CLINICAL DATA ACQUISITION UTILISING MOBILE TECHNOLOGY

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ABSTRACT

Title: Clinical data acquisition utilising mobile technology

Key terms: clinical trial; mobile technology; EDC; eDiary; ePRO; MCDAS.

The pharmaceutical industry is spending more and more on Research and Development (R&D) every year. In addition, these R&D costs are increasing at a faster rate than sales. In order to resolve this dilemma a significant increase in R&D productivity is required.

One of the main contributions to these R&D costs is the acquisition of data during clinical trials. The most important objective of a clinical trial is the collection of high-quality data. No matter how well a clinical trial is conducted, if the data quality is poor, a meaningful analysis is not possible. The data acquisition method therefore plays a significant role in the overall outcome of a clinical trial.

In this study a Mobile Clinical Data Acquisition System (MCDAS) was developed for the electronic collection of high-quality Patient-Reported Outcome (PRO) data. The system consisted of a cellular phone based electronic Diary (eDiary) for capturing data, and a website for administering the collected data. The system was designed so that it could be implemented on any clinical trials, no matter what data was collected.

The MCDAS was successfully implemented on two clinical trials. The study shows that electronically capturing clinical data improves the quality of data obtained, thereby reducing the time and costs associated with clinical trials.

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NOMENCLATURE

CRF	Case Report Form
EDC	Electronic Data Capture
RDC	Remote Data Capture
RDE	Remote Data Entry
FTP	File Transfer Protocol
PDC	Paper Data Collection
PDA	Personal Digital Assistant
GPRS	General Packet Radio Service
3G	Third Generation
MCDAS	Mobile Clinical Data Acquisition System
R&D	Research and Development
ePRO	electronic Patient Reported Outcome
eDiary	electronic patient diary
IRB	Institutional Review Board
CRA	Clinical Research Associate
SAE	Serious Adverse Event
CDISC	Clinical Data Interchange Standards Consortium
ODM	Operational Data Model
XML	eXtensible Markup Language
MIDP	Mobile Information Device Profile
CLDC	Connected Limited Device Configuration
J2ME	Java 2 Platform, Micro Edition
GUI	Graphical User Interface
EDGE	Enhanced Data Rates for GSM Evolution
Wi-Fi	Wireless Fidelity
API	Application Programming Interface
eSDI	electronic Source Data Interchange
UML	Unified Modelling Language

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CHAPTER 1

INTRODUCTION

Research and Development (R&D) costs for pharmaceutical companies are increasing at a faster rate than sales. In order to reduce these costs electronic methods for clinical data capture have been introduced. This study focuses on electronically gathering Patient-Reported Outcome (PRO) data by utilising mobile devices.

1 INTRODUCTION

1.1 The need for the study

The pharmaceutical industry is one of the most successful and influential. Last year (2006) the global spending on prescription drugs rose to a staggering US $602 billion [1]. In addition, this industry commits the largest percentage of its sales revenue to R&D than any other industry [2]. The R&D costs however are increasing at a faster rate than sales, which has become a major concern for this industry.

The majority of R&D costs for pharmaceutical companies are associated with clinical research. The average expenditure for the development of drugs in 2002 was an estimated US $403 million [3]. However, only a small fraction of all interventions sent through these costly procedures are eventually approved. Furthermore, once the interventions are approved, only a small fraction would return a profit [4].

A pharmaceutical company may be required to register for a patent, lasting for 20 years, before a clinical trial begins. The average duration for an intervention to reach the market is 11 years [5]. The company is therefore required to make up for its expenditure within 9 years, before a generic version of the intervention is introduced. In addition, rising competition is forcing pharmaceutical companies to complete clinical trials faster.

It has been estimated that by 2007 $40 billion in U.S. sales will be lost as a result of a slower R&D process and patent expiry [6]. In order for the R&D costs to correspond with the anticipated sales, costs would need to decrease by up to 40% [7]. Consequently, there would need to be a significant increase in R&D productivity to ensure these cost reductions. Since clinical research is the most expensive and time consuming process of R&D, alternative methods needed to be developed to aid in streamlining this process.

One of the major contributions to clinical research costs is the acquisition of clinical data. Data is collected during all stages of a clinical trial and in large quantities. The tried-and-tested Paper Data Capture (PDC) approach is the most common means for clinical data acquisition. However, data accuracy and completeness is normally poor and the duration between data submission and acceptance is usually prolonged.

Pharmaceutical companies have been trying to improve data quality, use skilled resources effectively, and reduce the time and cost associated with clinical trials for many years. One of these attempts has been the introduction of Electronic Data Capture (EDC). EDC ensures the collection of high-quality data thereby eliminating the delays experienced when using PDC. Although more time is required to initially create an EDC system, the overall trial duration is decreased.

EDC has previously been shown to be more efficient and cost effective than PDC. In a previous study, EDC costs were on average 5.8 times less than PDC [8]. Additionally, in a different study, significant improvements in the quality of data were observed [9]. Nonetheless, EDC is still not widely adopted by pharmaceutical companies, mainly due to the fact that PDC is a well established method for data capture.

Paper patient diaries are used for collecting PRO data in order to measure the compliance of an intervention being tested. However, the compliance of a patient in completing paper diaries is often poor. In addition, trial personnel can only obtain the paper diaries during site visits. Consequently, the patients are not monitored on a continuous basis which may result in major complications for the corresponding trial sponsor [10].

An electronic Diary (eDiary) was introduced to resolve these issues by validating data on entry and electronically submitting data directly to the trial personnel. These eDiaries have successfully been implemented on several different platforms which have shown promising results [11]. The most effective implementation however was the use of a mobile device.

The most commonly used and least expensive mobile device is the cellular phone. It is estimated that there are more than 2.4 billion mobile connections [12] in the world and still growing. Consequently, implementing an eDiary on a cellular phone would eliminate the hardware costs previously experienced with Personal Digital Assistant (PDA) based eDiaries, since majority of clinical trial participants already possess cellular phones.

1.2 Current systems

As previously discussed, patient diaries are used for capture PRO data throughout a clinical trial. This information is then used to measure the compliance of the intervention being tested. Currently different methods for PRO data acquisition exist [13].

1.2.1 Paper patient diary

The PRO data is captured directly onto a paper diary by the patient. The patient returns the diary to the trial coordinator during each site visit. The coordinator then captures this data on another form and sends the original paper diary to the trial sponsor.

1.2.2 Electronic Diary (eDiary): Disconnected System

The PRO data is captured on a mobile device with no communication capabilities (e.g. some Personal Digital Assistants (PDA)). The data is stored on the device until a site visit where it is copied on to the trial coordinator's PC. This data is kept at the trial coordinator before being transmitted to the sponsor where it is stored on a central server.

1.2.3 eDiary: Semi-Connected System

The PRO data is captured and stored on a mobile device with communication capabilities. When possible, the data is transmitted to the trial sponsor and stored on a central server. Once the data has been sent it is removed from the mobile device.

1.2.4 eDiary: Connected System

The mobile application is connected to a central server throughout the duration of data capture. The PRO data is sent directly to the central server as soon as data entry is

complete. Two examples of this system are Interactive Voice Response (IVR) and Interactive Web Response (IWR) which will be discussed later.

1.2.5 Evaluation of the systems

Paper patient diaries are the most inefficient method of PRO data collection. The quality of data is usually poor and the duration from data submission to acceptance is usually prolonged. Although a disconnected eDiary improves the quality of data as well as the duration to data approval, this information can only be observed when the patient visits the trial coordinator

Semi-connected and connected eDiaries allow data to be sent directly to the trial coordinator or sponsor prior to a site visit. Connected eDiaries send data directly after data entry ensuring that data is transmitted when requested. However if a connection is not available then the data cannot be captured, unlike a semi-connected and disconnected system.

The majority of eDiaries make use of PDAs. To supply every patient in a clinical trial with a PDA can become expensive. It would therefore be beneficial to use a low-cost cellular phone for the implementation of an eDiary system.

1.3 Objective and scope of the study

The main objective of this study was to develop a Mobile Clinical Data Acquisition System (MCDAS) for gathering Patient Report Outcome (PRO) data. This system will allow PRO data to be sent from a patient's cellular phone directly to the trial coordinator or sponsor.

Scope of the study:

- Develop a standard communication system between the patient and the trial coordinator/sponsor.

a. Develop or update a cellular phone application to allow high-quality PRO data to be sent to a central web server. This application ensures the validity of the data.
b. Develop a web server that receives data from the patient and displays the results in a clear and simple format.
c. Standardise the format of the data sent from the patient's cellular phone so that this system can be integrated with other systems.

- Develop a website where the trials and the patients can be administered.
- Test the system's practicality and accuracy using actual clinical trial data.

1.4 Contributions of this study

The system developed in this study is based on previous work conducted on EDC for clinical trials. PRO data acquisition systems utilising mobile devices is the primary focus of this study.

The author of this thesis contributed to this study by completing the following tasks.

- The design and implementation of a mobile phone application for capturing, validating and transmitting PRO data. The data captured on the mobile phone is transmitted directly to the web server for validation and analysis by the trial coordinator or sponsor.

- The development of a standardised format for sending PRO data from mobile devices. The PRO data is sent in a standard format so that it can be integrated with other systems.

- The development of a system for administrating patients, clinical trials, and PRO data. Patients, clinical trials and PRO data can be added, removed, and updated using a web-based system.

1.5 Beneficiaries of the study

1.5.1 Pharmaceutical industry

As previously stated the pharmaceutical industry is facing a dilemma of R&D costs increasing at a faster rate than sales. Introducing an electronic based system for data acquisition would reduce the overall clinical research costs. The duration of a trial would also be reduced allowing more trials to be conducted in the same time frame.

1.5.2 Trial coordinator and Clinical Research Associate (CRA)

Data collection by the trial coordinator would be simplified by the introduction of an electronic based system. The data captured by the coordinator would be of high-quality thereby requiring fewer queries to be resolved by the coordinator and Clinical Research Associate (CRA). The CRA would no longer be required to visit the clinical trial site to obtain the data and could verify the data electronically.

1.5.3 Trial sponsor

The data sent by the trial coordinator or CRA would already be in an electronic format. The trial sponsor would therefore not be required to capture the data on PC. Queries could be sent directly to the CRA electronically averting the need to post paper documents.

1.5.4 Consumer

The decrease in R&D costs for the pharmaceutical companies may be reflected in the price of interventions when they enter the market. Interventions may also be introduced into the market earlier.

1.6 Outline of the study

This document consists of 5 chapters.

Chapter 2 discusses the dilemma the pharmaceutical industry is currently facing. The steps involved in data acquisition during a clinical trial are described together with how technology has been used to improve this process. A comparison is also conducted between different methods for PRO data capture.

Chapter 3 discusses the development of the MDCAS. The objectives and requirements of the system are described. The design of the system based on these requirements is also illustrated. The mobile eDiary, website and communication method are discusses in more detail.

Chapter 4 demonstrates the implementation of the MCDAS through the use of two case studies. The effectiveness of the MCDAS on these trials together with possible improvements is also discussed.

Chapter 5 is the closure of this study. This chapter describes recommendations for future work as well as the contributions made by this study.

1.7 Conclusion

In the pharmaceutical industry there is a definite need for technology in clinical trials. Collection of high-quality data is an important aspect of these trials. Electronically capturing this data, specifically through the use of mobile devices, would help to significantly reduce the cost and time associated with this process.

CHAPTER 2

IMPORTANCE OF EFFICIENT CLINICAL TRIALS

This chapter discusses the current dilemma the pharmaceutical industry is facing. The steps involved in clinical trials as well as the data collected during each step are examined. Methods of data acquisition are described for improving the efficiency of clinical trials. Different approaches for collecting patient diary information are also compared.

2 IMPORTANCE OF EFFICIENT CLINICAL TRIALS

2.1 Introduction

The pharmaceutical industry is spending more and more on Research and Development (R&D) every year. The costs for R&D are growing at a higher rate than sales which has become a major concern for this industry [14]. Improved methods for reducing the costs and duration of the R&D process have been developed. However despite previous successful results these methods have not been widely adopted.

Clinical trials account for a large portion of R&D costs. Efficient data acquisition is an important requirement for conducting clinical trials. This chapter will focus on two methods of data acquisition, namely Paper Data Capture (PDC) and Electronic Data Capture (EDC). The advantages of using EDC over conventional PDC are explained. A comparison of the costs between EDC and PDC from a previous study is also illustrated.

This chapter examines different electronic methods for capturing patient diary information. It provides a comparison between Paper diaries, Interactive Voice Response Systems (IVRS), Interactive Web Response Systems (IWRS), and mobile eDiaries. Also discussed is the Clinical Data Interchange Standards Consortium (CDISC). This consortium creates standards for the clinical data collected, exchanged and submitted electronically.

2.2 The pharmaceutical industry

A pharmaceutical company is a commercial business licensed to research, develop, and sell new interventions (drugs, medical devices, diagnostic procedures, and treatment methods). The pharmaceutical industry is one of the most thriving and influential industries. Last year (2006) the global spending on prescription drugs rose by 7% from 2005 to a staggering US $602 billion [1].

Pharmaceutical companies accumulate costs on R&D from the day the development process begins until it is eventually approved for marketing. The R&D process for pharmaceutical companies is seen as an investment with potential returns only expected after a number of years. However the R&D costs are continuously on the increase [15]. This has resulted in the introduction of new methods to try reduce the time and cost associated with this process.

Only a small fraction of all the interventions that are sent through the costly procedures of pre-clinical testing, clinical trials, and monitoring are eventually approved. The average expenditure for the development of drugs in 2002 was an estimated US $403 million (including drugs that were not approved) [3]. Combining this with the costs of bringing the drugs to the market, a total of US $804 million was estimated.

A company may be required to register for a patent before a clinical trial begins. A typical patent exists for 20 years. However the average duration of a clinical trial from the time it begins until it reaches the market is 11 years [5]. If an 11 year clinical trial is conducted then the company will be required to make up their costs within 9 years. During these 9 years the company can charge high margins on their products before competing companies enter the market. These competing companies would then introduce a generic version of the product thereby reducing the costs considerably.

It has been estimated that by 2007 $40 billion in U.S. sales will be lost as a result of a slower R&D process and patent expiry [6]. The pharmaceutical industry commits a larger percentage of its sales revenue to R&D than any other industry [2]. As pharmaceutical companies earn more money, they spend more on R&D. The majority of new interventions return less profit than the costs for R&D, while only a small fraction make a profit [4].

R&D costs are increasing every year at a faster rate than sales. In order for the R&D costs to correspond with the anticipated sales, the costs would need to decrease by up to 40% [7]. There would need to be a significant increase in R&D productivity to ensure these

reductions in cost. Since clinical research is the most expensive and time consuming process of R&D, improved methods have been established to speed up this process.

Technology has been introduced into the pharmaceutical industry mainly to reduce the costs and time associate with clinical trials. Pharmaceutical companies are required to verify the safety and efficacy of their interventions in trials before marketing can begin. After thorough research and testing, the intervention is accepted by the regulatory authorities for marketing and distribution. It is therefore necessary for pharmaceutical companies to accelerate the trial processes, so that the intervention can be introduced into the market earlier.

2.3 Clinical trials

A clinical trial is a medical research study to determine the effects of new interventions on people. Clinical trials can vary from a small group of participants to an extremely large group with a duration ranging from one visit up to several years. Whether there is a positive or negative outcome of a trial the results help to expand on existing medical knowledge. The global clinical trial industry is estimated at US $10 billion with the opportunity for substantial growth in the future [16]

The two main costs associated with a clinical trial conducted by a pharmaceutical company are:

- Patient care costs

  These costs include the patient's medical costs (doctor visits, tests, hospital fees, etc) for the duration of the trial, which are usually covered by health insurance. The patient or his/her health insurance may need to pay for the costs if considered as standard health care.

- Research costs

  These arethe costs associate with clinical trial procedures such as data collection and management, medical professional costs, analysis of the results, and research

tests. These costs are covered by a trial sponsor (e.g. pharmaceutical company, charitable organisation, government).

Prior to the start of a clinical trial a protocol must be defined. A protocol describes the purpose of the trial, how and where the trial will be conducted, the inclusion/exclusion criteria for participation in the trial, and when the participants will be evaluated. The trial sponsor writes this protocol. The sponsor reviews the protocol for safety and suitability which is then reviewed by an Institutional Review Board (IRB).

Every trial is different and therefore a distinctive clinical trial cannot be defined. A clinical trial has strict criteria (age, gender, health status, etc) to determine who can and cannot participate in the trial. Once a participant agrees to take part he or she signs an informed consent form which specifies the benefits and risks, the participant's rights, and what the researcher expects of the participant. Any known or anticipated risks are explained to the participants before the trial.

The participants are then split into two groups, namely the treatment group and the control group. The treatment group receives the treatment and the control group gets a standard treatment or a placebo (harmless substance). The participants are assigned randomly to either group. When the participants do not know which group they belong to, it is known as a masked trial. When neither the participant nor doctor knows who belongs to which group, it is known as a double masked trial. This makes sure that the trial is not biased towards the values of the participant or doctor.

Once a participant has been placed on the trial she or he receives the dates for each visit. At each of these visits the doctor or nurse takes measurements (blood samples, blood pressure, etc) and records this data in the Case Report Form (CRF). A CRF is the primary data source containing all information and results of each participant. The trial coordinator is usually responsible for the collection and verification of this data. The principal investigator, who is usually a doctor, is the researcher in charge of the study [17].

At the start of the clinical trial each participant is given a diary that needs to be completed on a daily or weekly basis. The patient diary is used to measure the compliance of an intervention by obtaining Patient Reported Outcome (PRO) data. PRO data consists of all data relating to a patient's health status that is entered directly by a patient and not interpreted by anyone else.

The participant completes the diary and returns it to the trial coordinator at each visit. The trial coordinator captures this data on another form and places it in the CRF. Figure 1 illustrates an example of a typical patient diary questionnaire that should be completed on a daily basis.

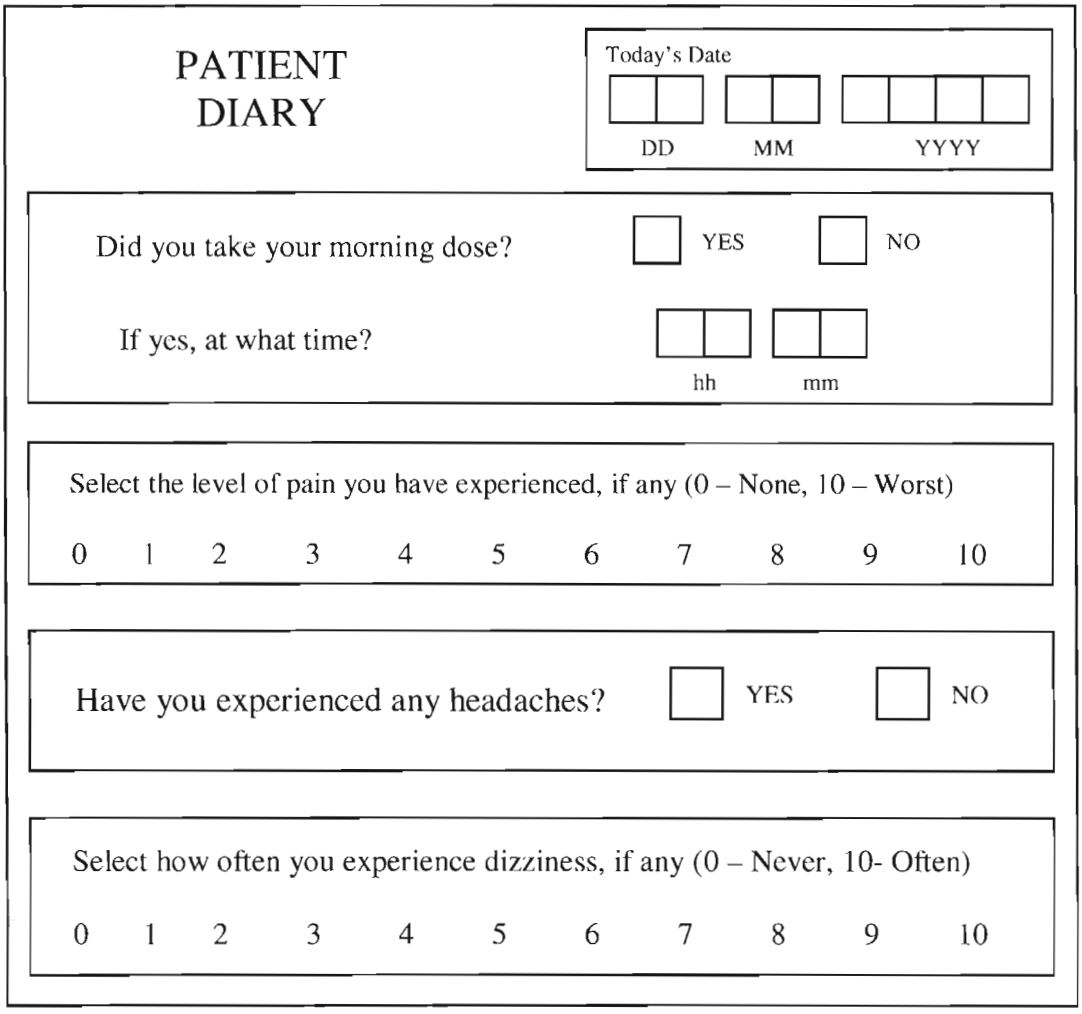


Figure 1 - Example questionnaire from patient diary

Before a pharmaceutical company can begin with human testing, extensive preclinical and laboratory research needs to be conducted (animal testing, computer simulations). Once the intervention has been accepted by the appropriate ethical bodies, human testing can begin. A clinical trial goes through four main phases of human testing (Figure 2) [18]:

- Phase I – consists of a small group of healthy volunteers (20-80) where researchers test new interventions to determine its safety, side effects and safe dosage range. These trials are mostly conducted where the patients are observed by full-time medical staff in an inpatient clinic.
- Phase II – consists of a larger group of volunteers (100-300) usually with the relevant illness. The researchers use this phase to determine the effectiveness, and further safety and side effects of the intervention.
- Phase III – researchers use this phase to compare the new intervention to standard interventions. This phase is conducted on an even larger group of volunteers (1000-3000). Once this phase is completed the information gathered is sent to various regulatory authorities for approval.
- Phase IV – once the intervention has been approved, studies of long term side effects on a larger patient population are conducted. If any adverse effects are detected, the intervention may be restricted or even withdrawn. Also optimal use, benefits and risks are determined for the intervention.

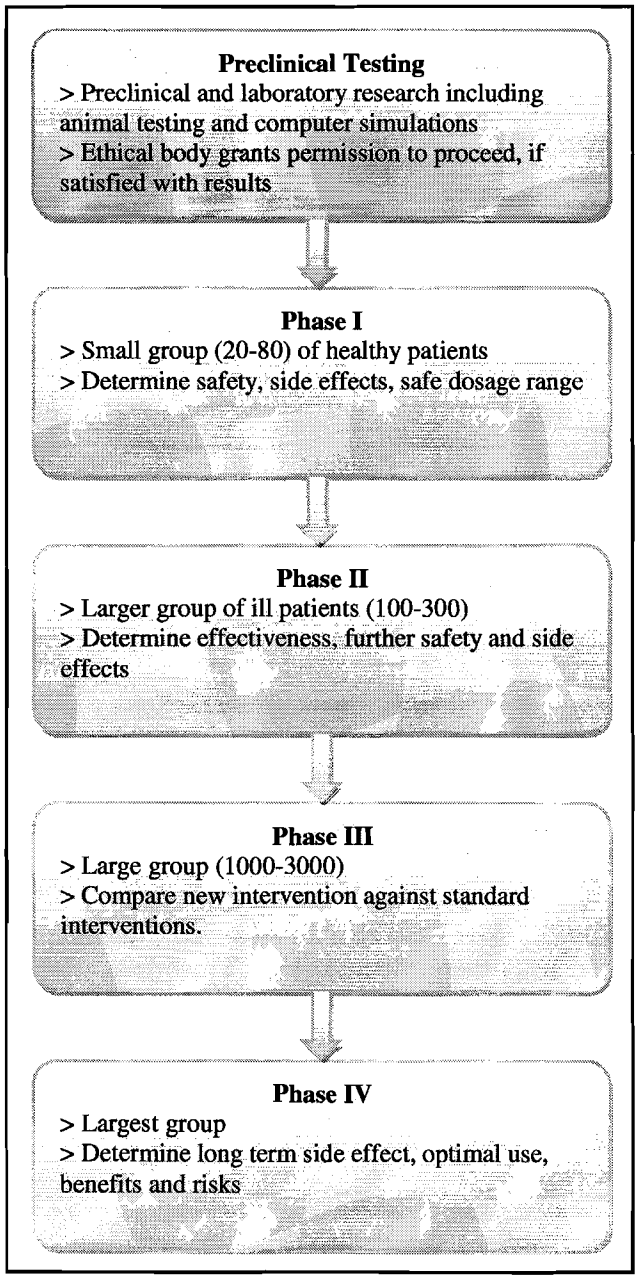


Figure 2 - Clinical trial phases

The procedures performed in a clinical trial are dependent on what type of trial is being conducted. The five different types of clinical trials are described in Table 1 [18].

