracts (175 words) are optional. The editor-in-chief retains the right to request a structured abstract for any manuscript. The table provided (see above) shows required (bold) and optional headings for structured abstracts based on the methodology used.

Text. For original research—including economic analyses, systematic reviews, and meta-analyses—use four main headings when arranging manuscript text: Introduction, Methods, Results, and Discussion.

Introduction. Set up the context of the research for readers concisely. Keep the Introduction section brief. Avoid repeating background or theory that can be found in textbooks or previously published articles; cite those sources instead. Always end the Introduction section with a clear statement of the study's objectives or hypotheses.

Methods. For studies involving humans, describe in the Methods section how participants were assembled and selected as well as the sites or setting from which they were recruited. Then, describe study procedures, including any interventions, measurements, and data-collection techniques. Use figures to diagram study processes, including the flow of participants through the study. Provide the number of subjects at each stage of recruitment and follow-up, including the number of subjects who declined to participate and the number of individuals who completed follow-up protocols.

For studies that have numeric data and use statistical inference, include a subsection that describes the methods used for statistical analysis, documenting also the statistical software used. For all studies, include a statement at the end of the Methods section that describes the role of the funding source for the study. If the study had no external funding source, or if the funding source had no role in the study, state so explicitly.

Results. This section should also be clear and concise—and it should report results only. (Implications, theories, opinions, and findings related to results should be confined to the Discussion section.) Fully describe the study sample so that readers can gauge how well the study's findings may apply to their patients (i.e., external validity). Then, present primary findings followed by any secondary and subgroup findings. Use tables and figures to demonstrate main characteristics of participants and major findings. Avoid redundancy among text, tables, and figures.

Discussion. Consider structuring the Discussion section as outlined below: Provide a brief synopsis of key findings with particular emphasis on how the findings add to the body of pertinent knowledge. Discuss possible mechanisms and explanations for the findings. Compare study results with relevant findings from other published work.

Discuss the limitations of the study and any methods used to minimize or compensate for those limitations.

Mention any crucial future research directions.

Summarize in a straightforward and circumspect manner the clinical implications of the work. It is common, but not required, to have a separate Conclusion heading.

Tables and figures. Excessive tabular material should be avoided; most data are better presented in text or figures. Information should never be duplicated among tables, text, and figures. Each table should be titled and appear on its own page.

Acknowledgments. MDM expects authors to acknowledge persons who have contributed to the scientific content of manuscripts or provided technical support. Authors must obtain written permission from anyone whom they wish to list in the Acknowledgments section on manuscript acceptance. The corresponding author must also affirm that he or she has listed everyone who contributed significantly to the work in the Acknowledgments section.

On manuscript acceptance, materials reprinted or adapted from other sources must be accompanied by a written statement from the author and the publisher granting permission to the publisher of MDM for reproduction. Questions regarding permissions may be directed to the SAGE Publications Permissions Department.

When authors submit a manuscript, they must disclose all financial relationships (both personal and institutional) that could be viewed as presenting a potential conflict of interest or that might otherwise bias their work. (If additional clearances are required by author institutions, these formal clearance statements must be provided by the authors in the manuscript as specified by their institutions.) To prevent ambiguity, authors must state explicitly whether potential conflicts do or do not exist. Potential conflicts include, but are not limited to, any financial relationship that involves conditions or tests or treatments discussed in the manuscript and alternatives to the tests or treatments for those conditions. Financial relationships (e.g., employment, consultancies, honoraria, stock ownership or options, paid expert testimony, grants, patents received or pending, royalties) are the most easily identifiable potential conflicts of interest—and the most likely to undermine the credibility of the journal, the authors, and the science itself.

Disclosure of these relationships is essential not only for original research manuscripts but also for review articles, letters, and editorials. MDM publishes conflict of interest disclosures. When authors are uncertain whether a potential conflict of interest exists, they should err on the side of full disclosure. All such disclosures should be listed in the Acknowledgments section, at the end of the manuscript.

ANNEXURE C: SUBMISSION AND ACCEPTANCE LETTERS

Annexure C.1: Confirmation of acceptance of Manuscript 1 (*PharmacoEconomics)*

Fwd: PECA-D-15-00172R2 - accepted but needs final editing

1 message

Johanita Burger <Johanita.Burger@nwu.ac.za> Thu, Nov 12, 2015 at 8:02 AM
To: Ilanca Roux <ilancaroux@gmail.com>

---------- Forwarded message ----------
From: PharmacoEconomics <em@editorialmanager.com>
To: "Johanita Riétte Burger" <johanita.burger@nwu.ac.za>
Cc:
Date: 11 Nov 2015 15:23:19 -0500
Subject: PECA-D-15-00172R2 - accepted but needs final editing
Dear Dr. Burger,

I am pleased to inform you that your submission "Cost-effectiveness modeling of sofosbuvir-containing regimens for chronic genotype 5 hepatitis C virus infection in South Africa" has been accepted for publication in
PharmacoEconomics

However, before your paper can be forwarded to our Production Department, you are requested to make the corrections below.