Screening	These trials are used to test for improved ways to detect diseases or other health conditions.
Diagnostic	These trials are performed to find out better methods for detecting diseases.
Prevention	These trials are carried out to determine alternative/improved methods for preventing illnesses from occurring or reoccurring.
Treatment	These trials are conducted to test experimental treatments or a combination of experimental treatments.
Supportive care	These trials are used to determine treatments for improving the quality of life of chronic patients.

Table 1 - Types of clinical trials

The participants work in conjunction with a research team for all types of trials. The research team consists of physicians, trial coordinators, a principal investigator and other healthcare professionals. The trial coordinator is the person responsible for data collection and other administrative tasks such as designing forms, generating reports, and following up on patients.

A Serious Adverse Event (SAE) is any undesirable event that may result in death, substantial risk of death, hospitalisation, disability, or even birth defects. These events should be reported to the trial sponsor immediately who in turn reports these events to the appropriate regulatory organization [19].

The CRA usually reviews the data collected by the trial coordinator every 6-8 weeks. This committee views the data for validity and completeness. If the data is incorrect or incomplete the information has to be recollected by the trial coordinator. The committee can then recommend whether the trial should be stopped, continued, or even extended [20].

2.4 Efficient clinical data acquisition

A clinical trial is the most expensive and significant process of R&D. The majority of the work performed during a clinical trial is the collection of data. By introducing improved methods of data acquisition, the cost and duration of a trial can be reduced significantly. Technology has been used in clinical trials for electronic capture and submission of data (EDC). EDC ensures the collection of high-quality data, thereby reducing the time and costs associated with clinical trials.

During phase I to IV of a clinical trial, patient data is collected to help monitor the effects of an intervention. The most important objective of a clinical trial is the collection of high-quality data. No matter how well a clinical trial is conducted, if the correct data is not collected, then a meaningful analysis will not be possible. The collection of low-quality data would make the trial futile and the costs to improve the quality of such data would be tremendous.

There are several ways of collecting data during a trial, starting from the most commonly used PDC to advanced EDC systems. These systems are discusses below.

2.4.1 Conventional PDC

Figure 3 illustrates the process involved in gathering clinical data using the conventional paper-based approach. The process consists of the following steps:

- The trial coordinator completes paper Case Report Forms (CRFs) by obtaining patients' information through patient diaries and medical tests;
- The CRA visits the trial coordinator and verifies the CRF data;
- If data queries exist, the coordinator resolves the queries or forwards the queries to the relevant patient.
- If there are no queries the CRA delivers the CRFs to the trial sponsor;
- The trial sponsor then examines the data for queries;

- If any queries exist that cannot be handled by the sponsor, the CRA returns the queries to the trial coordinator. These queries are usually generated 8-10 weeks after the CRFs are received;
- When no queries exist, the sponsor finalises and captures the data on computer.
- This procedure is continued until the data is accepted by the sponsor.

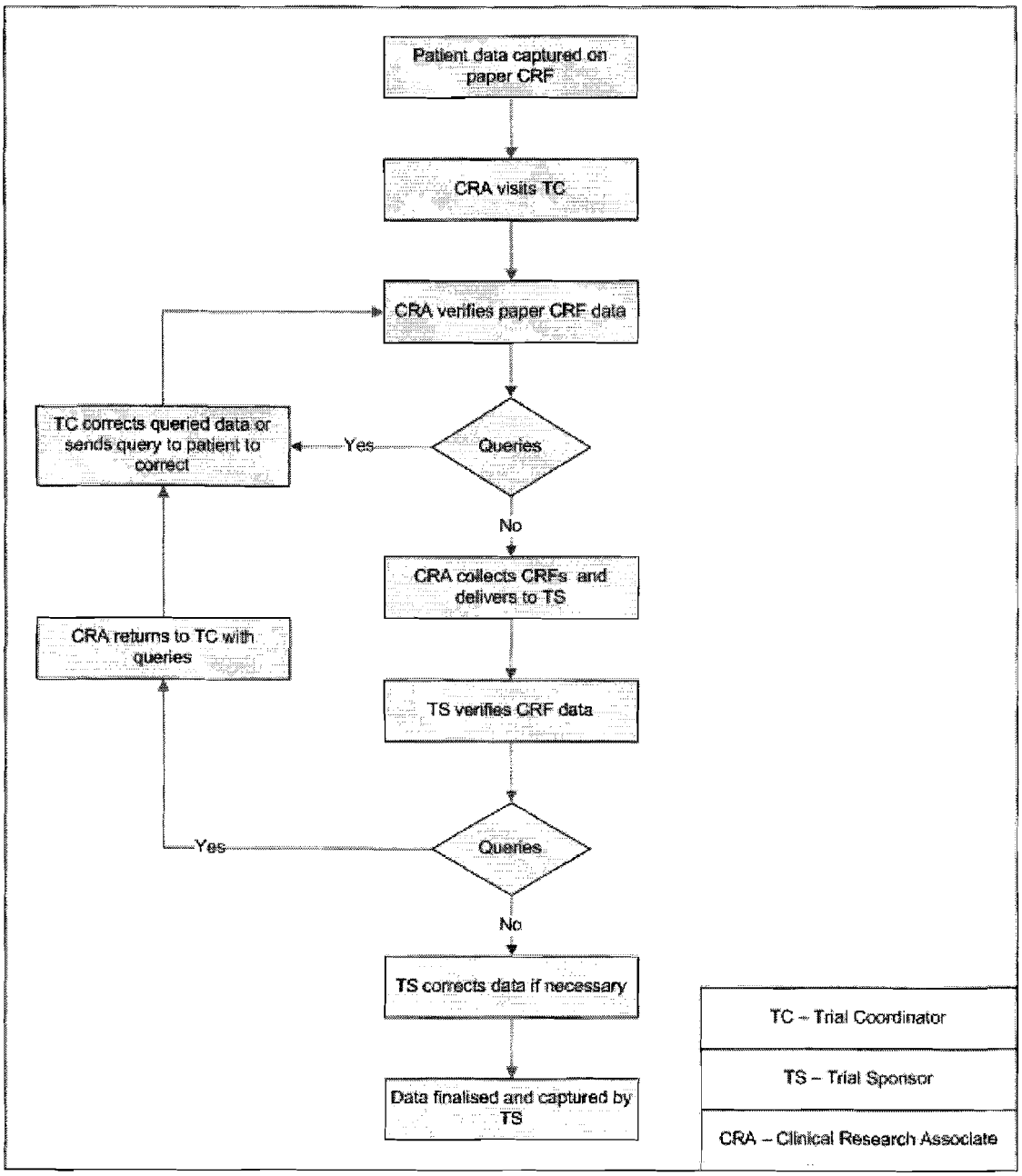


Figure 3 – Collection of clinical data using PDC

There are several drawbacks to this method that can delay the overall progress of a trial. These drawbacks are:

- Double data entry - both the trial coordinator and trial sponsor capture the same data.
- Prone to human errors - during data capture, the data may be copied incorrectly from one document to another.
- Query resolution delays - Sending a CRF, generating queries, and responding to these queries is a time consuming process. This process can become even more prolonged if queries are misunderstood or responded to incorrectly.
- Submission delays - The time associated with delivering paper CRFs to the trial sponsor and receiving the queries in response delays the overall progress of the trial.

However this method is still widely adopted because people are familiar with this tried-and-tested approach and see no reason to change. One method that has been introduced to improve PDC is the use of colour shade (screened) CRFs. This was based on the idea that using colour on CRFs will reduce data anomalies, thereby reducing the number of generated queries [21].

2.4.2 RDE prior to internet

RDE was invented in late 1980s to reduce the time interval between initial data acquisition and validation as well as to limit input errors [22]. The system decentralised the data capture process allowing trial coordinators to enter their own data at their own facilities. Specially trained medical staff (nurses, physicians, and other research coordinators) was used to enter data using portable computers supplied by the trial sponsors. This data was saved onto a floppy disk and sent to the sponsor periodically. When the internet was introduced RDE became known as EDC.

2.4.3 EDC

EDC allows submission of data directly between the coordinator, CRA, and research sponsor via the internet. This eliminates the delays experienced when sending paper

CRFs to the sponsor and receiving queries in return. The EDC process has the ability to accelerate the development of a clinical trial thereby decreasing trial costs as well as the time to market. However the adoption of such technology has been occurring at a relatively slow rate [23].

Figure 4 illustrates the process involved in gathering clinical data using the EDC approach. The process consists of the following steps:

- The trial coordinator completes an electronic CRF by obtaining patient information using patient diaries and medical tests. The system validates the data on entry, ensuring the data is complete and consistent;
- The coordinator submits the eCRF data directly to the CRA, without visiting the trial site;
- The CRA verifies the eCRF data and responds electronically;
- If data queries exist, the coordinator resolves the queries electronically or forwards the queries to the relevant patient.
- If there are no queries, the CRA submits the eCRFs to the trial sponsor;
- The trial sponsor then examines the electronic data;
- If any queries exist that cannot be handled by the sponsor, the queries are returned to the trial coordinator. These queries are generated and resolved without the delays experienced using the PDC method;
- When no queries exist, the sponsor finalises the data on computer;
- This procedure is continued until the data is accepted by the sponsor.

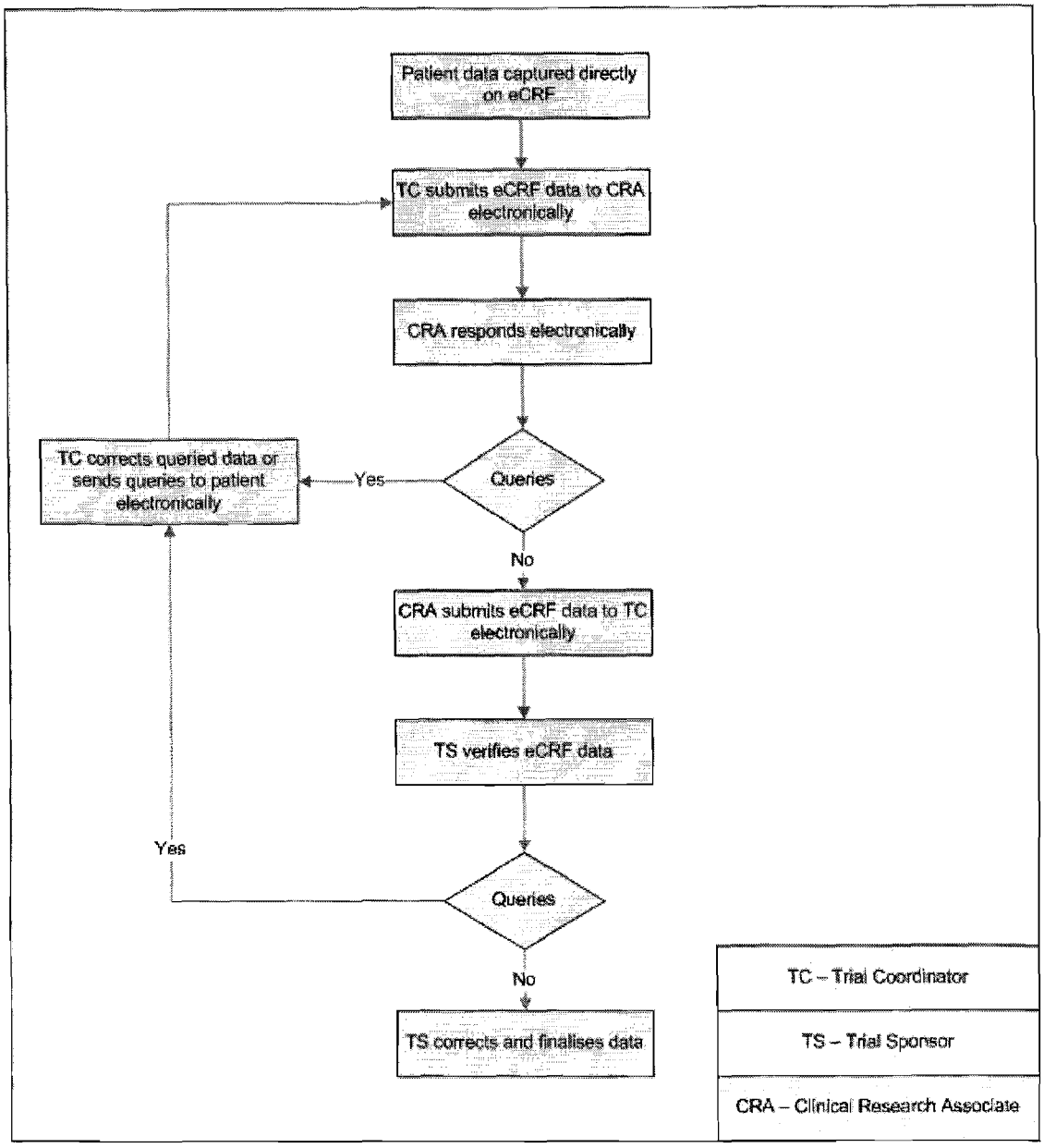


Figure 4 – Collection of clinical data using EDC

This system offers the following advantages:

- No double data entry - it is no longer necessary for the trial sponsor and coordinator to capture the same data.
- Data validation - when the eCRF entries have been captured, the system can verify the data for accuracy and completeness.

- Real-time access to the data - as soon as the data is entered it can be sent directly to the trial sponsor.
- Fewer data queries - there is a good possibility that fewer data queries would be returned, thereby shortening the duration between data acquisition and validation.
- Electronic query resolution - Data queries could be resolved electronically without the need for the prolonged paper approach.
- Reduced time and cost - the time, effort, and costs involved with obtaining and processing clinical trial data will decreased.

Previous studies have shown positive outcomes for pharmaceutical companies utilising EDC.

A study on the evaluation of eCRFs for a non-small-cell lung cancer clinical trial [24] showed that the majority of the users preferred the electronic based system. It was found that:

- 80% of the participants preferred the eCRFs over the paper-based CRFs.
- 94% of the participants indicated that the eCRFs were easy to complete.
- 100% of the participants preferred registering patients on-line.

A study on Clinical Operations Online (COOL) – A world wide web-based approach to running clinical trials [25], also showed that the majority of participants preferred utilising EDC. This study involved 894 patients from 78 centres across 9 countries. It was found that:

- 84% of the centre staff and 100% of the sponsor staff found the eCRF easy to use.
- 95% of the sponsor staff stated that the system supported their work.
- 71% of the participants stated that the system provided a definite advantage in comparison to other alternatives.

A study comparing the difference between the efficiency of EDC and PDC was previously conducted [9]. Results were collected from 10 Phase-III studies, involving 6700 participants, over a period of three and a half years.

- The costs for raising and resolving queries were reduced six-fold.

- The number of queries produced per participant as well as the percentage of incorrect data was reduced twenty-fold.
- The percentage of queries due to invalid data reduced by half.
- There were no queries as a result of missing data or data requiring clarification.

2.5 Cost analysis

A previous study compared the difference between the costs of EDC and PDC [8]. Costs for 19 actual EDC trials from Phase I to Phase IIIb were compared against well-known paper-based costs. These comparisons are illustrated in Figure 5. By observing the graph, it can be seen that the costs were reduced, on average, by 5.8 fold using EDC.

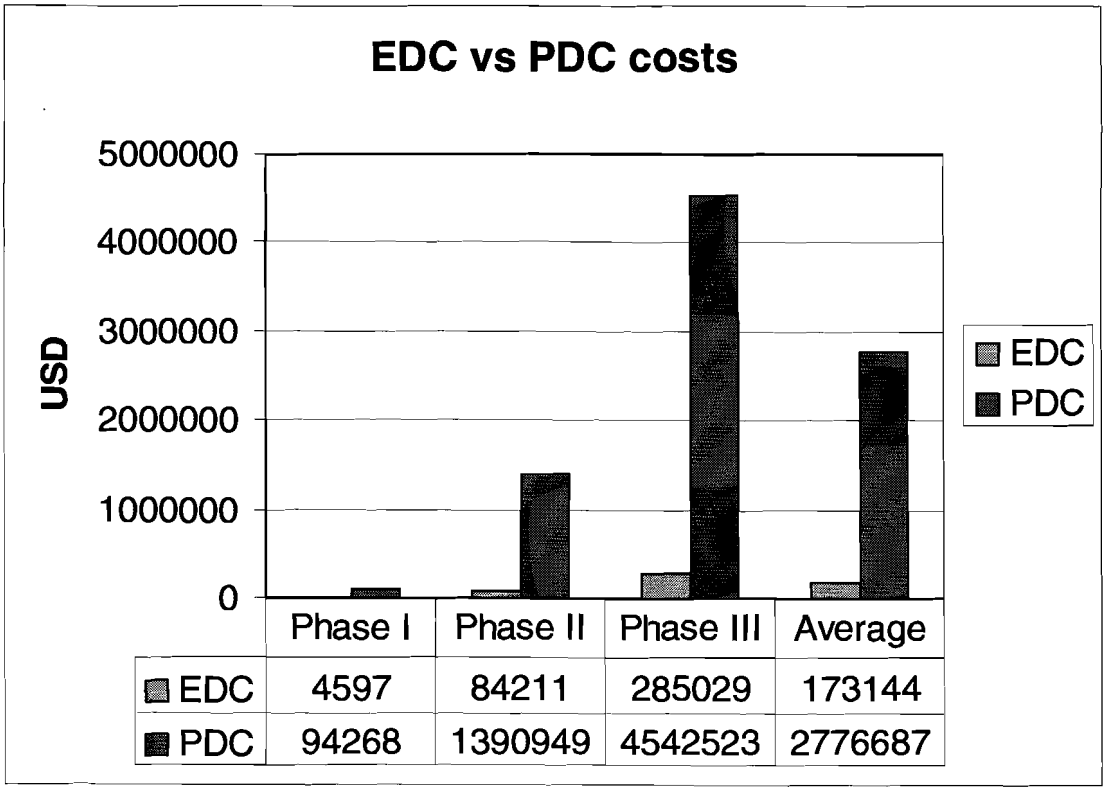


Figure 5 - EDC vs PDC costs for phase I - III of a trial

2.6 Mobile technology

Mobile technology over the last decade has improved considerably. These improvements have not only been in the functionality of mobile devices but also in their increase in popularity. Many industries have adopted the use of mobile devices to help streamline their daily activities. These devices have been used effectively in education, medicine, sports, and trade.

The three most commonly used mobile devices are the PDA, the mobile phone and the smartphone. All these devices have their advantages and disadvantages:

- A PDA is a pocket computer that was initially used as a personal organiser but has enhanced over the years to include functionality such as email, internet browsing and word processing. The majority of handheld systems used in the medical field make use of PDAs. A PDA has an advantage over other handheld devices because of its strong processor, additional memory and large screen. Conversely, all these advantages come at a higher price.
- A mobile phone, also known as a cellular phone, is the most commonly used handheld device. These devices are popular because of their low-cost and practicality.
- A smartphone is a combination of a mobile phone and a PDA. The smartphone is similar to a mobile phone except with additional PDA features.

Mobile phones these days far out number the amount of computers used today. It is estimated that there are more than 2.4 billion mobile connections [12] in comparison to the estimated 840 million computers in the world today. Combining this with the fact that the majority of these mobile phones are always on-hand makes it an ideal platform for clinical trial applications.

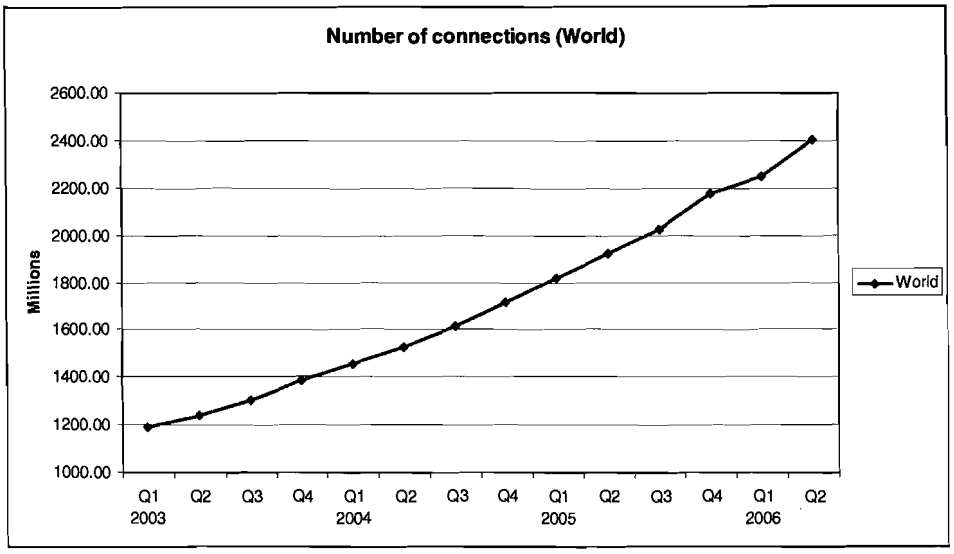


Figure 6 - Number of mobile connections from Q1 2003 until Q2 2006

Mobile devices use different technologies for wirelessly transmitting and receiving data. Bluetooth, Infra Red and WiFi are normally used for transmitting data within a specific proximity to other devices at high transmission rates. However if data is sent from remote locations outside a specific range, General Packet Radio Service (GPRS), Enhanced Data Rates for GSM Evolution (EDGE) or Third Generation (3G) would be used. For clinical trial applications it would be more practical to use GPRS, EDGE or 3G to send data because the majority of the participants are remotely located.

2.7 eDiary

As previously stated a patient diary is used to measure the compliance of an intervention by obtaining PRO data on a set basis [26]. However patients often forget to complete these diaries on the requested days and fill them in prior to their site visits [27]. Patients also sometimes forget to bring these diaries in during a site visit. The solution to these problems is the introduction of electronic-based patient diaries (eDiaries).

An eDiary is a system that electronically captures data thereby offering the same advantages as previously discussed for EDC. The system validates the data when entered

and eliminates the need for double data entry. The data can be time stamped to ensure the patient completes the entries on the correct days. The patient also does not need to remember returning the diary during each visit.

Since the sponsor and coordinator have access to real-time data, the patient can be monitored on a continuous basis. The effects of the intervention can be determined before a patient comes in for a visit. If any adverse event occurs or was about to occur as a result of the intervention, the trial coordinator or sponsor would be notified immediately. Previously there has been inadequate observation of patients during trials that have resulted in major complications for the trial sponsor [10].

There are three different types of eDiary systems, namely disconnected, semi-connected, and connected systems [13].

- A disconnected eDiary system captures PRO data on a mobile device with no communication capabilities. The data is stored on the device and later copied to a PC at the trial coordinator. The data is then transmitted to the trial sponsor where it is stored on a central server.
- A semi-connected eDiary system captures PRO data on a mobile device with communication capabilities. When possible, the data is transmitted to the trial sponsor, stored on the central server, and removed from the mobile device.
- A Connected eDiary systems captures and sends PRO data directly to the central server as soon as data entry is complete. Two examples of this system are Interactive Voice Response System (IVRS) and Interactive Web Response System (IWRS).

Connected eDiary systems have been successfully implemented on several platforms. These will be discussed below.

2.7.1 Interactive Voice Response System (IVRS)

An IVRS is an automated telephone system that provides a user with pre-defined voice menus that are responded to by a touch-tone keypad selection. This system is suited for

trials with short durations where diary questions are brief with minimal possible answers. An IVRS implementation of the questionnaire in Figure 1 would be as follows:

IVRS: "Please enter your patient ID number"
Patient: Enters ID using keypad
IVRS: "Did you take your morning dose?"
Patient: Responses with keypad 1 for yes or keypad 2 for no
IVRS: "What level of pain have you experienced?"
Patient: Reponses with keypad 0 for no pain and keypad 9 for unbearable pain
IVRS: "Have you experience any headaches?"
Patient: Responses with keypad 1 for yes or keypad 2 for no headaches
IVRS: "Select how often you experience dizziness?"
Patient: Reponses with keypad 0 for never and keypad 9 for often

Once the information is entered, it is saved to the database to be reviewed by the coordinator or sponsor. The system ensures that the data is complete by only allowing the user to progress to the next question once the current question is answered. There is still the possibility for the user to enter the information incorrectly if the wrong button is pressed.

IVR systems however cannot support trials where:

- Diary questions are complex or require lengthy responses.
- The questionnaires take long to complete.
- Where visuals such as images or scales are used.

2.7.2 Interactive Web Response System (IWRS)

IWRS is the web-based approach to capturing PRO data. It is similar to IVRS but instead of using a touch-tone keypad for data capture a webpage is used. IWR does not experience the same disadvantages as IVR. It is possible to ask complex questions on a webpage and allow for lengthy responses. Only one question can be asked at a time using

IVR unlike IWR where multiple questions are displayed on a webpage. Images, visual scales, and other graphics can also be added to a webpage.

2.7.3 Mobile eDiary

Using a mobile device is a suitable platform for eDiaries because it is carried with the patient wherever he or she goes. The majority of these patients use mobile devices on a daily basis and would be familiar with the operation of the device. However certain factors have to be taken into account when designing a mobile eDiary [22]:

1. Research ethics boards require all data that is collected to be properly protected in case the data is lost or stolen.
2. Mobile devices have limited memory, processing power and battery life. The first two problems may restrict the functionality of the mobile application. Also some mobile devices lose their data when the battery life runs out.
3. When connecting to a cellular network it may be impossible to send or receive data because there is no network coverage.
4. To supply every patient with a mobile device can become costly.

PDAs are commonly used in clinical trials because of its performance as well as its touch screen capabilities. Data entry is simplified by simulating the means in which paper questionnaires are completed. PDAs have been used successfully in previous studies [28]. It was determine that 94% of the patients completed their diaries to the required standards. However PDAs are more expensive than other mobile devices thereby requiring an initial investment for the trial.

To reduce the costs on hardware, it would be beneficial to develop an eDiary on the less expensive cellular phone. Since the majority of these patients may already own cellular phones, there would no longer be additional hardware costs.

When utilising a cellular phone, limited process power, less memory and a small screen becomes more of a concern. Questionnaires need to become even simpler and responses

even shorter than before. However cellular phones are the most commonly used mobile device in the world.

2.7.4 Comparison

Previously a study on choosing the best method for collecting PRO trial data was conducted [29]. This study presents 11 important factors to consider when evaluating different methods of data collection. During this study, paper diaries, IVR systems, and handheld eDiaries were evaluated against these 11 factors. It was concluded that the handheld eDiaries produced high-quality data, more data per patient, and allowed for real-time data analysis.

Table 2 shows the results from the study for paper diaries, IVR systems, and handheld eDiaries. Also included is an evaluation of an IWR system against the 11 factors. This evaluation was conducted in the same manner as the previous study.

The 11 factors used to evaluate the study are:

1. Data Quality – the accuracy and completeness of the data collected.
2. Trial Timelines – the duration from data acquisition to data validation.
3. Branching Logic – how well a patient follows a logical response structure.
4. Visual Measures – the visuals used to simplify data entry (e.g. visual scales).
5. Subject Compliance - how well the patient complies to correct and complete data entry.
6. Sample size – how many patients are required to achieved successful trial results.
7. Training – is training required prior to the use of the system.
8. Survey Length & complexity – the complexity of the questionnaires as well as the length of the responses.
9. Mid-study Changes – how the system will be affected if the required data to be captured had to change.
10. Global Deployment – how well the system will operate in more than one country.
11. Sensitive Indications – how well the system keeps the privacy of the data.

Factors	Paper	IVR	IWR	Handheld eDiaries
Data Quality	Poor	Superior	Superior	Superior
Trial Timelines	Poor	Superior	Superior	Superior
Branching Logic	Adequate	Superior	Superior	Superior
Visual Measures	Adequate	Poor	Superior	Superior
Subject Compliance	Poor	Adequate	Superior	Superior
Sample size	Poor	Adequate	Superior	Superior
Training	Superior	Superior	Adequate	Adequate
Survey Length & complexity	Superior	Poor	Superior	Adequate
Mid-study Changes	Poor	Superior	Superior	Superior
Global Deployment	Poor	Adequate	Superior	Adequate
Sensitive Indications	Poor	Superior	Superior	Superior

Table 2 – Comparing different methods for implementing patient diaries

2.8 CDISC

CDISC is an open, multidisciplinary, non-profit organization created to develop and support global, platform-independent standards for electronic clinical data acquisition, exchange and submission [30].

These standards have been created for:

- System interoperability – Systems can exchange and utilize data amongst one another thereby operating coherently as one large system;
- Improved process efficiency – Exchanging standardised data ensures that the data interchange process is efficient. Interchanging unstandardised data would require the data to be converted by each system;
- Increased longevity – As the systems evolve the standards remain the same ensuring that data interchange still takes place amongst the systems;
- Easier data management – The clinical data can be easily understood and managed by referring to the data standards.

2.9 Summary

Technology has been introduced into clinical trials to resolve the dilemma the pharmaceutical industry is currently facing. The PDC approach to data acquisition usually produces low-quality data and prolongs the duration between data submission and acceptance. EDC has shown successful results but is still not widely adopted by pharmaceutical companies. eDiaries are used for collecting PRO data with the most practical implementation being on a mobile device.

CHAPTER 3

DEVELOPMENT OF THE MCDAS

This chapter describes the objective and design of the MCDAS. The requirements for the system are discussed together with the steps involved in the design to meet these requirements.

3 DEVELOPMENT OF THE MCDAS

3.1 Introduction

A MCDAS is developed to ensure the transmission of high-quality PRO data. The system is designed to capture and submit complete and consistent data directly to trial personnel, for the purpose of administration. The system is designed to make clinical data capture, acquisition and administration easier.

This chapter looks into the design of the three main sections of this system, namely the mobile eDiary, the website and the communication method. A standard data structure is created for the submitted information. The website is designed for easy data access and navigation, whilst still protecting the data against unauthorised access. The mobile eDiary validates data on entry thereby ensuring the completion of all data entries.

3.2 Objective and advantages of the system

The main objective of this system is to send high-quality PRO data directly from a cellular phone to a central web server. A standard format for the transmitted data is developed for integration with other systems. The trial coordinator can add, remove, update and backup patient and trial information on the website.

The advantages of the system are as follows:

- PRO data is validated on entry to ensure the transmission of high-quality data to the trial coordinator and sponsor;
- The data is sent electronically, to the trial coordinator, thereby eliminating double data entry and enabling real-time access to PRO data;
- Possibly fewer data queries would be returned, thereby shortening the duration between data acquisition and validation.

3.3 Technology overview

3.3.1 Cellular phones

As previously discussed cellular phones are used by a large fraction of the world population. Cell phones have become an everyday accessory because of their low-cost and practicality. Many people rely on cell phone not only for communication capabilities but also for the additional features that it has to offer (e.g. calendars, address books, etc).

When developing a cell phone application the following constraints need to be taken into account:

- Display – The small screen size and limited graphical capabilities restricts the amount of information that can be displayed on the Graphical User Interface (GUI) at a particular time. The GUIs therefore need to be designed carefully to ensure all required elements and data is displayed;
- Input – The keypad of the cell phone limits the speed at which data can be captured. The data entry process should be user-friendly and might include a list of choices and simple item selection;
- Processor and Memory – The limited memory and processor power might restrict the size and complexity of the application. The application should be simple as well as store a limited amount of data;

Several technologies exist for transmitting and receiving data via a cell phone. Technologies such as Bluetooth, Infra Red and Wi-Fi are used for transmitting data to other devices in a close proximity. Such technologies enable fast data transmission rates (e.g. Bluetooth transmits up to 2.1Mb/s). GPRS, EDGE and 3G are used for transmitting data through the cellular network usually to a remote server connected via the internet.

3.3.2 Java 2 Platform, Micro Edition (J2ME) development

J2ME is used for the development of software for resource-constrained devices such as cellular phones. J2ME is optimised for devices with extremely limited memory, slow

processors, small screen sizes and alternative input methods. Currently, majority of cellular phones support J2ME applications [31].

J2ME for cellular phones can be divided into three parts namely (Figure 7) [32]:

- Configurations – This is a complete Java runtime environment consisting of a limited Java virtual machine (KVM), native code to interface with the underlying system and a small set of core classes. J2ME defines the Connection Limited Device Configuration (CLDC) for cellular phones.
- Profiles – This provides additional classes to a configuration to add support for specific device capabilities. A device must support an entire profile since none of the functionality of a profile can be optional. J2ME provides the Mobile Information Device Profile (MIDP) for cellular phones.
- Optional Packages – This is a set of Application Programming Interfaces (APIs) that provides additional functionality that is not supported by all devices with the same profile (e.g. Bluetooth API, Mobile Media API).

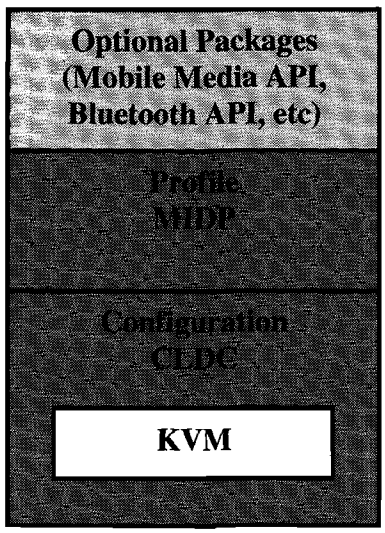


Figure 7 - J2ME Stack for cellular phone

Device manufactures preinstall the KVM and associate APIs on the cellular phone. A cellular phone therefore has a predefined configuration and profile. The mobile software developer needs to be aware of the configuration and profile version so that he or she is

aware of the available APIs. Optional packages are usually not preinstalled by the device manufacturer but rather packaged with the developed application.

3.3.3 Symbian development

Symbian is a compact Operating System (OS) designed specifically to meet the sophisticated requirements of mobile devices. The OS focuses on conserving memory, storage space, battery life and CPU power while still offering a good set of functionality. Symbian OS is similarly designed to most desktop OS systems by supporting multitasking, multithreading, and memory protection [33].

Symbian OS is open to third party development by providing tools for application development. However the development of applications for Symbian OS can become extremely complex. This has been solved by the introduction of Appforge Crossfire [34]. Appforge Crossfire allows a Symbian application to be developed in Visual Basic thereby simplifying the process of software development. This means that more powerful and effective applications can be developed with less effort.

3.3.4 J2ME vs. Symbian

Table 3 shows a comparison between J2ME development and Symbian OS development with and without Appforge Crossfire. Six factors were used to compare these three approaches.

These six factors are [35]:

1. Learning curve: how quickly a developer learns to develop in the programming language;
2. Available functionality: the functions available for developing mobile applications;
3. Developer support: the amount and quality of support available for developers;
4. Market share: the share of the market that utilises these platforms;
5. Development platforms: the software used for developing mobile applications;
6. Development software costs: the costs associated with the application development software.

	J2ME	Symbian OS without Appforge	Symbian OS with Appforge
Learning Curve	Average	Difficult	Excellent
Available Functionality	Depends on device capabilities	No Restriction	No Restriction
Developer support	Excellent	Excellent	Good
Market share	Majority of the market	Mainly Nokia phones	Mainly Nokia phones
Development platforms	Excellent (Netbeans, EclipseME)	Excellent (Carbide C++)	Excellent (VB 6, VB.NET)
Development software costs	Free	Varies	- US $1000 and US $30 per client for Crossfire - VB 6 or VB.net licence costs

Table 3 - Comparison between J2ME and Symbian OS

3.4 Requirements definition

3.4.1 Hardware and software requirements

The system consists of two main hardware components, namely the cell phone used by the patient, and the web server that stores, receives and manages the PRO data. The three main software components are the cell phone software, the web server software and the web browser.

The requirements for the cell phone are:

- Symbian OS with Appforge Crossfire or J2ME with MIDP 2.0 and CLDC 1.0;
- GPRS, EDGE, or 3G capabilities.

- Adequate memory for the installation of an application.

The requirements for the web server are:

- PHP and MySQL support;
- JAD and SIS mime types for direct download of mobile applications to cellular phones.

The requirements for the web browser are:

- JavaScript support;
- IE5 or higher, Mozilla Firefox v 1.0 or higher.

3.4.2 User requirements

The two main users of the system are, the patient using the cell phone eDiary and the trial personnel using the website for data administration.

The user requirements are as follows:

Mobile eDiary

- Ease-of-use: The eDiary should be straight-forward to use. The process of transmitting the data should be a simple click of a button. The navigation between the forms should be logical;
- Practicality: The cellular phone data capture should be an efficient process. Data should be captured by simply selecting from set of options. It should not be an inconvenience using the application;
- Display: The characters on the cell phone should be legible. Element size should be adjusted according to the cellular phone screen size;
- Cognitive process: The user should understand the questions being asked and how to answer the questions.

Website

- Ease-of-use - The website layout should be simple and the required information should be easy to find.

- Displayed data - The data should be displayed in a clear and simple format. There should also be an option to display the data in a more detailed format;
- Navigation – The navigation between web pages should be simple and logical. The home webpage should be accessible from any other webpage.

3.4.3 System requirements

The requirements were based on the Food and Drug Administration (FDA) requirements for source documents in clinical trials [36].

The system requirements are as follows:

Mobile eDiary

- Data validation: The eDiary shall validate the captured data before being transmitted thereby ensuring complete and consistent PRO data. The summarised data should be displayed after capture, so that the patient can verify the data before being transmitted;
- Accurate data capture: The accuracy of the data captured shall be ensured by limiting the values that can be entered or by selecting from a set of options.
- Authorised data submission: Only authorised patients shall be allowed to transmit data. The patient logs in to the eDiary with his or hers username and password;
- Reliable: The data is stored on the cell phone before transmission so that, in the case of an unsuccessful upload of data to the web server, it can be sent at a later stage.

Website

- Authorised data access: The data shall be protected against unauthorised access. Only the trial personnel shall be allowed to view and modify the data;
- Tracking data changes: Any changes to the originally captured data shall be recorded. If data is modified then it should be marked as modified so that the other users are aware of these changes;
- Accurate data copy: Authorised personnel shall be permitted to making accurate copies of the stored data. This person would be responsible for the protection of this data;

- Administration - Patient and trial details shall be administered on the website. This however is not an implementation of an eCRF or Clinical Data Management Systems (CDMS). Only the name and contact details of the patient and the name, dates and description of the trial shall be captured. If required, it is possible to obtain this information from the CRF.

3.5 System and software design

3.5.1 Mobile eDiary

The purpose of the mobile eDiary is to capture complete and accurate data on the cell phone and to transmit this data to a web server. The mobile eDiary is responsible for capturing, validating, storing and transmitting PRO data. The patient is required to login to the application before he or she can capture and transmit data thereby ensuring the integrity of the transmitted data.

The design of the mobile application is represented by the use of the Unified Modeling Language (UML) which is a standard for Object Oriented (OO) software design.

UML

As with any field of engineering, systems first need to be designed and documented before implementation can begin. All fields of engineering have a standard method of documentation. The equivalent for software engineering is UML. UML is a graphical language for visualising, specifying, constructing, and documenting software systems [37]. UML ensures that software systems are professionally designed and documented before being implemented.

There are three main types of behavioural modeling diagrams in UML [38]:

- Use Case diagram - A use case diagram is a description of the systems behaviour from an end-user's perspective. The diagram shows which users interact with the system together with the functionality that the system must provide. It is a technique used for gathering the requirements of the system.

- Activity diagram - The activity diagram illustrates the flow of control from the start of an activity until the end including all the decisions that need to be made. Activity diagrams are useful for describing the processes involved in the business activities.
- Sequence diagram - A sequence diagram is a graphical representation of the interaction between objects over a certain period, illustrating the flow of messages between these objects. The interactions between objects take place in a particular sequence with time represented as a vertical progression.

Use case diagram

Figure 8 illustrates the use case diagram for the mobile eDiary. It can be seen from the diagram that the patient is responsible for logging in, capturing data and logging out. The procedure of data transfer includes the processes involved in data capture, validation and storage on the mobile device. The web server interacts with the system during data transfer.

As previously mentioned the Use Case diagram is used for obtaining the system requirements. The requirements for this system are illustrated in the diagram as follows:

- Data validation – Data validation by the cell phone occurs directly after data capture.
- Accurate data capture – The data capture process improves the accuracy of the data by limiting what data can be entered.
- Authorised data submission - The patient is required to login and logout of the cell phone application. Only once the patient logs in, can he or she capture and transmit the data.
- Reliable – Saving the data on the cell phone occurs during the data transfer process. This ensures that the data can be submitted later if the transfer process is unsuccessful.

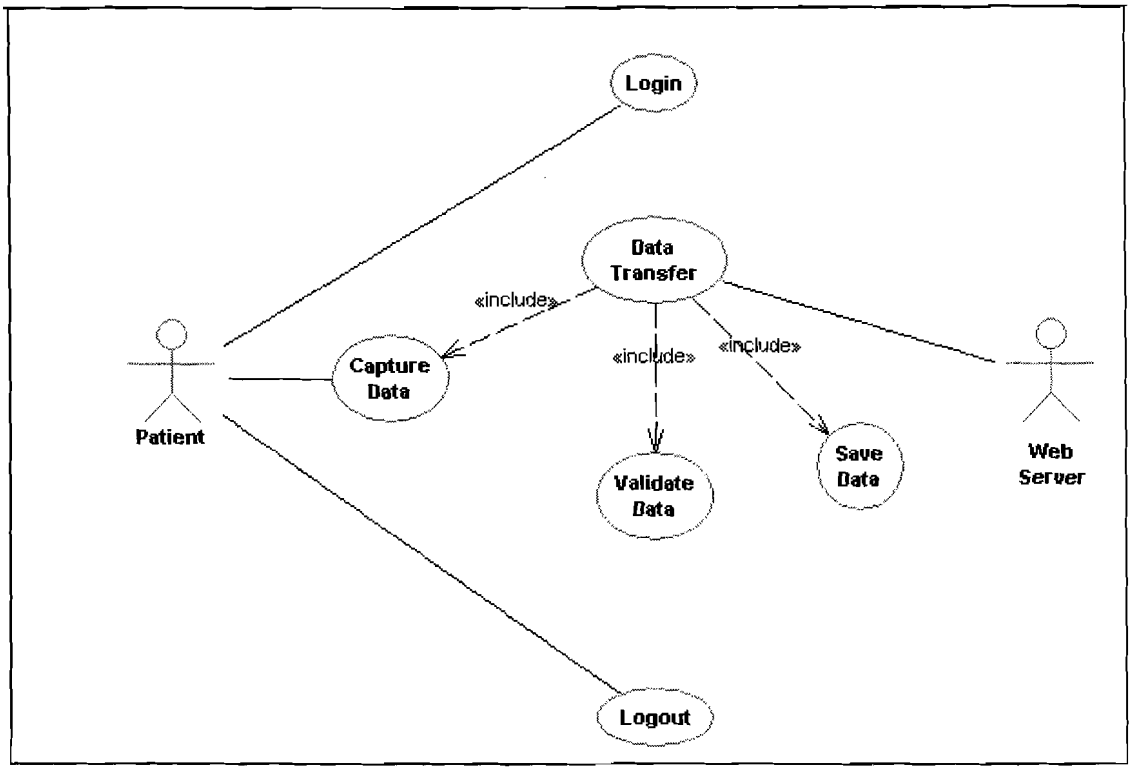


Figure 8 - Use case diagram for the mobile eDiary

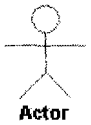
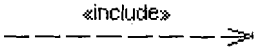
	**Actor** – This is a user or another system that interacts with the system being developed.
	**Use Case** – This is a function provided by the system to its user.
	Relationship – This illustrates the relationship between a user and a use case.
	**Include Association** – This indicates that a use cases includes the functionality of another use case.

Table 4 - Use case diagram elements

Activity diagram

Figure 9 illustrates the activity diagram for the mobile eDiary. The diagram illustrates the flow of control throughout the data transmission process. It is also divided into three swimlanes namely the patient, the eDiary, and the web server. These swimlanes indicate which part of the system performs which activities.

The activity diagram illustrates the following steps:

1. The patient enters his or her username and password;
2. The eDiary validates the login details
   - 2.1 If the login details are invalid the eDiary determines the number of login attempts. If it is greater than three attempts the application exits otherwise the system returns to step 1.
   - 2.2 If the login details are valid the system continues to the next step;
3. The patient is then asked whether he or she wants to capture new data
   - 3.1 If the patient selects 'no' then the system skips to step 7.
   - 3.2 If the patient selects 'yes' the system continues to the next step ;

4 The patient captures the required data;

5 The data is then validated by the system.
   - 5.1 If the data is invalid the system returns to step 4 with the appropriate message
   - 5.2 If the data is valid then the system continues to the next step;

6 The eDiary saves the captured data;

7 The patient selects whether he or she wants to send the data.
   - 7.1 If the patient selects 'no' the system skips to step 21.
   - 7.2 If the patient selects 'yes' the system continues to the next step.

8 The system determines whether there is any queued data to be sent
   - 8.1 If no queued data exists then the system skips to step 18.
   - 8.2 If queued data exists, the system continues to the next step;

9 The eDiary sends the username and password to the server for login;

10 The web server attempts to login using the username and password
   - 10.1 If the login is unsuccessful the system continues to the next step.
   - 10.2 If the login is successful the system skips to step 11;

11 The eDiary displays that there was an unsuccessful login and the system skips to step 18;

12 The web server establishes a session for the patient;

13 The web server sends a request for the captured data as well as the queries from previously captured data.

14 The eDiary determines if there are any queries

14.1 If queries exist then the eDiary analyses the queries and continues to the next step.

14.2 If no queries exist then the system skips to step 15.

15 The patient captures the queried data.

16 The eDiary sends the requested data to the web server;

17 The web server attempts to save the data to the database

17.1 If this is unsuccessful the web server determines the number of attempts. If it is greater than three attempts the system continues to the next step, otherwise the system returns to step 12.