In order to submit your corrected manuscript, please access
the following web site:

http://peca.edmgr.com/

I look forward to receiving your final version of the manuscript within the next 14 days.

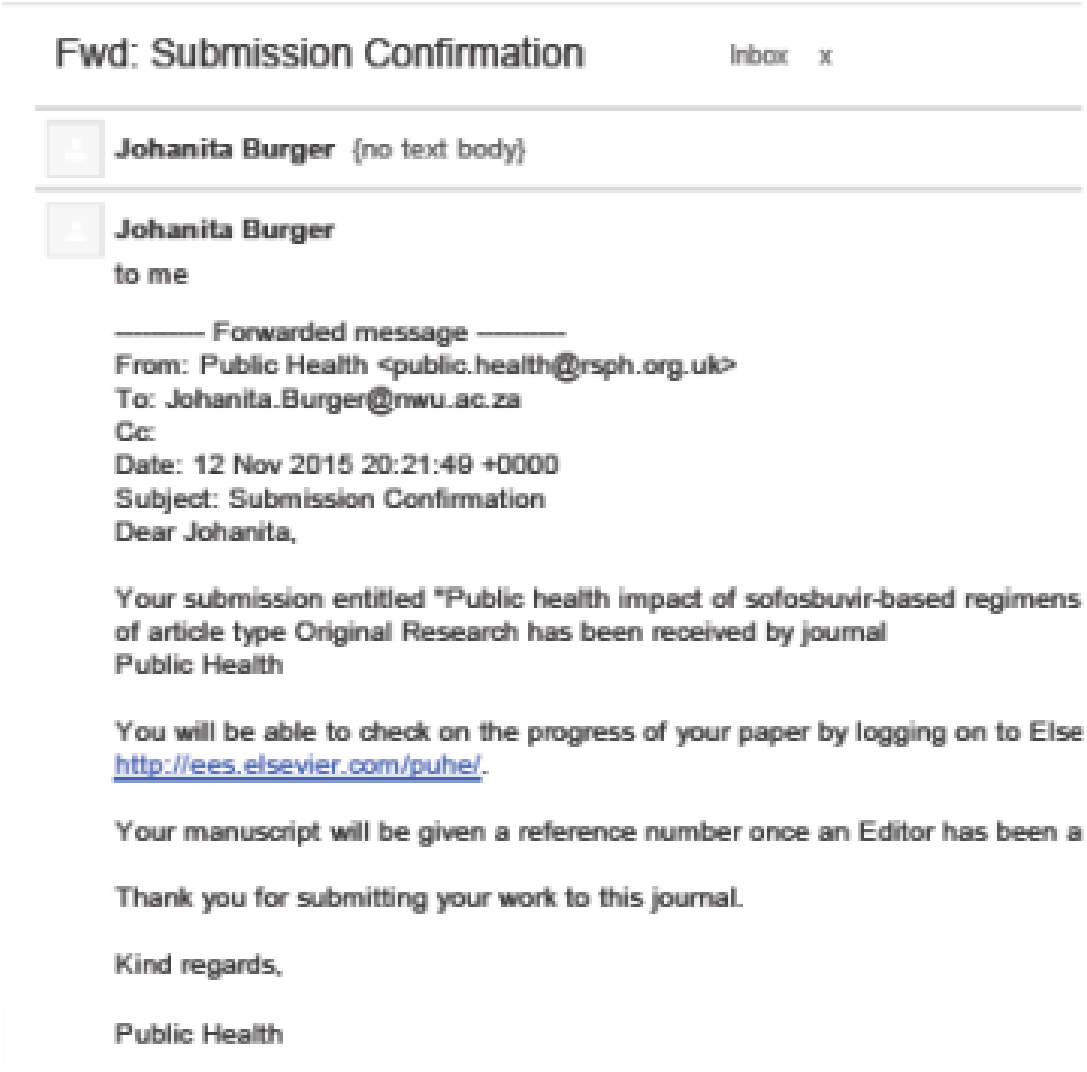
With kind regards,

Chris Carswell, MSc, MRPharmS
Editor in Chief
PharmacoEconomics

Comments from the Editor:

1. Can you define all abbreviations in fig legends
2. Can you please temper the concluding statements a little i.e. "Outcomes from this analysis suggest....."
"....may be cost effective...."

Annexure C.2: Confirmation of submission of Manuscript 2 to Public Health



Fwd: Submission Confirmation Inbox x

Johanita Burger {no text body}

Johanita Burger

to me

---------- Forwarded message ----------
From: Public Health <public.health@rsph.org.uk>
To: Johanita.Burger@nwu.ac.za
Cc:
Date: 12 Nov 2015 20:21:49 +0000
Subject: Submission Confirmation
Dear Johanita,

Your submission entitled "Public health impact of sofosbuvir-based regimens
of article type Original Research has been received by journal
Public Health

You will be able to check on the progress of your paper by logging on to Else
http://ees.elsevier.com/puhe/.

Your manuscript will be given a reference number once an Editor has been a

Thank you for submitting your work to this journal.

Kind regards,

Public Health