17.2 If this is successful then the system continues to the next step;

18 The web server terminates the patient's session;

19 The eDiary marks the data as sent if the web server saved the data successfully, otherwise, it marks it as unsent;

20 The eDiary displays whether the data transmission was successful or not. If it was unsuccessful the eDiary specifies the reason why ;

21 The patient accepts the web server's response, specifying the result of the data transmission process;

22 The patient logs out the eDiary.

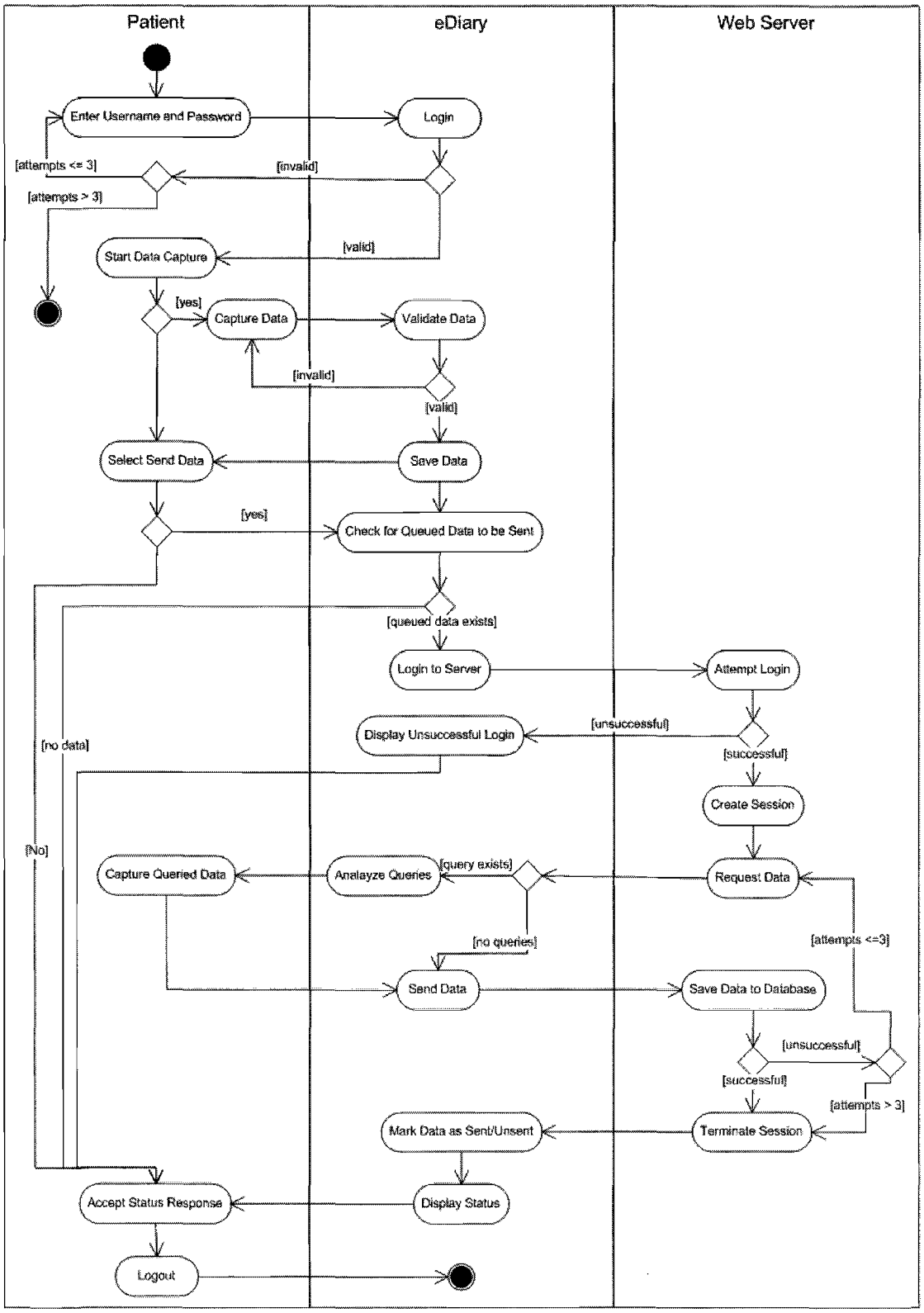


Figure 9 - Activity diagram for the mobile eDiary

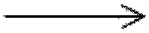
	**Initial State** – This depicts the start of an activity.
	**Final State** – This depicts the end of an activity.
	**Action State** – This is a single step within an activity.
	**Decision** – This is a node at which control can flow in different directions depending on which guard condition is met.
	**Control Flow** – This shows the flow of control from one action to another.

Table 5 - Activity diagram elements

Sequence diagram

Figure 10 illustrates the sequence diagram for the mobile eDiary. It shows the same sequence of events as the activity diagram but includes the system objects and the messages passed between them. The following objects are shown in the sequence diagram:

- aControl – This controls the operations of the data transmission process. It is mainly responsible for obtaining data from the mobile input forms.
- aLoginForm – This is a cell phone input form for obtaining the patient's username and password;
- CaptureChoiceForm – This is a cell phone input form requesting whether the patient needs to capture new data.
- MobileCaptureForm – This is a cell phone input form for capturing the data to be sent.
- MobileDataManager – This is responsible for the storage of all data on the cell phone including the login details. It is also responsible for validating the data, logging in to the web server, sending the data to the web server and marking the data as sent or unsent.

- aWebLoginManager – This is responsible for managing the logging in of the eDiary to the web server as well as creating and terminating the patient's session.
- aWebDBManager – This is responsible for saving and extracting data from the database on the web server.

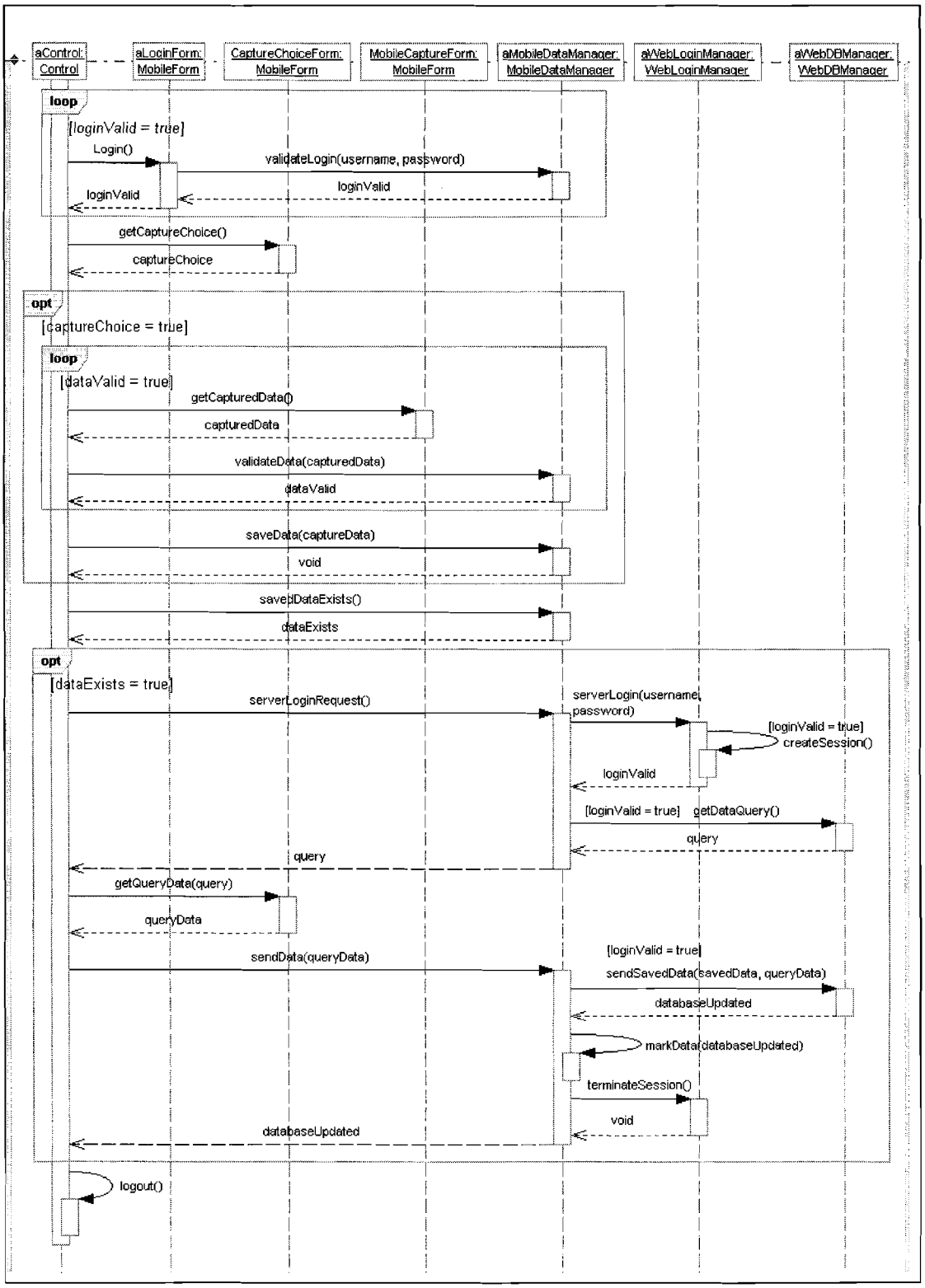


Figure 10 - Sequence diagram for the mobile eDiary

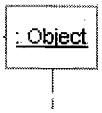
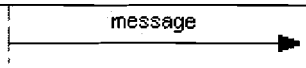
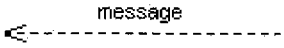
	**Object** – This is an instance of a class within the system together with the object's timeline represented as a dashed line.
	**Action** – This is the action taken by an actor or object.
	**Synchronous Call** – The object sending the message waits for a response before proceeding.
	**Call Return** – This is the message returned from an object.
	**Option** – Only if the guard condition is met does the actions within the option take place.
	**Loop** – The actions within the loop will repeat until the guard condition is met.

Table 6 - Sequence diagram elements

3.5.2 Website

The main purpose of the website is to administer PRO data to ensure its accuracy, completeness and consistency. The website allows the trial coordinator to view the data and to generate queries accordingly. These queries are saved in the database and responded to once the patient logs in from his or her cell phone.

The website requires trial personnel to login before data can be viewed or updated thereby ensuring the protection of the data. To ensure easier PRO data access the web pages are structured according to which trial a patient belongs. The website allows for the administering of patient and trial information. This information can also be imported and exported to and from external files.

The following languages are used for the website development:

- Hyper Text Markup Language (HTML): used for creating the web pages;
- JavaScript: used to add functionality to the web page that is not possible in HTML alone (client-side scripting);
- Cascading Style Sheets (CSS): used to describe the style and layout of the web pages;
- PHP: used for creating dynamic web pages (server-side scripting);
- MySQL: used for managing the database on the web server.

The design of a website can be illustrated by the use of the following diagrams:

- Site diagram: A site diagram is an illustration of the layout of an entire website. The diagram shows all the web pages making up the website and the links between each of them. The contents of each of the web pages are also illustrated on the diagram.
- Flowchart: A flowchart is used to illustrate the steps involved in a process. These diagrams show the flow of the process, decisions that are made, actions that are performed and information that is displayed and stored. Flowcharts are useful in visualising the processes involved in a system as well as determining flaws within a process.
- Web page layout: This is the design of how the elements on a web page are organised (how a web page will look).
- Database model: This is the design of the database showing the tables and the relationships between these tables.

Site diagram

There exist three different structures for building websites, namely sequential, hierarchical and network. The sequential structure is used when the navigation flows in a sequence from one page to another. The hierarchical structure is used when the website is organised around a single home page and the web pages are organised into a hierarchy. The network structure is used when all pages are linked to one another.

Figure 11 illustrates the site diagram for the website being created. It can be seen that the hierarchical structure was used for the design. However, as shown in Figure 12 the website also shows traits of a network structure.

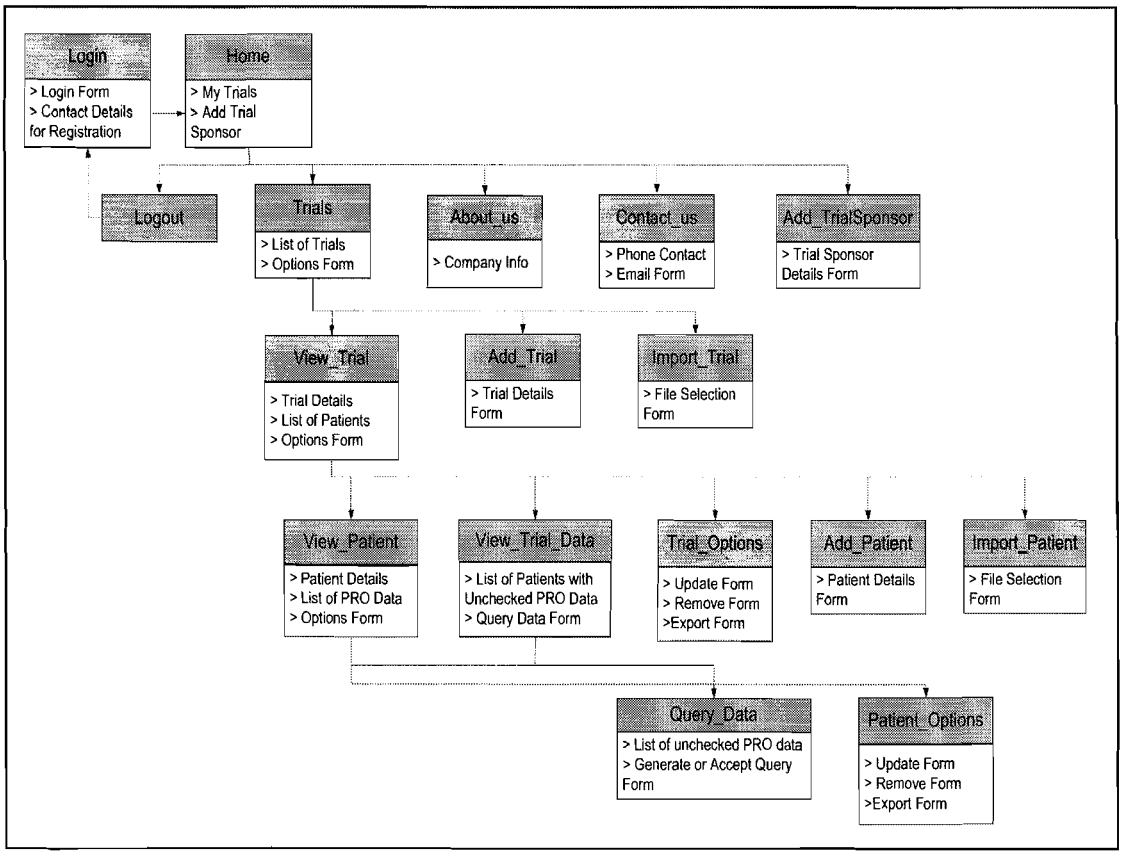


Figure 11 – Site diagram

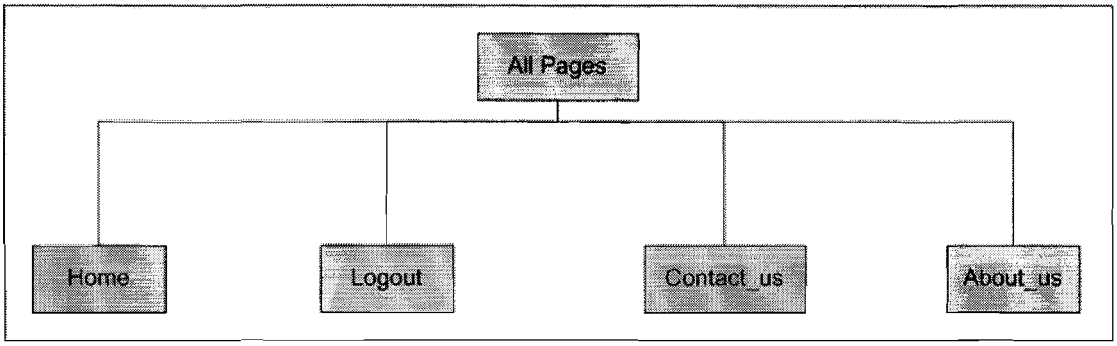


Figure 12 - Common links on the web pages

Flow diagrams

Figure 13 illustrates the web pages involved in the login process. The Login web page contains the contact details of the administrator for registration and a login form for capturing the username and password. After the user has logged in he or she is granted

access to the Home page. This page allows the user to select the list of trials currently being conducted or to add another trial sponsor. The user then has the possibility to logout, which returns him or her to the Login page.

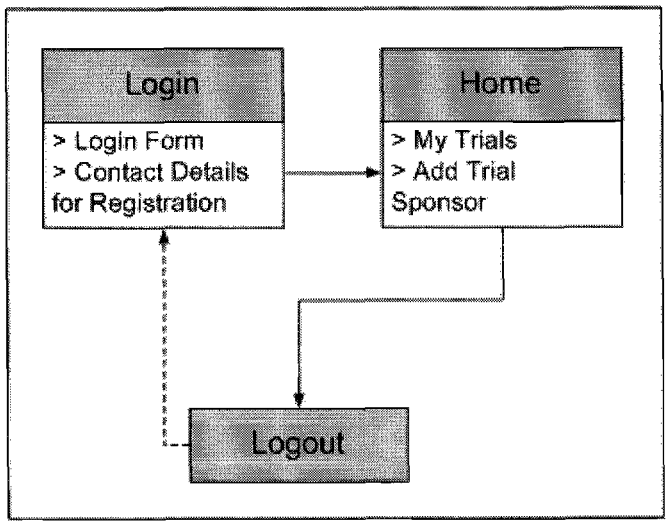


Figure 13 - Login section of site diagram

Figure 14 illustrates the flowchart for the login process to the website. This follows the normal login procedure by validating the username and password and granting access if the login details are correct. Once the login is successful a PHP session is created. This session is used to hold user information which is available to all pages in the website. When the user chooses to logout the session is destroyed and the website returns to the login page.

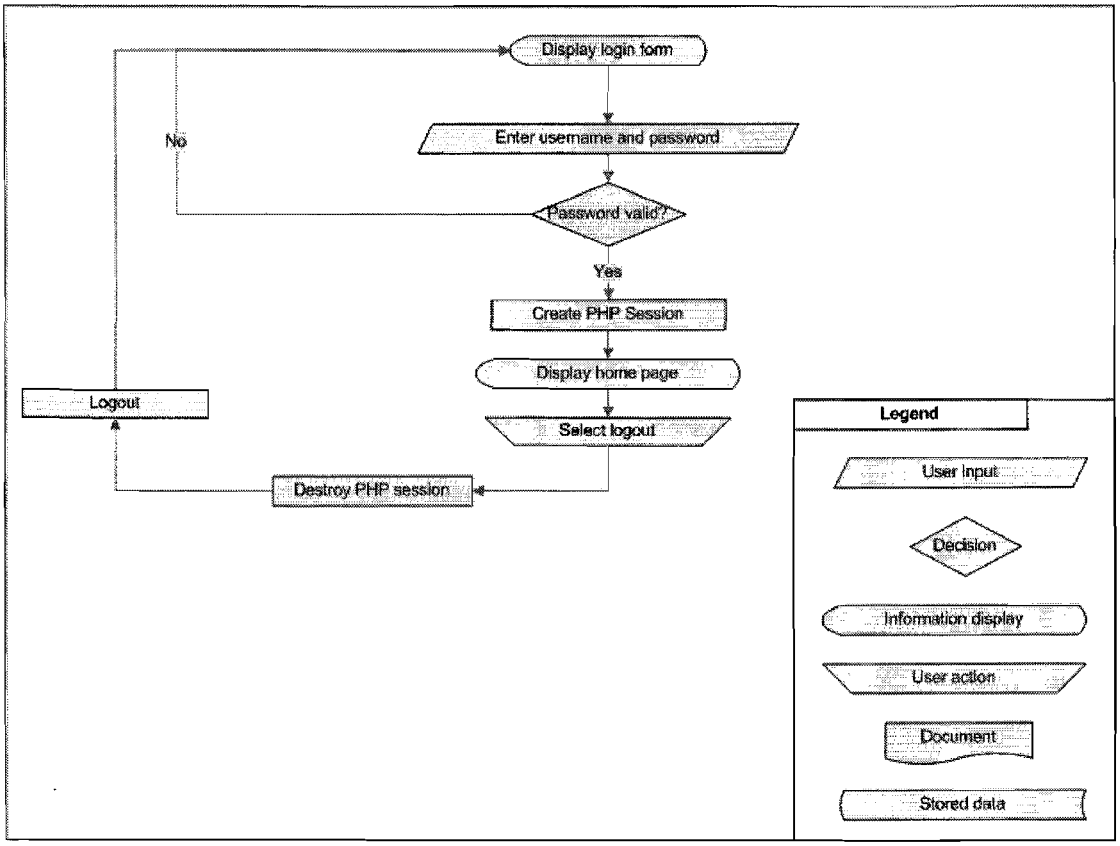


Figure 14 - Flowchart of the login process to the website using a web browser

Figure 15 illustrates the web pages involved in the process of administering the trial data. This process involved the adding, importing, updating, removing, and exporting trial data. The Trials web page shows a list of current trials being conducted under the logged in trial personnel. The user has the possibility to select whether to view a selected trial or to import or add a new trial.

If the user selects to view a specific trial then the trial details and a list of patients under that trial are displayed. The user then has the option to either view a list of patients with unchecked data or to update, remove or export the trial data. The user can also select to import a new trial by selecting the file location or to add a new trial by capturing new data.

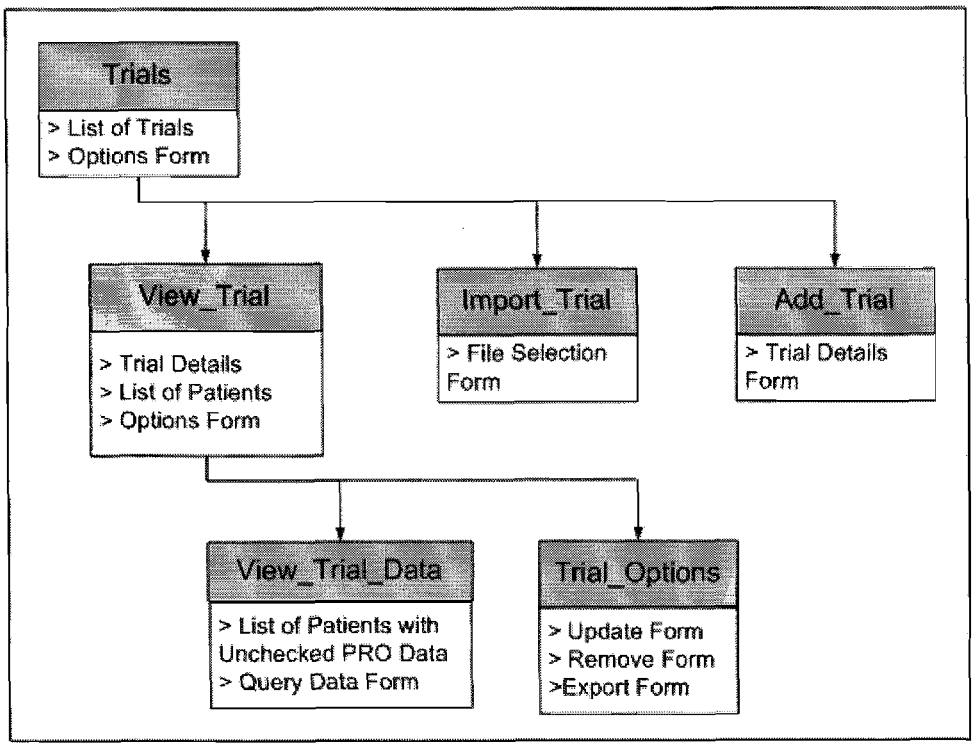


Figure 15 - Trial administration section of the site diagram

Figure 16 illustrates the process of adding a new trial to the system. The trial personnel make use of the CRF to capture the trial details. Once this data is captured, it is validated by the system. If the entry is invalid, it returns an error message otherwise it saves the new entry into the database.

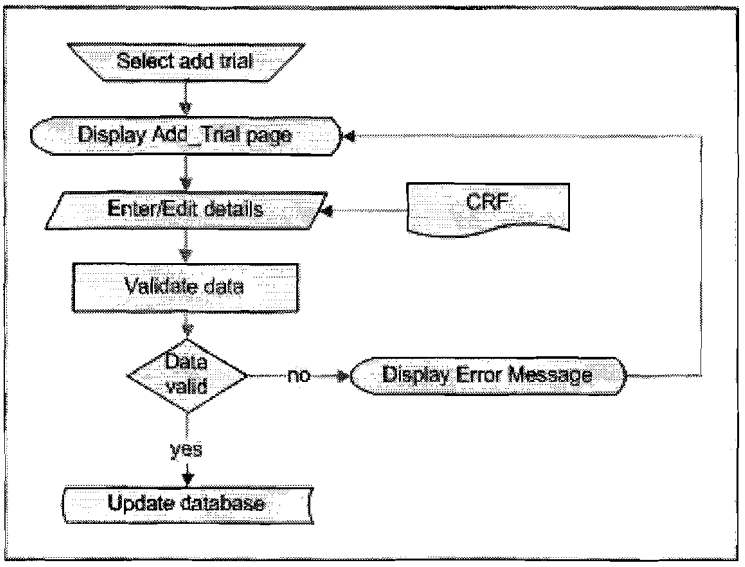


Figure 16 – Flowchart for adding a new trial

Figure 17 shows the process of importing trial data. The user first selects the file location of the external file containing the data to be imported. The system then obtains this file, extracts the data from it and imports it into the database.

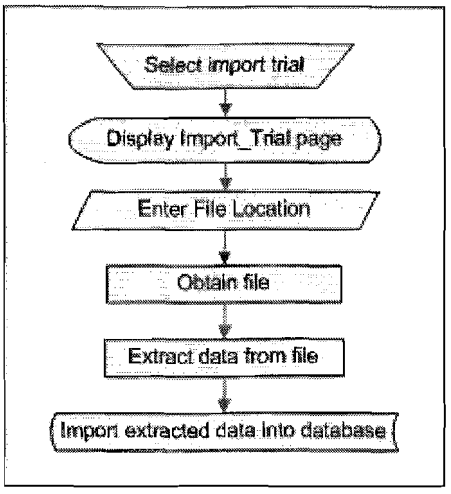


Figure 17 - Flowchart for importing a new trial into the database

Figure 18 illustrates the process of updating trial data. The existing trial data is extracted from the database and inserted into the entry fields. The user then edits these details using the CRF. The system validates the entries and updates the database accordingly.

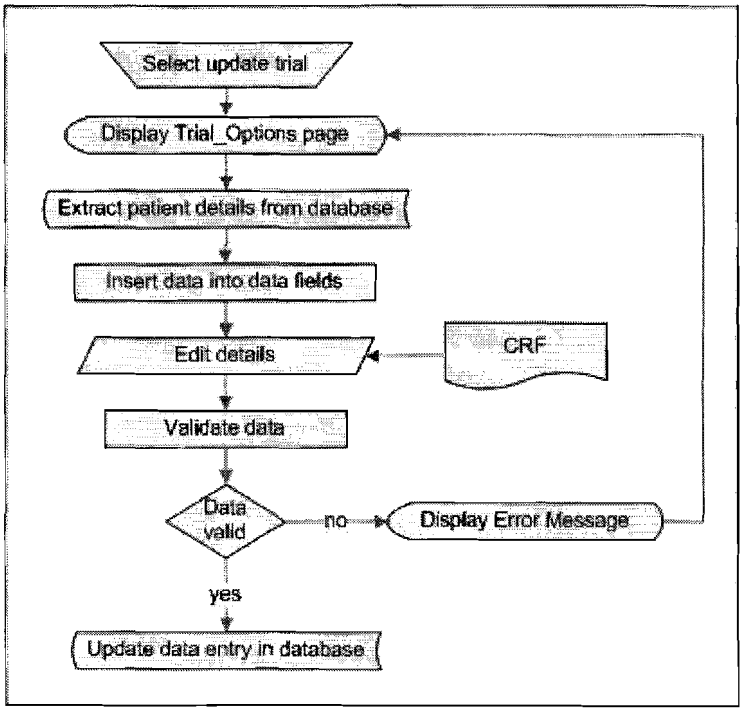


Figure 18 – Flowchart for updating a current trial

Figure 19 shows the process of removing a trial from the database. Once the trial is selected the user confirms the deletion and the entry is deleted from the database together with all the PRO data.

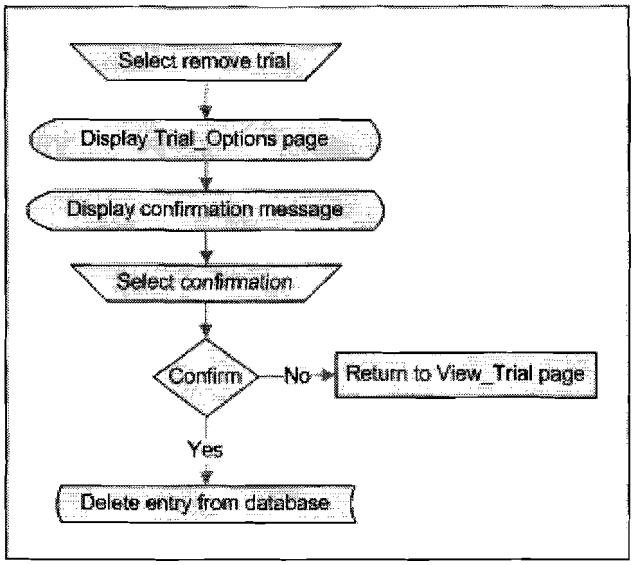


Figure 19 - Flowchart for removing a current trial

Figure 20 illustrates the process of exporting trial data to an external file. The user specifies the name and location of the file and then tries to create the file. If the file cannot be created then an error message is displayed otherwise the data is extracted from the database and written to the created file.

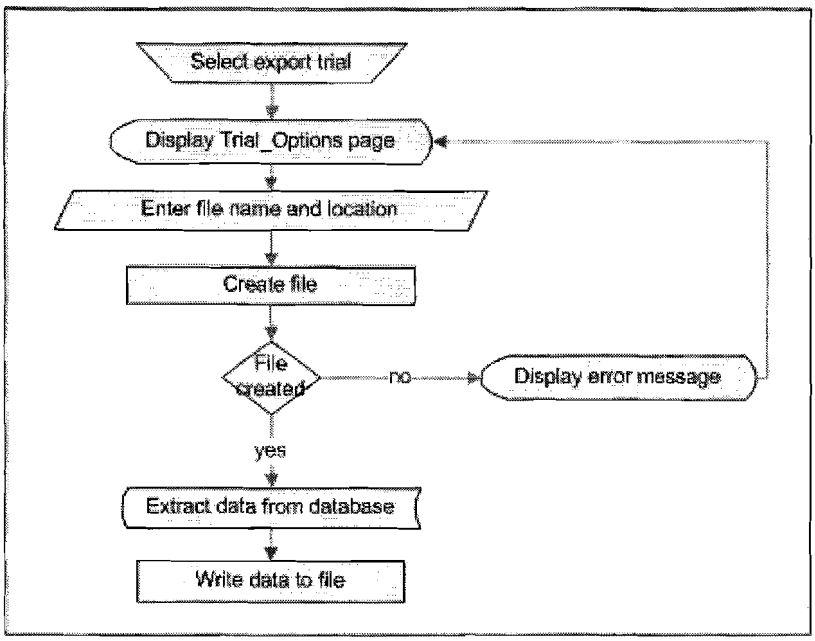


Figure 20 - Flowchart for exporting trial data to an external file

Figure 21 illustrates the web pages used for administering patient data. The administration of this data is conducted in the same manner as with administering the trial data. The only difference is the data that is captured and the table in which the data is stored.

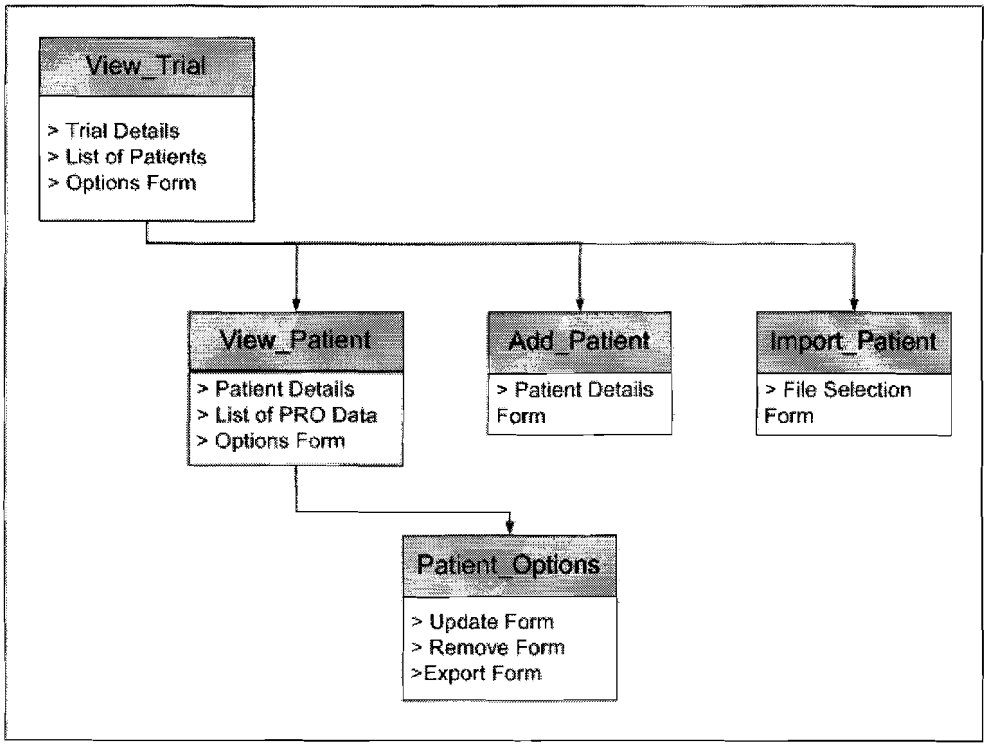


Figure 21 - Patient administration section of the site diagram

Figure 22 illustrates the web pages involved with generating data queries. The View_Trial_Data web page shows a list of all the unchecked PRO data for the selected trial. The View_Patient web page displays the patient's details together with a list of all submitted PRO data. From both of these web pages the user has the option to select and query an entry.

The Query_Data web page displays a list of unchecked PRO data for the selected patient. The user has the option to either accept the data or to generate a query. When the user selects to query an entry he or she is required to give a query message. This message is to ensure the patient is aware of the error within the entry.

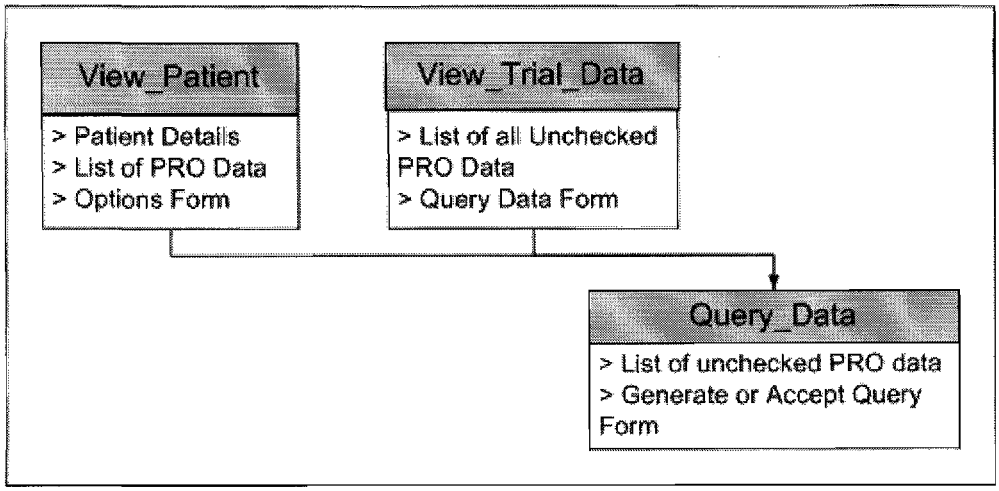


Figure 22 - Query section of site diagram

Figure 23 illustrates the processes involved with generating a data query. The process starts by selecting whether to view a specific patient's data or to view the data for an entire trial. As previously mentioned the View_Trial_Data web page displays a list of all unchecked PRO data. The View_Patient web page displays a list of all PRO data for the selected patient. Both of these web pages allow the user to select an entry to be queried.

On the Query_Data page the user examines the selected data entry to find any errors. If no errors are found then the status of the data is updated to 'checked' and 'valid'. This ensures that the trial coordinator does not recheck the data. The data entry is also time stamped to record the changes made to the data. If errors are found within the data then the trial coordinator generates queries accord to these errors. These queries are then saved to the database and the data status is updated to 'checked' but still 'invalid'.

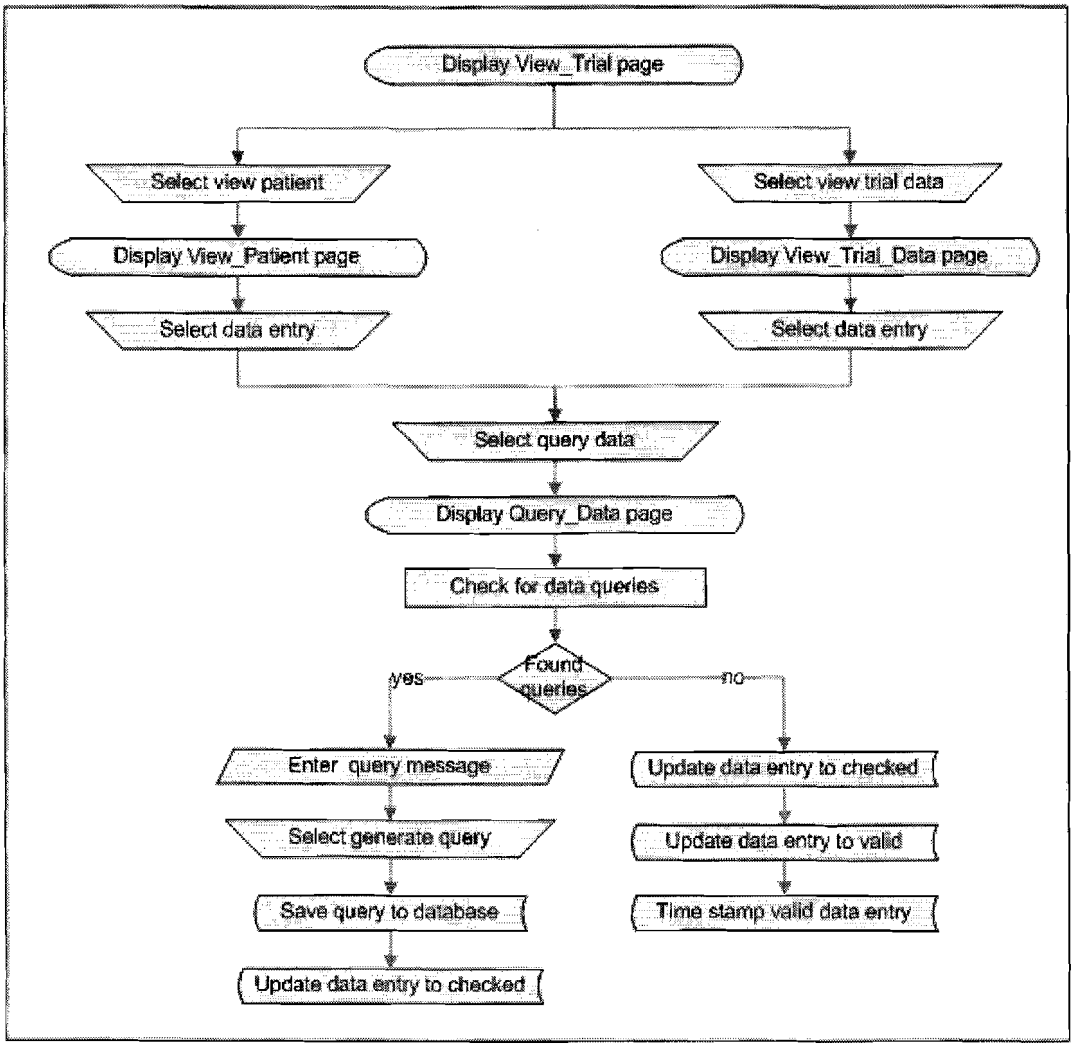


Figure 23 - Flowchart for querying PRO data

Database model

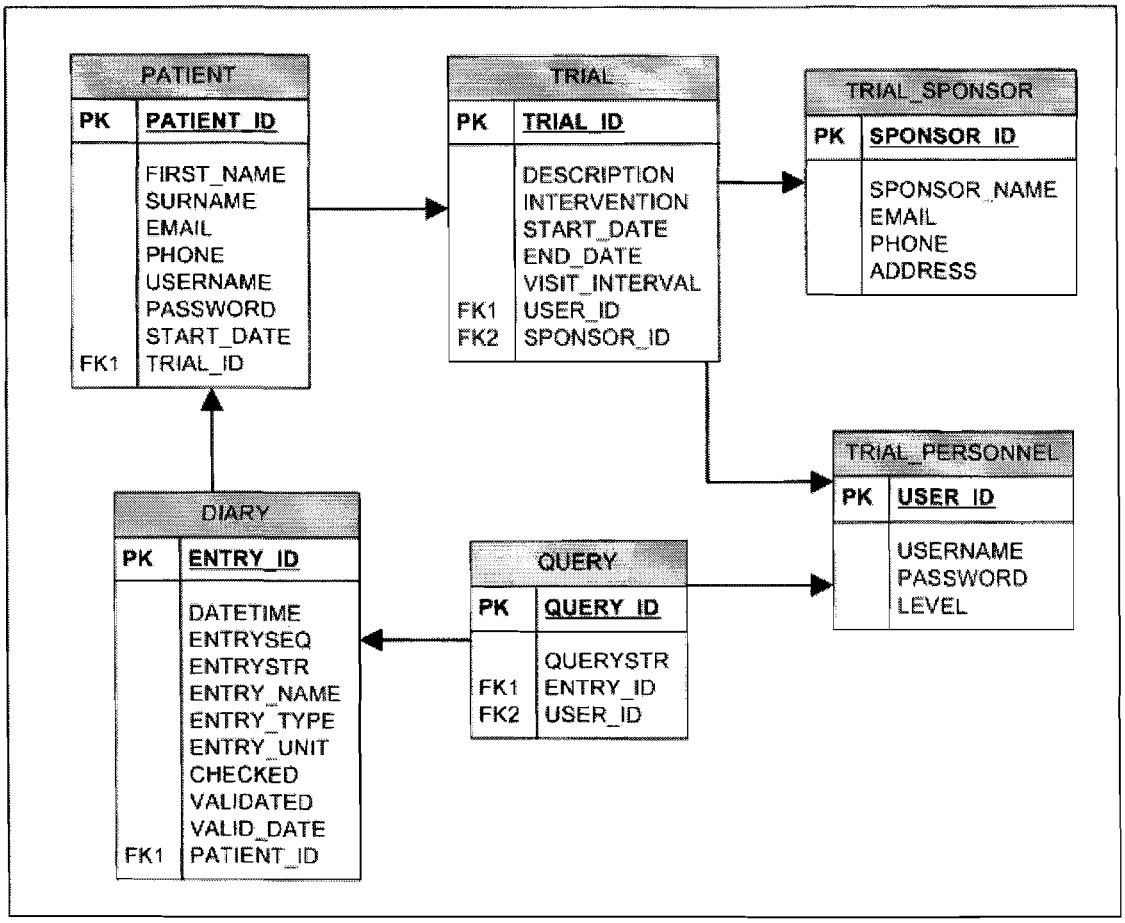


Figure 24 - Database design for website

Figure 24 illustrates the database design for the website including all tables, columns and associations.

The database consists of the following tables:

PATIENT

The patient table contains all the patients' information. This information includes the patient's name, contact details, login details, the date he or she started the trial and which trial he or she belongs to.

TRIAL

The trial table contains information about the clinical trials being conducted. This information includes a description of the trial, the intervention being tested, the start and

end date of the trial, the interval between site visits and the trial sponsor and coordinator conducting the trial.

TRIAL_PERSONNEL

The trial personnel table contains information about personnel involved with the trial who are allowed to access and edit the stored data. This information includes the username, password and level of access.

DIARY

The diary table contains all submitted PRO data entries. The table records the date and time the entry was submitted, the sequence of the data entry, the entry value, the name of each entry, the type and unit of each entry, whether the data has been checked, whether the data has been validated, the date it was validated and the patient who submitted the entry.

QUERY

The query table contains all the queries submitted by the trial personnel. The table includes a query string, the id of the entry being queried and the id of the trial personnel who submitted the query. The query string specifies the elements of the entry that are being queried.

TRIAL_SPONSOR

The trial sponsor table contains information about the trial sponsor. This information includes the name of the sponsor, the sponsor's contact details and the location of the trial sponsor.

Web page layout

Figure 25 illustrates the simple layout for the web pages. It is separated into three sections namely the logo, the navigation bar with links to the other pages specified in Figure 12, and the page content.

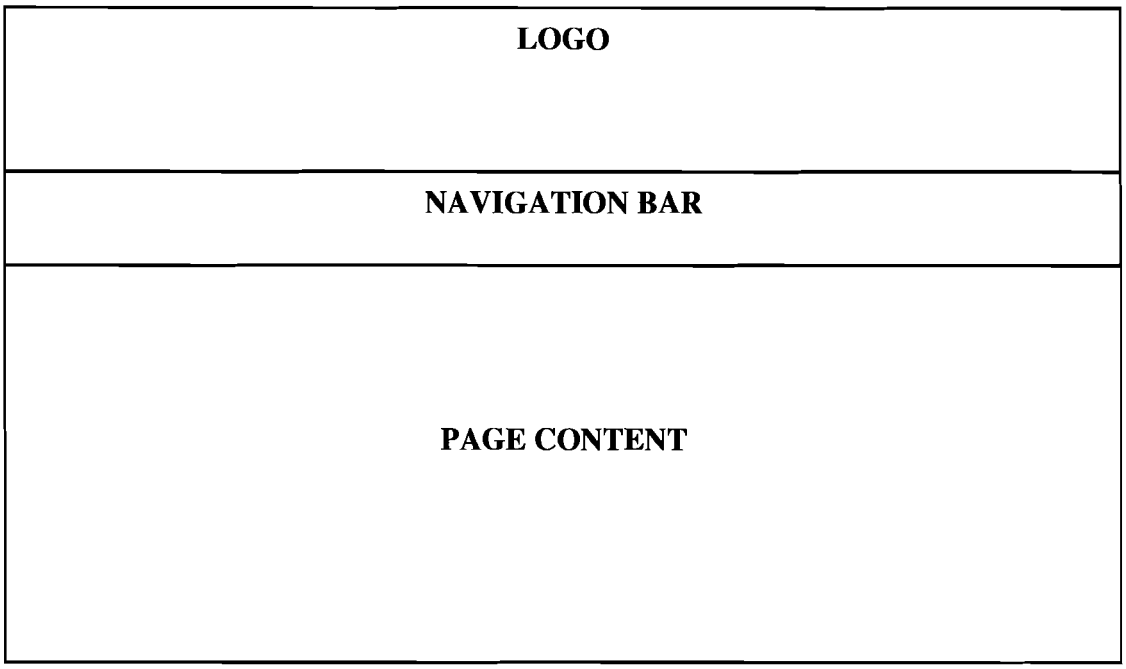


Figure 25 - Simple webpage layout

3.5.3 Communication method

The communication system consists of a cellular phone transmitting PRO data to a web server by the use of Over The Air (OTA) transmission such as GPRS or 3G. A Hypertext Transfer Protocol (HTTP) connection is established between the cell phone and web server. The connection can only be established by the cell phone. The cell phone is therefore required to fetch any responses from the web server.

The following data is sent from the cell phone to the server and saved into the DIARY table:

PATIENT_ID: The unique id of the patient transmitting the data.

DATETIME: The date and time at which the PRO data was captured on the cell phone. The date and time stamp ensures that the patient completes the requested data on the required days.

ENTRYSEQ: The sequence in which the entries are transmitted;

ENTRYSTR: A string of all the entries sent. All the unsent entries are sent together;

ENTRY_NAMES: A string of all the entry names;

ENTRY_TYPES: A string of all the entry types. Each type is associated to a number:

0. No type
1. String
2. Integer
3. Double
4. Boolean;

ENTRY_UNITS: A string of all the units of the entries.

QUERY_RES: (Optional) The response to a query.

QUERY_ID: (Optional) The id of the query responded to.

All captured entries not previously sent by the cell phone are sent together. Once these entries are received by the web server it separates them and saves them into the database.

When the trial coordinator examines the received data, queries are generated and saved into the QUERY table. The next time the patient's cell phone logs into the web server the cell phone application fetches the query, analyses it, and requests the patient to recapture the required data. This data is then sent back to the web server where it updates the previous entry in the DIARY table. This process continues until the data is accepted by the trial sponsor.

During this entire process the state of the data changes (Figure 26). When the data is initially received from the patient the state of the data is set to 'invalid' and 'unchecked'. Invalid means that the data has not yet been accepted by the trial coordinator and unchecked means that the data has not yet been examined by the trial coordinator.

When the trial coordinator examines the data and queries are generated the state of the data is changed to 'checked'. This ensures that when the mobile eDiary logs in it can determine whether there are any queries waiting. If no queries exist then the state of the data is changed to 'valid' and 'checked'. The data is then saved into the database and cannot be changed again.

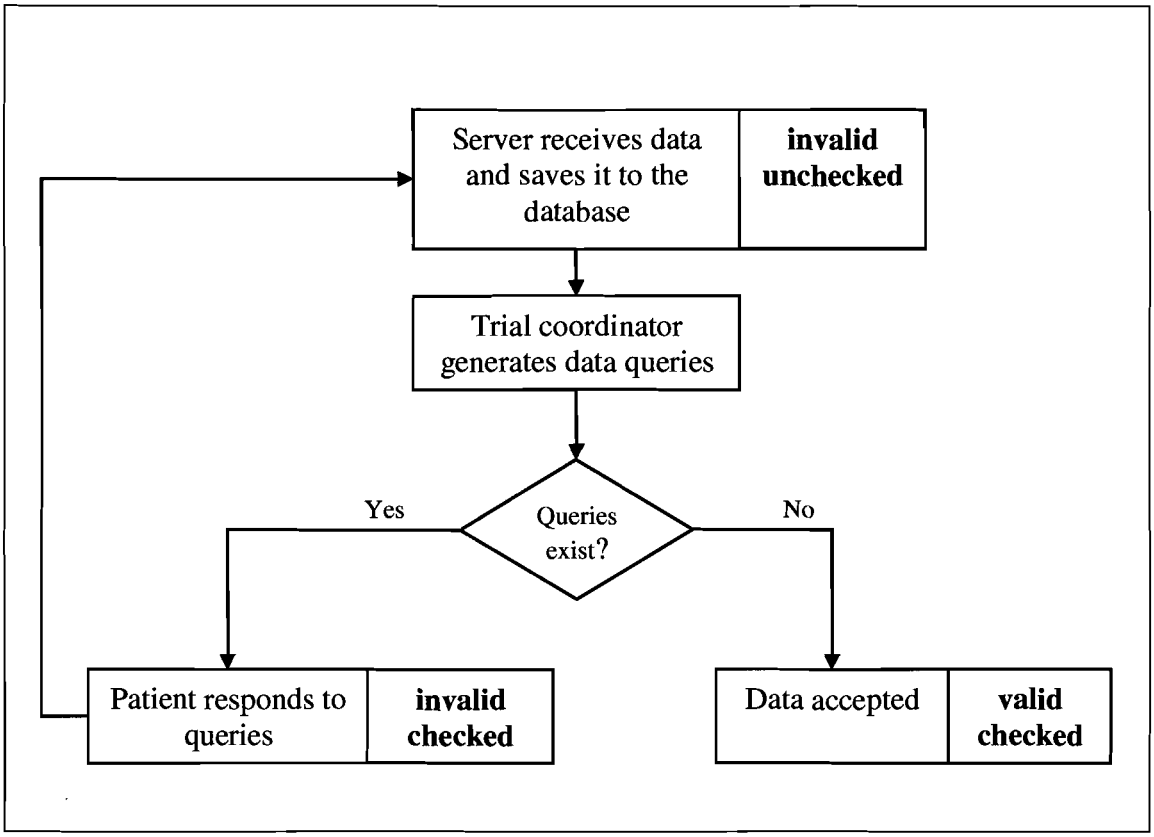


Figure 26 – The data states during query process

3.6 Summary

This chapter discussed the design of the MCDAS. The design was separated into three main sections, namely the mobile eDiary, the website and the method for communication. The system design ensured the entire process of obtaining PRO data was electronic based.

The mobile eDiary was designed for capturing, validating, storing and transmitting data as well as for resolving queries. The eDiary ensured the reliability of the data submission process by storing the data before transmission took place. The login process protected the application against the capture and submission of data by unauthorised users.

The website was designed to simplify the process of PRO data administration as well as the process of generating electronic queries. Access to data was simplified by structuring the website according the trials being conducted. Queries could be resolved electronically without the need for the trial coordinator to contact the patients. The transmitted data format was standardised to ensure that it could be implements across other applications.

CHAPTER 4

IMPLEMENTATION OF THE MCDAS

The implementation of the MCDAS on two different clinical trials is described in this chapter. The efficiency of the two trials together with the completeness, consistency and accuracy of the collected PRO data is also examined.

4 IMPLEMENTATION OF THE MCDAS

4.1 Introduction

The effectiveness of the MCDAS is tested by implementing the designed system on two clinical trials. The two case studies are conducted to ensure the system successfully collects and resolves the captured data, by meeting the requirements specified in chapter 3. The objective of the case studies is to determine the improvement in the acquisition of data rather than the success of the intervention in the conducted trials.

This chapter discusses the implementation of the three sections making up the MCDAS, namely the mobile eDiary, the website and the communication method. The first case study required a new eDiary to be developed to validate and submit the captured data. The second case study required the adaptation an existing eDiary to support PRO data submission. The website was created for the trial coordinator to administer the collected data for the two trials. The overall outcome of the trials using the MCDAS is also discussed.

4.2 Case study I: Weight loss clinical trial

4.2.1 Clinical trial

Two overweight but healthy patients were introduced to the ets-concept for weight loss [39]. These patients were required to measure their weights using a high precision digital scale supplied by the trial coordinator. The patients captured their weights on their cellular phones on a weekly basis and transmitted this data to the trial coordinator. Table 7 shows the bodily characteristics of the patients together with the cellular phone used to capture data.

Patient Id	1	2
Age	37	38
Gender	Male	Female
Height (m)	1.73	1.66
Pre-trial weight (kg)	99.5	78.0
Pre-trial BMI	33.4	28.1
Target weight (kg)	78.0	57.0
Post-trial weight (kg)	78.8	57.5
Post-trial BMI	26.5	20.7
Cellular phone	Nokia 6600 (MIDP 2.0, CLDC 1.0)	Sony Ericsson W800i (MIDP 2.0 CLDC 1.1)

Table 7 - Bodily characteristics of the two patients on the weight loss trial

The Body Mass Index (BMI) shown in Table 7 is a simple numeric measure to determine whether the patient is over-weight, under-weight or at a healthy weight. The BMI is calculated as follows [40]:

$$BMI = {weight(kg)}/{height^2(m^2)}$$

where

Under-weight	BMI < 18.5
Healthy weight	18.5 < BMI < 24.9
Over-weight	25 < BMI > 29.9
Obese	30 < BMI

The procedure used in the implementation of the MCDAS on this trial was as follows:

- A simple weight loss eDiary application was developed to capture the weight of the patients over the period of the trial.
- Both patients were given a copy of the weight loss eDiary application to load onto their cell phones.

- The patients captured and transmitted their weight on a weekly basis i.e. every Monday for patient 1 and every Friday for patient 2 (Appendix A).
- A website was developed where the trial and patient details were added.
- The website was used by trial coordinator for administering the captured data and generating data queries.
- The patient used the mobile eDiary to respond to these generated queries.

The MCDAS was used for this trial to ensure the capture of complete, consistent and accurate PRO data.

4.2.2 MCDAS

Mobile eDiary

The weight loss eDiary was used for capturing and transmitting the patient's weight, on a weekly basis. This mobile application was developed to validate the captured data, to ensure successful data transmission and to respond to queries generated by the trial coordinator. The developed application met all the requirements specified in chapter 3.

The eDiary application was developed in J2ME. This platform is supported by the majority of cellular phones and requires no development software costs. The application was created with simplicity in mind to ensure that it could be implemented on even the most basic J2ME cellular phone. The requirements for the weight loss eDiary are the following:

- J2ME with MIDP 2.0 and CLDC 1.0;
- GPRS capabilities;
- 9kB of available memory.

Figure 27 illustrates the flow of control for the developed weight loss eDiary application. The application is divided into five sections, namely authorisation, data capture and validation, query resolution, data submission and the web server response.

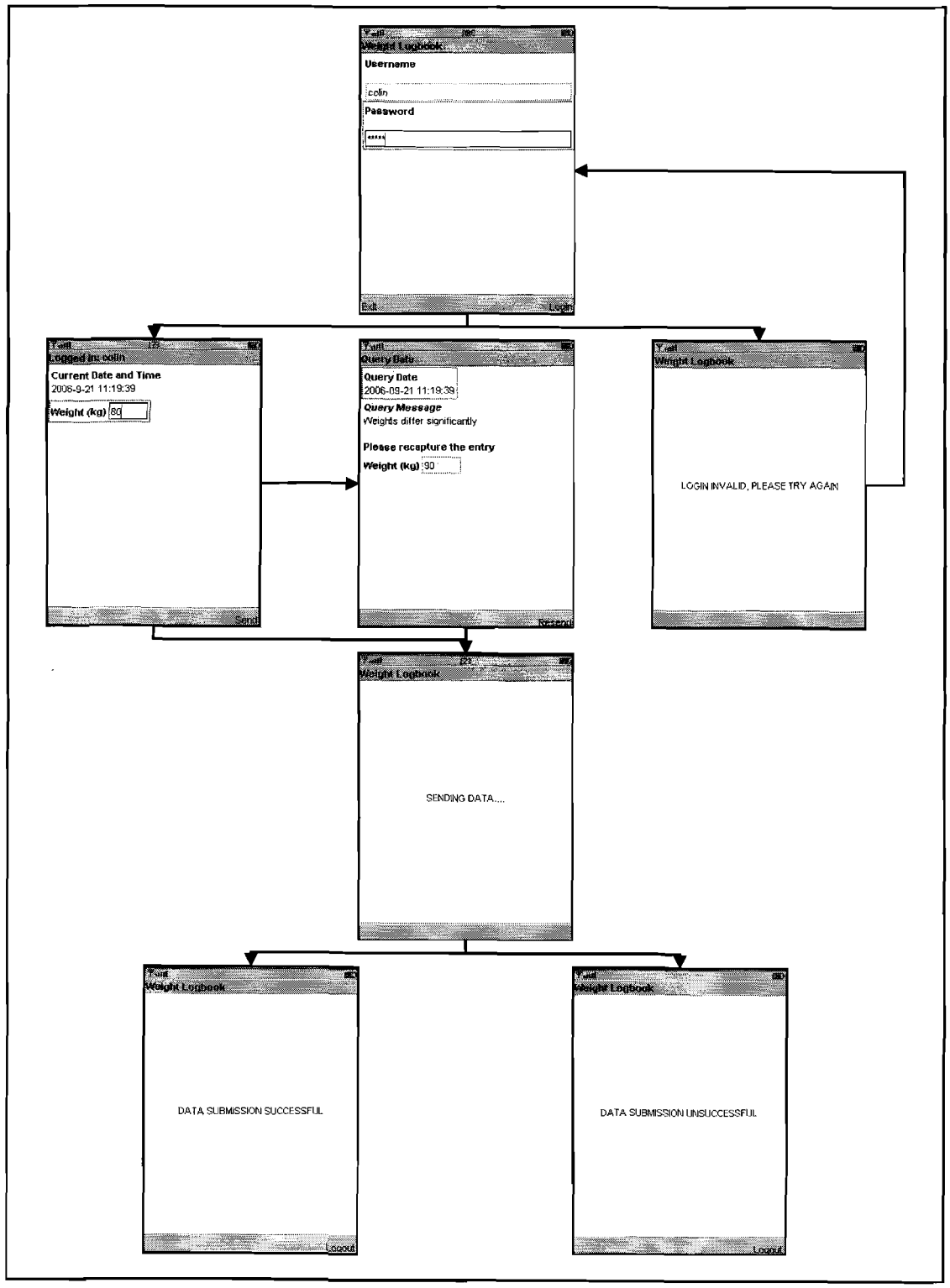


Figure 27 – The weight loss eDiary

Authorisation

The application begins by requesting authorisation from the patient. This process includes:

- assigning a username and password to the patient prior to the trial;
- logging in to the mobile eDiary using the assigned login details;
- notifying the patient when the login was unsuccessful and returning to the login form.

Data capture and validation

When the login is successful the patient is sent to the weight logbook to capture his or her weight for the current week. The logbook contains the current date and time, which is used to time stamp the data, as well as text field for capturing the patient's weight. The eDiary validates the captured data entry by:

- ensuring a value is entered;
- limiting the entry to only numeric values;
- limiting the weight between 20 kg and 200 kg.

These validations reduce the possibility of incorrect data capture by the patient.

Query resolution

After the patient has completed his or her weight for the current week, the eDiary sends a request to the server for outstanding data queries. The eDiary sends the username and password of the patient to the server and receives the data query as a response. If any queries exist, the eDiary will display the date and time the queried entry was captured, the entry error and a text field to re-capture the entry.

Data submission

The patient then selects to send the data. The data submission process includes:

- sending the captured data to the server;
- sending the query response;
- logging out of the server.

This process can be interrupted by an unsuccessful login to the server or an error while querying the database.

Web server response

Once the data is received by the server it is saved into the database and a response is returned. The response specifies whether the data was successfully saved into the database. The patient is informed of the response and required to logout of the application. If the data transmission is unsuccessful the data is kept on the mobile device to be sent at a later stage.

Website

The objective of the website is to administer the collected PRO data. The website ensures easy access to all captured data thereby simplifying the processes of data validation. Figure 28 displays the process of using the developed website for the weight loss clinical trial to view and query collected data entries

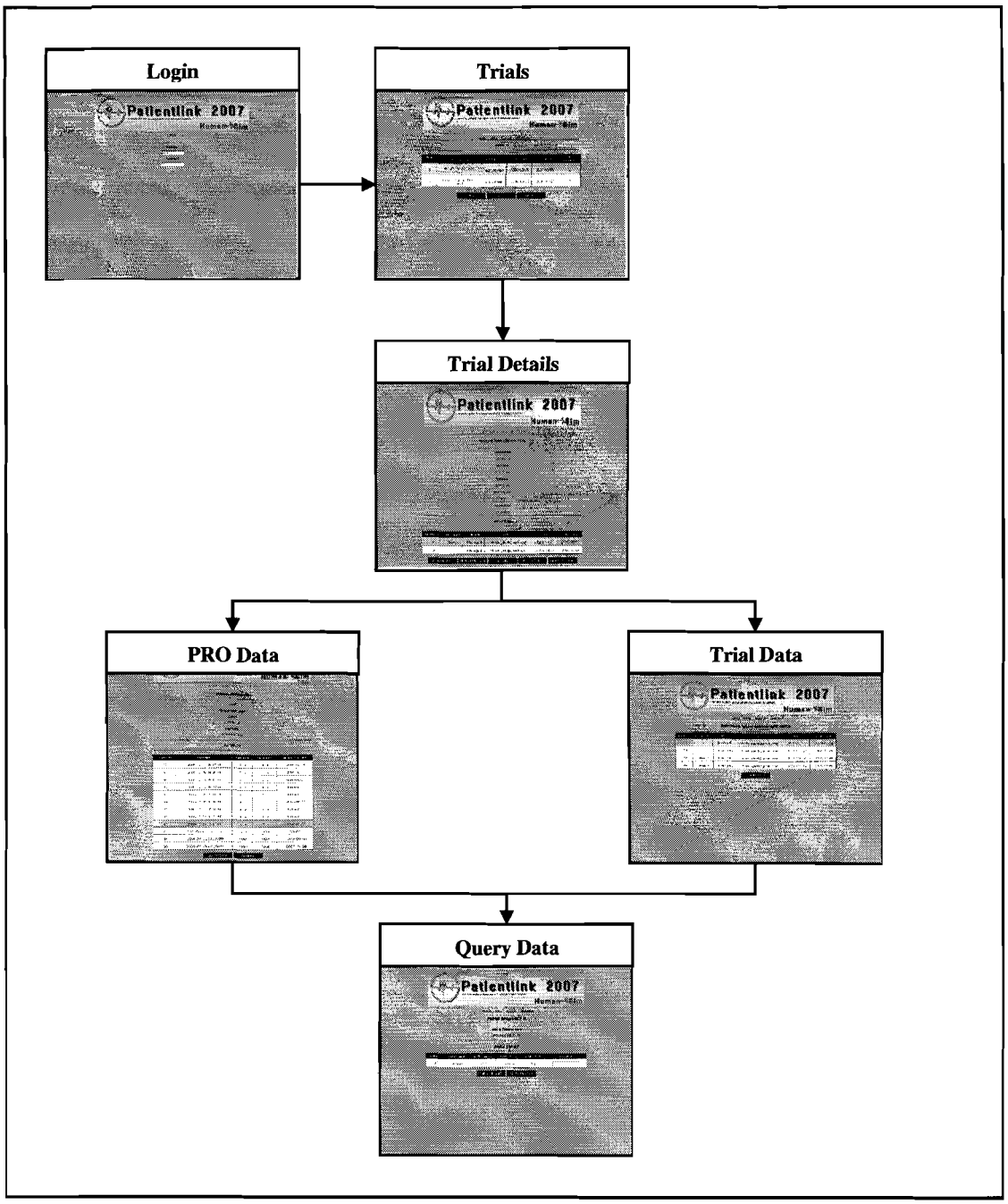


Figure 28 - Viewing and querying the captured data for the weight loss trial

The website ensures the collected data is protected by requesting authorisation from the trial coordinator. When the coordinator has successfully logged in, a list of current trials are shown. The coordinator selects the weight loss clinical trial from the list to view the trial and patient details. The coordinator can then select whether to view all unchecked

entries or view only the captured entries for the selected patient. Finally, an entry from the list of data can be selected to either accept the data or generate a query.

The web pages displayed in Figure 28 are described below. The login web page is simply a login form used to capture the coordinator's username and password.

Trials

Prior to a trial, the patient and trial details are added to the website. Figure 29 illustrates the web page that displays a list of current trials being conducted by the coordinator. The light blue row indicates the trial that is currently selected, in this case the weight loss clinical trial. A trial can be added to the list by either capturing the details or importing the details from an external comma separated values (csv) file.

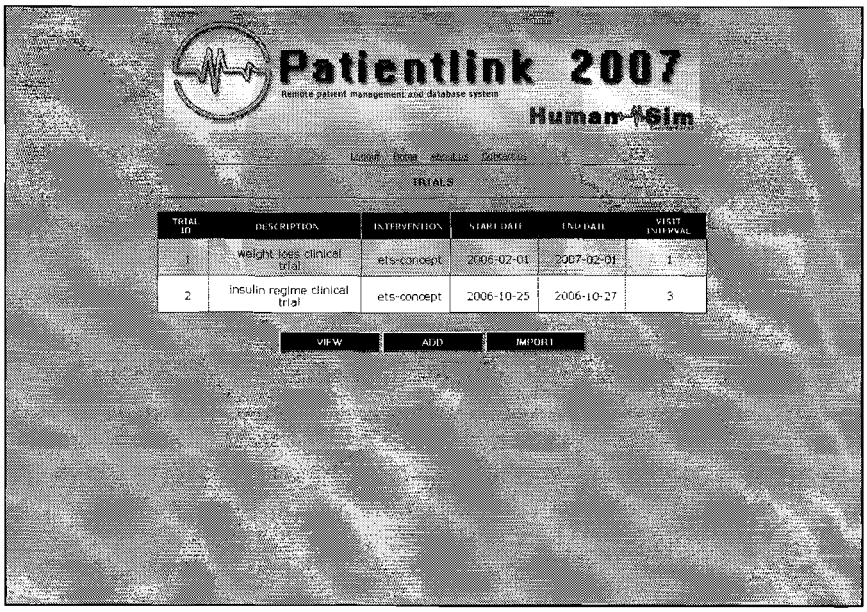


Figure 29 – The list of trials being conducted

Trial Details

After selecting to view the weight loss trial, the web page in Figure 30 is displayed. This shows the details of the weight loss clinical trial, together with a table of the two monitored patients. The coordinator can select whether to add or import a new patient,

edit a selected patient, view a selected patient's captured data or view the captured data for the entire trial.

Figure 30 – The weight loss clinical trial details

PRO Data

Figure 31 illustrates the details and submitted PRO data for patient 1. The entries within the PRO data table are displayed in different colours. The colours represent the following entry states:

- Blue – The entry has been checked and validated (Accepted data);
- Orange – The entry has been checked but not validated (Unresolved queries);
- Red – The entry has neither been checked nor validated (Unchecked data).

The different colours aid the coordinator in locating the patient's unresolved entries and unchecked data. The coordinator can select an unresolved entry to obtain the patient's contact details. For an unchecked data entry, the coordinator can either generate a query or accept the data entry.

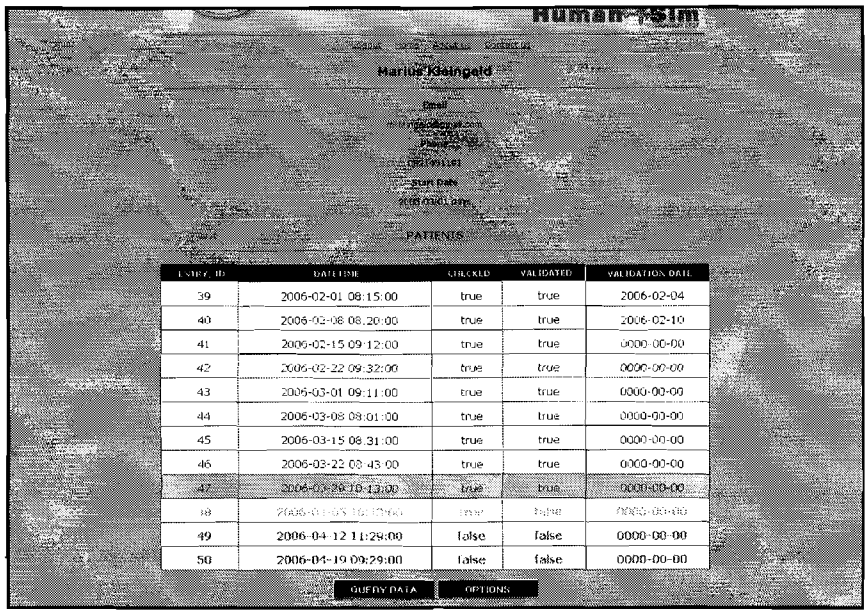


Figure 31 - The list of PRO data for the selected patient under the weight loss trial

Trial Data

Figure 32 shows a table of all unchecked PRO data for the trial. The table ensures that the coordinator is aware of all submitted PRO data that needs to be checked and validated. The coordinator can select an entry from the table and query the data.

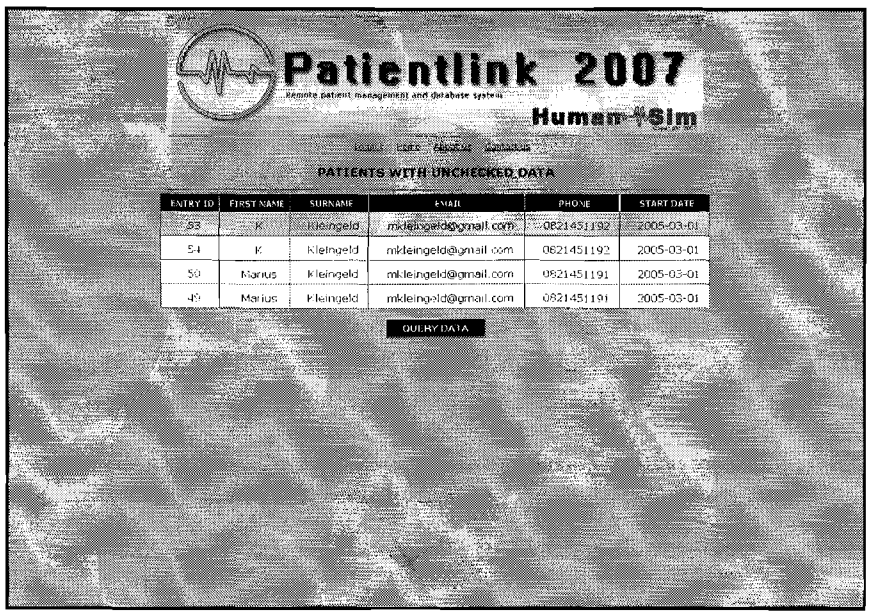


Figure 32 – The list of patients with unchecked data for the weight loss trial

Query Data

Figure 33 illustrates the query form for the selected entry. On this form the coordinator can either accept the entry or generate a query. If the coordinator selects the latter then he or she is required to enter a reason. This reason or query message is saved in the database and received by the patient's cellular phone once he or she logs in. When the coordinator accepts the weight, the entry is saved as 'valid' and cannot be updated again.

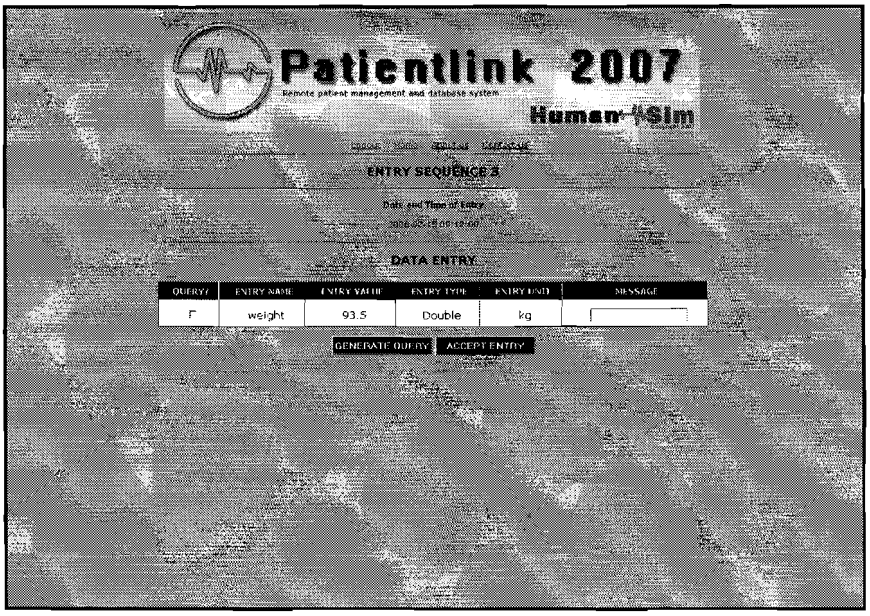


Figure 33 – The web page used to query data entries

The website was developed using the three following languages:

- MySQL – used for creating and managing the database designed in chapter 3.
- PHP – used for querying the MySQL database (adding, removing, selecting, updating entries in the database), creating and terminating user sessions, protecting authorised web pages and displaying the results on the web page.
- Javascript – used for developing the selectable rows in a table, validating completeness of patient and trial details and for setting variables posted between the web pages.

Communication method

The data format specified in chapter 3 is used for the submission of data from the cellular phone. The following demonstrates a single data entry sent by the patient's cell phone:

PATIENT_ID – 1

DATETIME – 2006-02-13 08:15

ENTRYSEQ – 1

ENTRYSTR – 93.6

ENTRY_NAMES – weight

ENTRY_TYPES – 3

ENTRY_UNITS – kg

QUERY_RES – 96.0

QUERY_ID – 1

The data sent from the cellular phone consists of the weight captured for the current week and the response to an existing query. QUERY_RES and QUERY_ID are optional fields that are only submitted by the cellular phone when responding to a query. The QUERY_RES value will replace the previous entry in the database and the query will be deleted from the QUERY table. The state of the data entry will be changed to unchecked to ensure that the coordinator rechecks the entry.

4.2.3 Outcome

Figure 34 and Figure 35 illustrates the graphs of the captured results (Appendix A) for the two patients over a 12 month period. The blue continuous lines indicate the weights initially captured by the patients on their cellular phones. The peaks on the blue graph represent possible errors while the red dots indicate the correct weights recaptured by the patient after responding to a query. The coordinator identified the drastic changes between weights and generated the appropriate queries which were resolved by the patient.

In Figure 34 the captured results for patient 1 are shown. The four peaks represent the weights that were incorrectly captured and successfully resolved. Figure 35 illustrates the captured results for patient 2, where 2 incorrect entries were resolved. The coordinator noticed the significant change in weight from one week to the next and generated the corresponding query. The query was received by the patient the following week when he or she logged in to capture a new entry. The patient then responded with the corrected entry.

The queries generated by the coordinator for patient 1 were for the following errors:
69kg was entered instead of the intended 96kg;
96.1kg was entered instead of the intended 91.6kg;
89.1kg was entered instead of the intended 81.9kg;
87.2kg was entered instead of the intended 78.2kg.

In the case of patient 2, the following errors were queried and successfully resolved:
77.1kg was entered instead of the intended 71.7kg;
61.6kg was entered instead of the intended 66.1kg.

All errors were created by the patient accidentally swapping values around (e.g. 69 and 96). The eDiary could possibly be updated to eliminate these errors by storing the previous entry and comparing it to the currently captured entry. The patient would then be required to recapture the invalid entry before submission. This validation would remove all the errors that were captured during this trial.

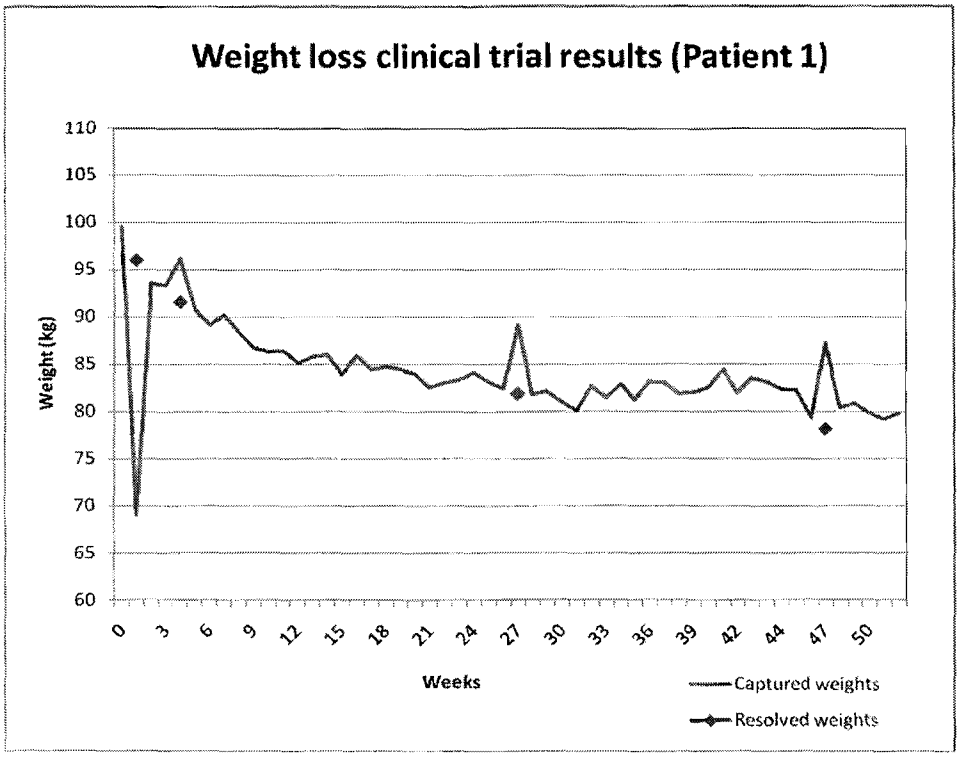


Figure 34 - Weight loss clinical trial results for Patient 1

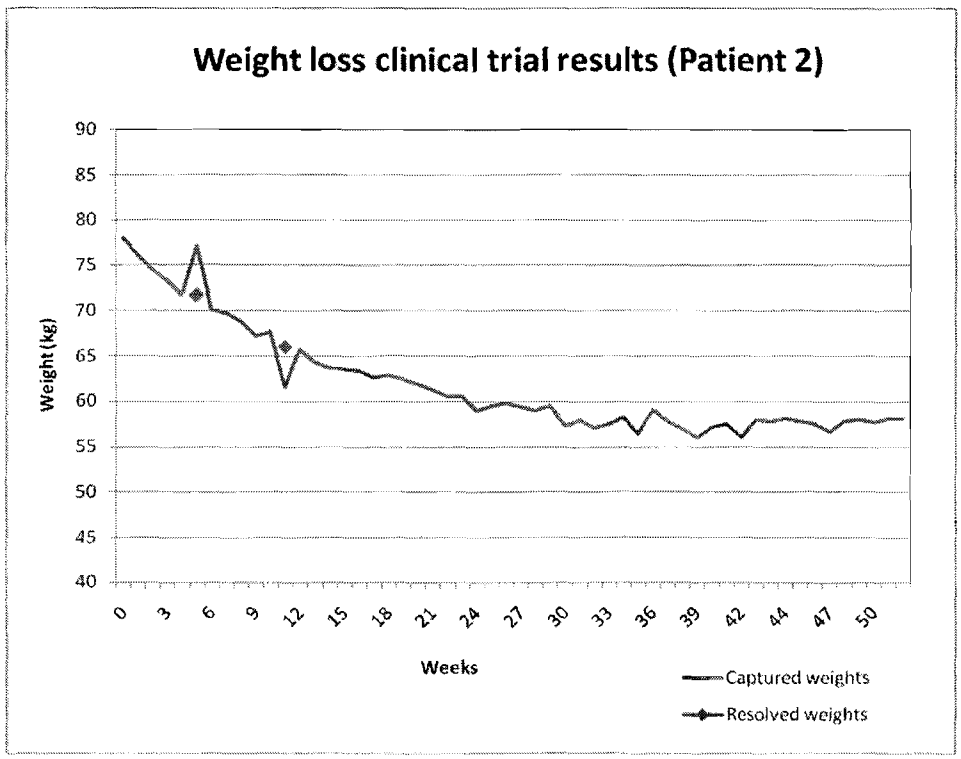


Figure 35 - Weight loss clinical trial results for Patient 2

In certain instances it may have been possible for the patient to capture an incorrect weight that differed from the intended weight by only a few kilograms. These errors would not be noticed by the coordinator and would remain in the final data. However, these small errors would not influence the overall outcome of the trial.

In summary, the incorrect entries identified by the trial coordinator were easily and successfully resolved by the patient. Furthermore, the MCDAS has shown a significant improvement over existing PDC and disconnected eDiary systems. With the use of MCDAS, incorrect values were identified and resolved much earlier in the trial process, thereby yielding more accurate, reliable, meaningful and complete results.

Utilising the MCDAS in a weight loss trial introduces another major advantage. The trial coordinator can monitor the patient and ensure that he or she is following a specified diet plan correctly. If the current diet plan is not working correctly the coordinator can adjust the plan for the specific patient. This ensures that the trial is conducted in the required manner and the correct results are obtained.

4.3 Case study II: Insulin regime clinical trial

4.3.1 Clinical trial

The objective of the insulin regime clinical trial was to determine the correct insulin regime for diabetic patients. The trial originally collected PRO data by utilising paper diaries (logbooks) that were completed on a daily basis. The patients were required to capture their daily food intake, exercise activities, blood glucose measurements and insulin bolus values. The date and time, description and value of each of these entries were logged by the patient.

After the duration of the trial, the paper diaries were collected and the information was captured by the trial coordinator on computer. When errors were found, the coordinator

generated a paper query and submitted it to the patient. The patient then corrected the queried data and sent it back to the trial coordinator. This process was repeated until the data was correctly captured.

The captured data was then utilised by the *"Automated type 1 diabetes blood glucose control diagnostic system"* [41]. This system is used to assist medical personnel in determining the blood glucose control performance for Type 1 diabetic patients. The system utilizes the logged information to determine the glucose and insulin sensitivity of the patient.

Appendix B illustrates a paper diary completed over a period of 3 days. In certain instances the entries in the diary are illegible and incomplete. This made it difficult for the coordinator to capture accurate and complete data on computer. There was also no way of determining whether the patient captured the data on the specified date and time. The patient could have completed the diary the day of a site visit, thereby affecting the accuracy and consistency of the collected data.

The PDC approach used for this trial experienced the problems that were discussed in chapter 3. The data captured was inaccurate, incomplete and inconsistent. The time associate with resolving queries was prolonged and the queries were often misunderstood. This process of data acquisition was improved by the use of the MCDAS.

A type 1 diabetic patient was used for this case study. The patient's details are shown in Table 8. The table also specifies the patient's Target Glucose, Total Daily Dosage (TDD) long-acting (basal) insulin, TDD short-acting (bolus) insulin and the ets Required Daily Allowance (RDA).

Patient ID	3
Gender	Female
Age	18
Weight (kg)	75

Height (m)	1.66
Activity level	Med
Target glucose (mmol/l)	4
TDD basal insulin (U)	22
TDD bolus insulin (U)	42
Ets RDA (ets)	25
Cellular phone	Nokia 6600 (MIDP 2.0, CLDC 1.0)

Table 8 - Patient details for insulin regime trial

The patient captured her information over a 3 day period using the developed mobile eDiary application. The eDiary was developed to capture the patient's food intake, exercise activities, blood glucose measurements and insulin bolus values on a daily basis. The data was sent to the trial coordinator once a day after all entries had been captured. The data was then administered and queried by the trial coordinator using the website.

The objective of this case study was to determine the improvement of data acquisition using the MCDAS over the previously used PDC method. The MCDAS was used for this case study to aid in the process of PRO data acquisition.

4.3.2 MCDAS

Mobile eDiary

A cell phone application (ets insulin bolus calculator) was previously developed to capture the same PRO data as the paper diary [42]. The application was used to calculate accurate insulin boluses for Type 1 diabetics. This application however did not submit the data directly to the trial coordinator. There was also no electronic system for administering the captured PRO data.

This ets insulin bolus calculator is an implementation of a disconnected eDiary system. The patient is required to capture the data on a daily basis for the duration of the trial.

When the trial is completed the patient returns the cell phone to the trial coordinator to transfer the data onto a PC. This diary however did not utilise the communication capabilities provided by the cellular phone.

The mobile eDiary was adapted to support direct data transmission for this case study. The existing application already ensured the validation, saving and time stamping of the captured data. The only required additions to the application were, authorised eDiary access, data submission and query resolution capabilities.

The existing ets insulin bolus calculator was developed using Appforge Crossfire under Symbian OS. A data submission library was created and added to the existing application for authorisation, data submission and query resolution. The library was created independent to the eDiary so that it could be used by other Symbian applications. The cell phone requirements for the developed application are:

- Symbian OS with Appforge Crossfire;
- GPRS capabilities;
- 360kB of available memory.

Figure 36 illustrates the data submission process using the ets insulin bolus calculator. The application is also divided into five sections, namely authorisation, data capture and validation, query resolution, data submission and the web server response.

Authorisation

The process begins by requesting authorisation from the patient. As previously mentioned, the trial coordinator assigns a username and password to each patient prior to the trial. If the login is unsuccessful the eDiary returns to the login form.

Data capture and validation

When the login is successful the main menu of the previous application is displayed. The patient logs his or her daily food intake, exercise activities, blood glucose measurements

and insulin bolus values via this menu. The patient can also view all the entries for the current day via the logbook. This menu is described in more detail in [42].

Query resolution

Before the captured data can be sent, the eDiary sends a request to the server for outstanding data queries. If a query exists, the date and time of entry and the query message is displayed. The patient then has the option to reselect the intended entry.

Data submission

Once the patient has captured all the entries and resolved all queries for the current day, he or she is required to send the logbook data. The patient may only send the logbook entries once a day. If the entries have previously been sent for that day, the new data overwrites the old data in the database. When the data is successfully sent, the patient is informed and the data is removed from the cellular phone

Web server response

As previously mentioned, the response returned by the server specifies whether the data was successfully saved into the database. The patient is informed of the response and logs out of the application. If the data transmission is unsuccessful the data is kept on the mobile device to be sent at a later stage.

The data submission process described in this case study is the same as for the previous case study. The only difference is the approach used for capturing the data entries. The first case study required the patient to capture his or her weight by entering numerical values while this case study requires the patient to select an entry from a list of options.

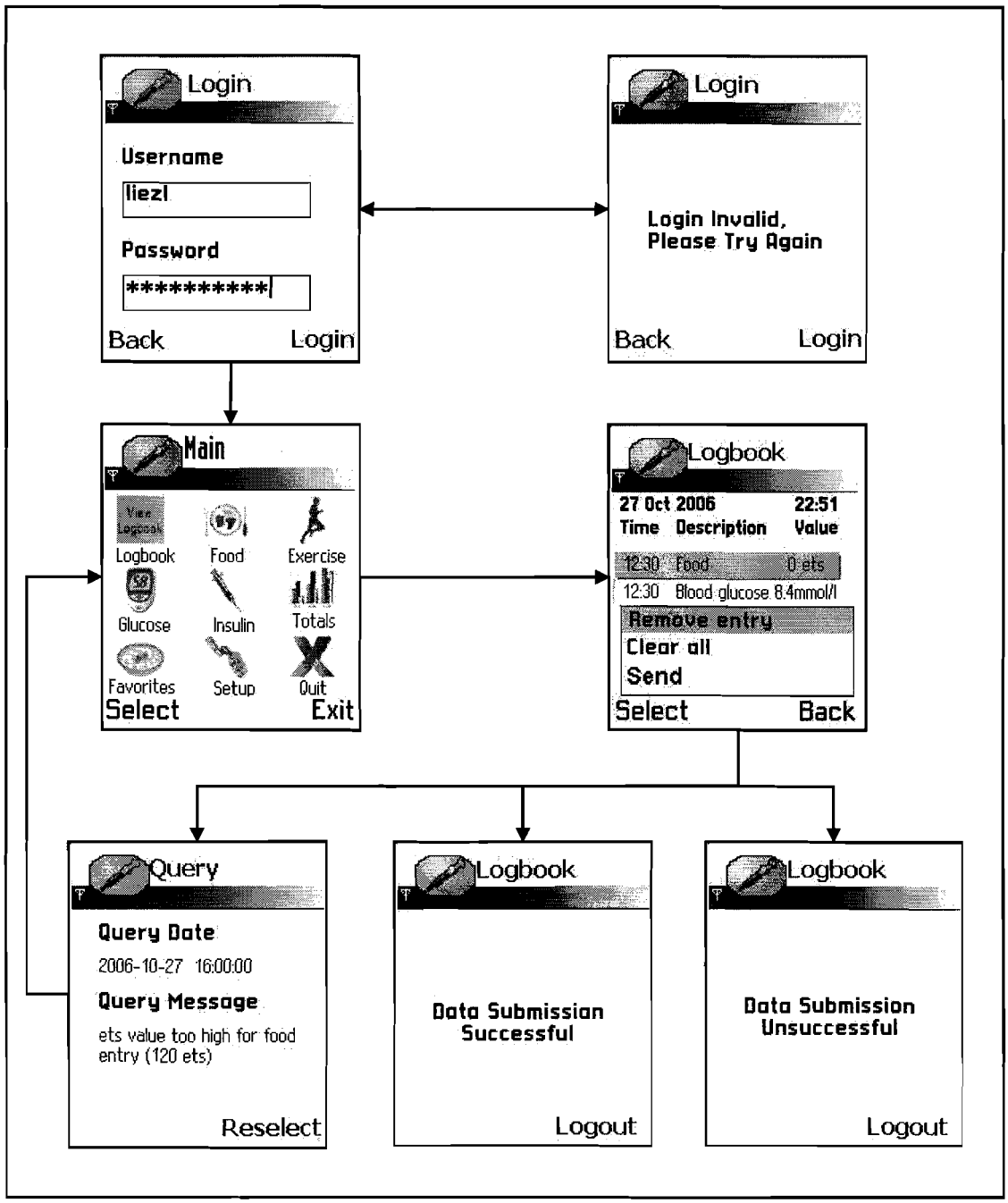


Figure 36 – ets insulin bolus calculator with data submission

Figure 37 shows the logbook of the first day of data capture for the patient under the trial. The data is logged from 12:30 PM until 9:30 PM. These logbook entries are the data sent at the end of the day to the trial coordinator. The logbook displays the date and time of capture as well as the types and values of each entry.

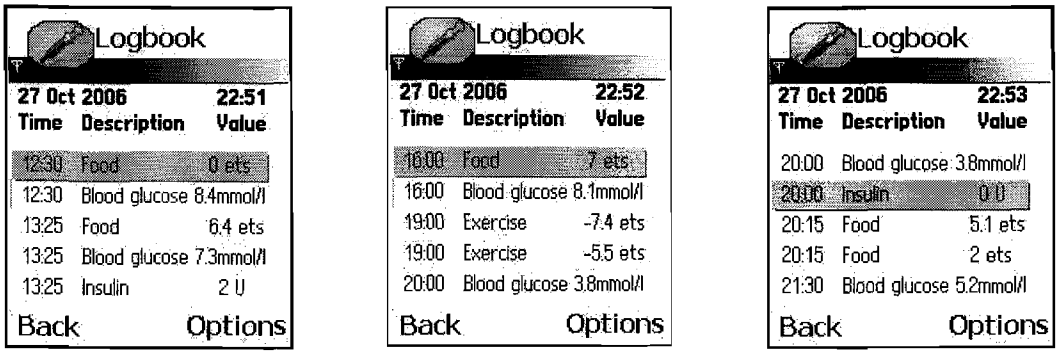


Figure 37 - Logbook for the third day of data capture

Website

As previously mentioned the website is responsible for administering the received PRO data. The website is structured in such a way that it can be used for more than one clinical trial at a time as illustrated in Figure 29. The same web pages are used for all clinical trials added to the website. The only difference is the data that is displayed.

Figure 38 illustrates the details for the insulin regime clinical trial together with the single patient under this trial. Figure 39 shows a table of all the entries for the first day of data capture. As it was previously mentioned the entries in red are 'unchecked' and 'invalid' which is the case with all the entries in this table. The rest of the web pages are the same as described in the weight loss case study.

Figure 38 - The insulin regime clinical trial details

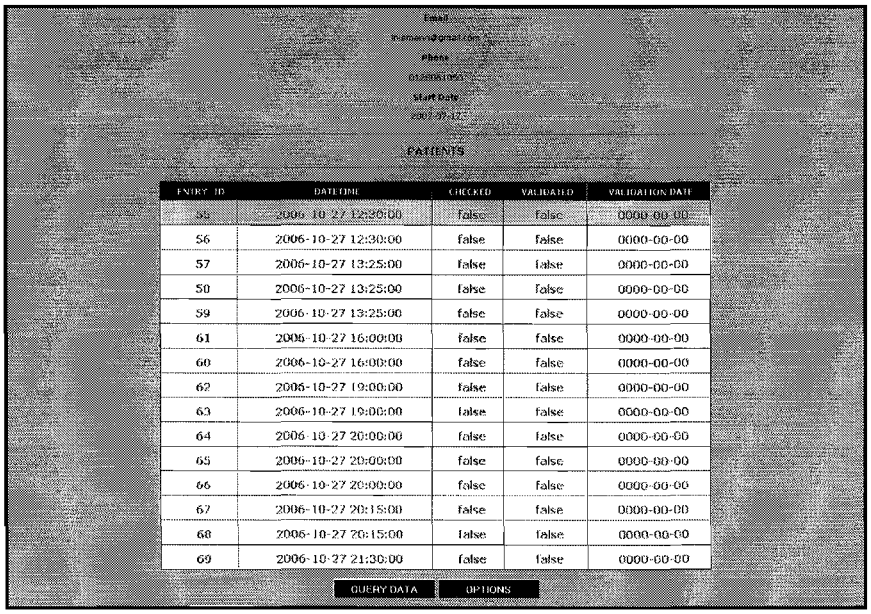


Figure 39 - List of PRO data for the third day of capture

Communication method

The data is sent from the cellular phone to the web server using the format specified in chapter 3. The following shows the first five data entries sent on the first day of the trial:

PATIENT_ID – 3

DATETIME – 2005-07-01 12:30, 2005-07-01 12:30, 2005-07-01 13:25, 2005-07-01 13:25, 2005-07-01 13:25

ENTRYSEQ – 3

ENTRYSTR – 0, 8.4, 6.4, 7.3, 2

ENTRY_NAMES – food, blood glucose, food, blood glucose, insulin

ENTRY_TYPES – 3, 3, 3, 3, 2

ENTRY_UNITS – ets, mmoll, ets, mmoll, u

QUERY_RES – 3.4

QUERY_ID - 3

The entries for each day are sent together in one string. When this data is received by the web server it is separated and saved into the database. The ENTRY_NAMES has four possibilities namely food, exercise, insulin and blood glucose. The ENRTY_UNITS has three options namely ets, u, and mmoll. As previously mentioned QUERY_RES is the response to a query generated by the trial coordinator.

4.3.3 Outcome

Appendix B illustrates the data that was obtained over the duration of the trial from the diabetic patient. All the entries that were captured by the patient were accepted by the coordinator. There were no queries generated and no entries that were required to be resolved by the patient. This case study however was also conducted to compare the time associated with data acquisition using PDC, the disconnected eDiary and the MCDAS.

Previous trials collected diabetic patients' data using the PDC and disconnected eDiary system. The time associated with these trials was used to compare these systems with the implemented MCDAS.

Table 9 illustrates the time comparison between these different methods. The table compares the time it takes to perform the following activities:

- PRO data received by trial coordinator – The advantage of the MCDAS over the PDC system and the disconnected system is that the data could be reviewed on a daily basis.
- Data capture on PC by trial coordinator – In the case of the disconnected system and the MCDAS the data did not have to be recaptured by the trial coordinator. However with the disconnected system, the PRO data was downloaded onto a PC using a USB cable (time includes setting up the connection). Whereas, with the MCDAS the data was automatically uploaded to the web server.
- Query resolution –Both the PDC and disconnected system required a two way paper postal method to resolve queries, whereas, the MCDAS allowed queries to be resolved electronically.

	PDC	Disconnected eDiary	MCDAS
PRO data received by trial coordinator	After 3 days	After 3 days	Daily
Data capture on PC by trial coordinator	1 hour	10 minutes	Automatically
Query resolution	10 days (includes postage)	10 days (includes postage)	1 day

Table 9 - Time comparison

The results clearly showed the time savings achieved by using the MCDAS.

4.4 Summary

This chapter discussed the implementation of the MCDAS on two clinical trials. The first trial used the MCDAS to capture 2 patients' weights on a daily basis for the duration of 12 months. All the data was successfully captured and resolved. The second trial made use of the MCDAS for capturing a patient's daily food intake, exercise activities, blood

glucose measurements and insulin bolus values. The system was shown to improve the duration involved with capturing data and resolving queries, compared to the previously used PDC.

Both clinical trials captured complete, consistent and accurate PRO data. The system generated and resolved queries electronically without the prolonged duration of resolving paper queries. The clinical data acquisition process was simplified and the overall duration of the trials were decreased. The two case studies successfully showed that the MCDAS not only improves the quality of the captured data but also reduces the cost and time associated with a clinical trial.

CHAPTER 5

CLOSURE

This chapter concludes the study and discusses suggestions for future work. Also mentioned are the contributions made by this study.

5 CLOSURE

5.1 Introduction

Previous research has shown that the majority of clinical trials still make use of PDC to record data. Although attempts have been made to speed up this process and deliver more accurate results, systems are still proven to be inadequate and are not widely adopted. Existing systems usually require high initial hardware costs and provide limited access to the captured data.

For this study a system was developed to capture and administer PRO data. The system ensured that the data acquisition process was efficient by providing access to complete, accurate and consistent data. The effectiveness of the system was verified by the conduction of two different case studies. This chapter discusses the contributions made by this study as well as recommended future work.

5.2 Summary of contributions

The system was successfully developed and met the requirements specified in chapter 3. This study makes the following contributions:

- Improved PRO data: The system ensured the PRO data was accurate, complete and consistent. The data was validated on entry as well as by the trial coordinator. The coordinator would generate queries which would need to be resolved before the patient could capture more data.
- Efficient data acquisition process: The system allowed direct transmission of data from the patient to the trial coordinator. Fewer electronic queries were generated thereby reducing the time to resolve queries. The process of PRO data acquisition was simpler and faster than PDC systems.
- Easier data access and management: The website allowed easy access and administration of PRO data. This data could be accessed through the internet from

any location by authorised personnel. The coordinator could add, remove and update patient and trial information as well as view and generate queries for the submitted PRO data.

- Common mobile devices used: The system was implemented on commonly used mobile devices thereby reducing the initial hardware costs. The majority of patients already owned cellular phones which were capable of supporting the mobile eDiary.
- Patient monitoring: The trial coordinator could view the PRO data on a continuous basis after it had been submitted. The coordinator could therefore determine the effective of the clinical trial earlier than before.

5.3 Recommendations of future work

In this study a system was created that could be used by any trial no matter what PRO data was collected. However certain trials may require specific functionality that is not supplied by the system. This trial specific functionality can be developed and easily integrated with the MCDAS. The following future work is recommended:

- Allow the system to be customised for a specific trial (e.g. create additional web pages for displaying results. Allow additional information to be sent from the mobile device).
- Conduct more comprehensive case studies to test the system.
- Integrate the created standard for data submission with the CDISC standard.
- Integrate the system with existing CDMS and eCRF systems.
- Generate reports for the data exported from the website.

5.4 Novelty of this study

The acquisition of PRO data using a mobile device is not a new concept. However creating a standardised system for the collection and administration of this data is novel. The novelty of the study can be seen from the following aspects of the developed system:

- The system is standardised so that it can be utilized by any trial. Existing systems are developed for only a single trial at a time.
- The eDiary is simple and can be implemented on most mobile devices. The majority of existing eDiaries are limited to PDAs.
- The website allows easy access and administration of PRO data through the internet.

5.5 Closure

The objective of the study specified in chapter 1 was "*to develop a mobile clinical data acquisition system (MCDAS) for gathering Patient Report Outcome (PRO) data*". This objective was accomplished by successfully meeting all the requirements specified in chapter 3. The proposed '*mobile clinical data acquisition system*' could save sponsors millions by either terminating a failing clinical trial project early, or shortening the time for the intervention to the market place.

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APPENDIX A

WEIGHT LOSS PRO DATA

APPENDIX A: WEIGHT LOSS PRO DATA

Week	Patient 1				
	Mass	BMI	Change	Aim	Corrections
0	99.5	33.4		78	
1	69	32.3	3.5	78	96
2	93.5	31.4	2.5	78	
3	93.3	31.4	0.2	78	
4	96.1	30.8	1.7	78	91.6
5	90.7	30.5	0.9	78	
6	89.1	29.9	1.6	78	
7	90.2	30.3	-1.1	78	
8	88.4	29.7	0.5	78	
9	86.7	29.1	0.2	78	
10	86.3	29	-0.1	78	
11	86.4	29	0.5	78	
12	85.1	28.6	1.7	78	
13	85.8	28.8	0.4	78	
14	86	28.9	-0.6	78	
15	83.9	28.2	0.5	78	
16	85.9	28.9	-2.2	78	
17	84.4	28.4	0.6	78	
18	84.7	28.5	-0.1	78	
19	84.4	28.4	0.3	78	
20	83.9	28.2	0.4	78	
21	82.5	27.7	0	78	
22	83	27.9	-0.1	78	
23	83.3	28	-0.1	78	
24	84.1	28.3	-1.6	78	
25	83.1	27.9	-1.4	78	
26	82.4	27.7	-0.8	78	
27	89.1	27.5	0.2	78	81.9
28	81.8	27.5	0.2	78	
29	82.1	27.6	-0.8	78	
30	81	27.2	-0.5	78	
31	80.1	26.9	0.2	78	
32	82.6	27.8	0.6	78	
33	81.4	27.4	0	78	
34	82.8	27.8	-1.3	78	
35	81.2	27.3	0.7	78	
36	83.1	27.9	-0.7	78	
37	83	27.9	-0.3	78	
38	81.8	27.5	0.6	78	

39	82	27.6	0.2	78	
40	82.5	27.7	0	78	
41	84.4	28.4	-2.7	78	
42	81.9	27.5	0.9	78	
43	83.5	28.1	-2.7	78	
43	83.1	27.9	-1.6	78	
44	82.3	27.7	-1.3	78	
45	82.2	27.6	-2.3	78	
46	79.3	26.6	-0.3	78	
47	87.2	26.3	-0.4	78	78.2
48	80.4	27	-0.3	78	
49	80.8	27.2	-0.7	78	
50	79.8	26.8	-0.4	78	
51	79.2	26.6	1.2	78	
52	79.8	26.8	-0.6	78	

Table 10 - Patient 1 weights for weight loss clinical trial

Week	Patient 2				
	Mass	BMI	Change	Aim	Corrections
0	78	28.1		57	
1	76	27.4	2	57	
2	74.5	26.9	1.5	57	
3	73.3	26.4	1.2	57	
4	71.8	25.9	1.5	57	
5	77.1	25.9	0.1	57	71.7
6	70.1	25.3	1.6	57	
7	69.8	25.2	0.3	57	
8	68.8	24.8	0.2	57	
9	67.3	24.3	0.2	57	
10	67.7	24.4	-0.9	57	
11	61.6	23.8	0.4	57	66.1
12	65.8	23.7	0.3	57	
13	64.3	23.2	0.2	57	
14	63.7	23	0.1	57	
15	63.6	22.9	-0.2	57	
16	63.4	22.9	-0.2	57	
17	62.7	22.6	-0.5	57	
18	62.9	22.7	0.1	57	
19	62.4	22.5	0.2	57	

20	61.9	22.3	0.3	57	
21	61.3	22.1	-0.6	57	
22	60.6	21.8	0.1	57	
23	60.6	21.9	-0.6	57	
24	59	21.3	-0.5	57	
25	59.5	21.5	-1	57	
26	59.8	21.6	-0.7	57	
27	59.4	21.4	-0.3	57	
28	59	21.3	-0.8	57	
29	59.5	21.5	-0.7	57	
30	57.3	20.7	-0.4	57	
31	57.9	20.9	-0.7	57	
32	57.1	20.6	-0.3	57	
33	57.5	20.7	-0.5	57	
34	58.2	21	-0.4	57	
35	56.5	20.4	-0.1	57	
36	59.1	21.3	-0.5	57	
37	57.8	20.8	-1	57	
38	56.9	20.5	0.3	57	
39	56.1	20.2	-0.4	57	
40	57.2	20.6	-0.1	57	
41	57.5	20.7	-0.5	57	
42	56.1	20.2	0.9	57	
43	58	20.9	-0.8	57	
43	57.8	20.8	0	57	
44	58.1	21	-0.5	57	
45	57.8	20.8	-1.1	57	
46	57.5	20.7	-0.2	57	
47	56.7	20.5	-0.1	57	
48	57.8	20.8	0.1	57	
49	58	20.9	-0.2	57	
50	57.7	20.8	0	57	
51	58.1	21	0.1	57	
52	58.1	21	0	57	

Table 11 - Patient 2 weights for weight loss clinical trial

APPENDIX B

INSULIN REGIME PRO DATA

APPENDIX B: INSULIN REGIME PRO DATA

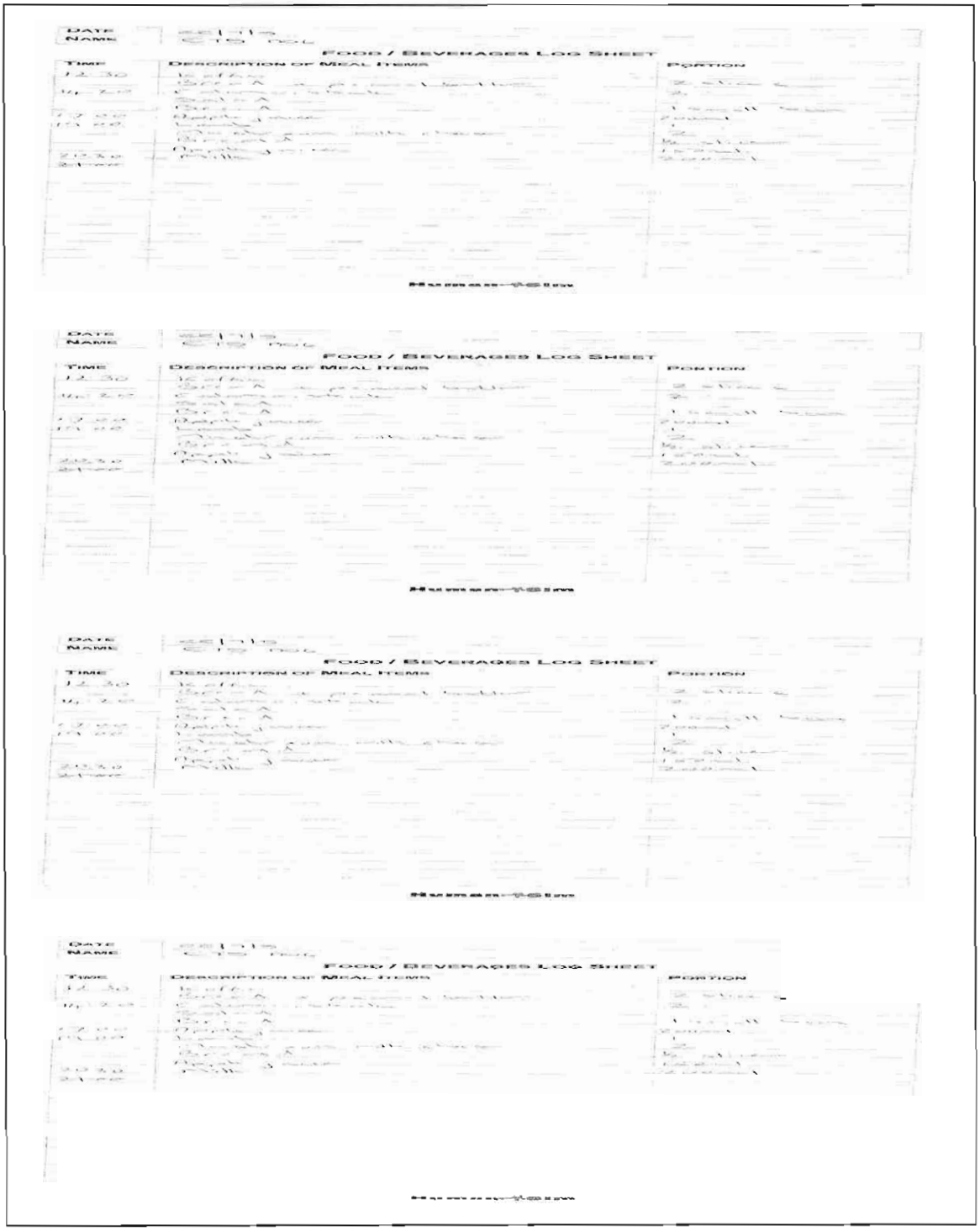

Figure 40 - Insulin regime paper diary page 1/6

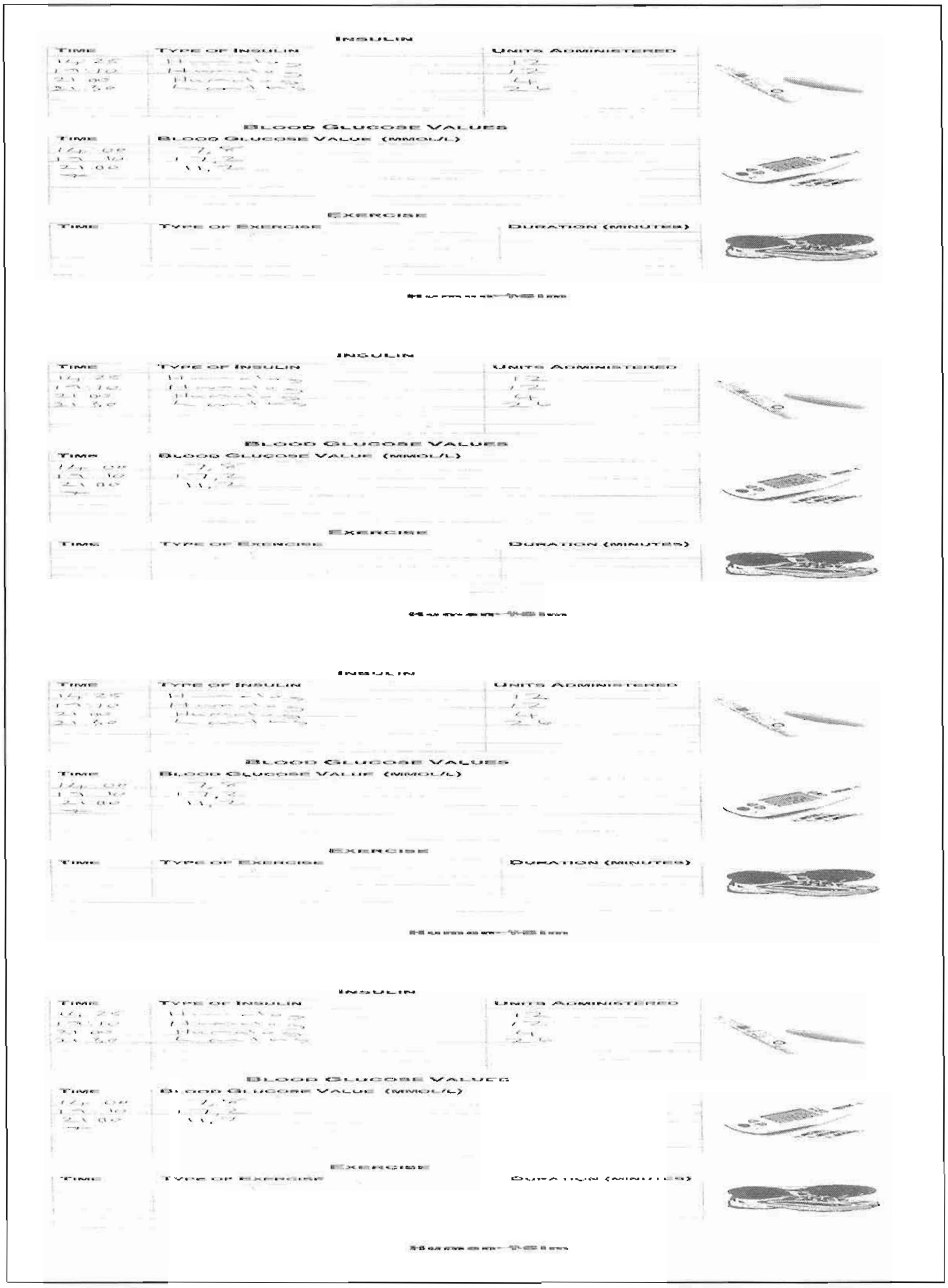

Figure 41 - Insulin regime paper diary page 2/6

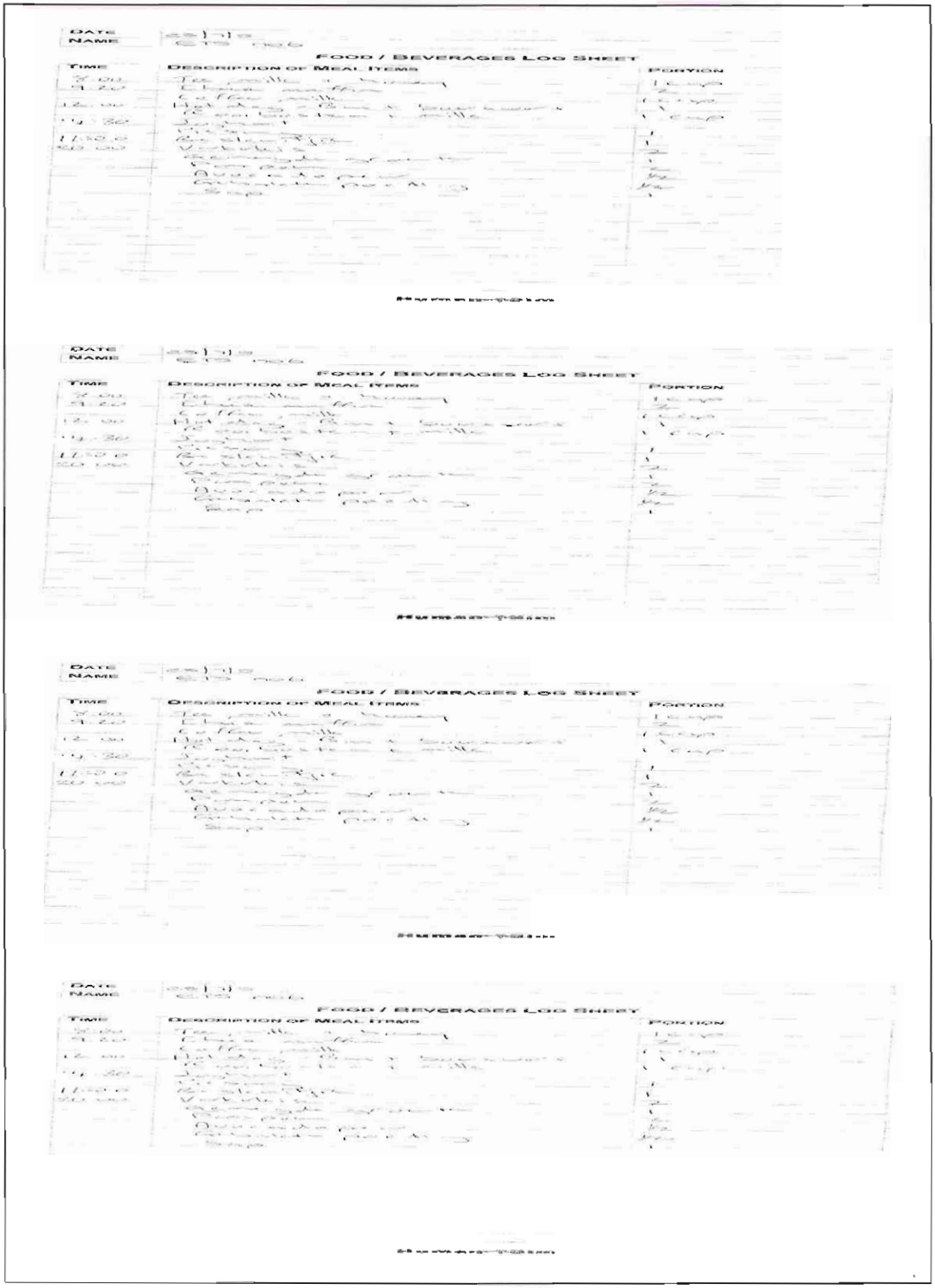

Figure 42 - Insulin regime paper diary page 3/6

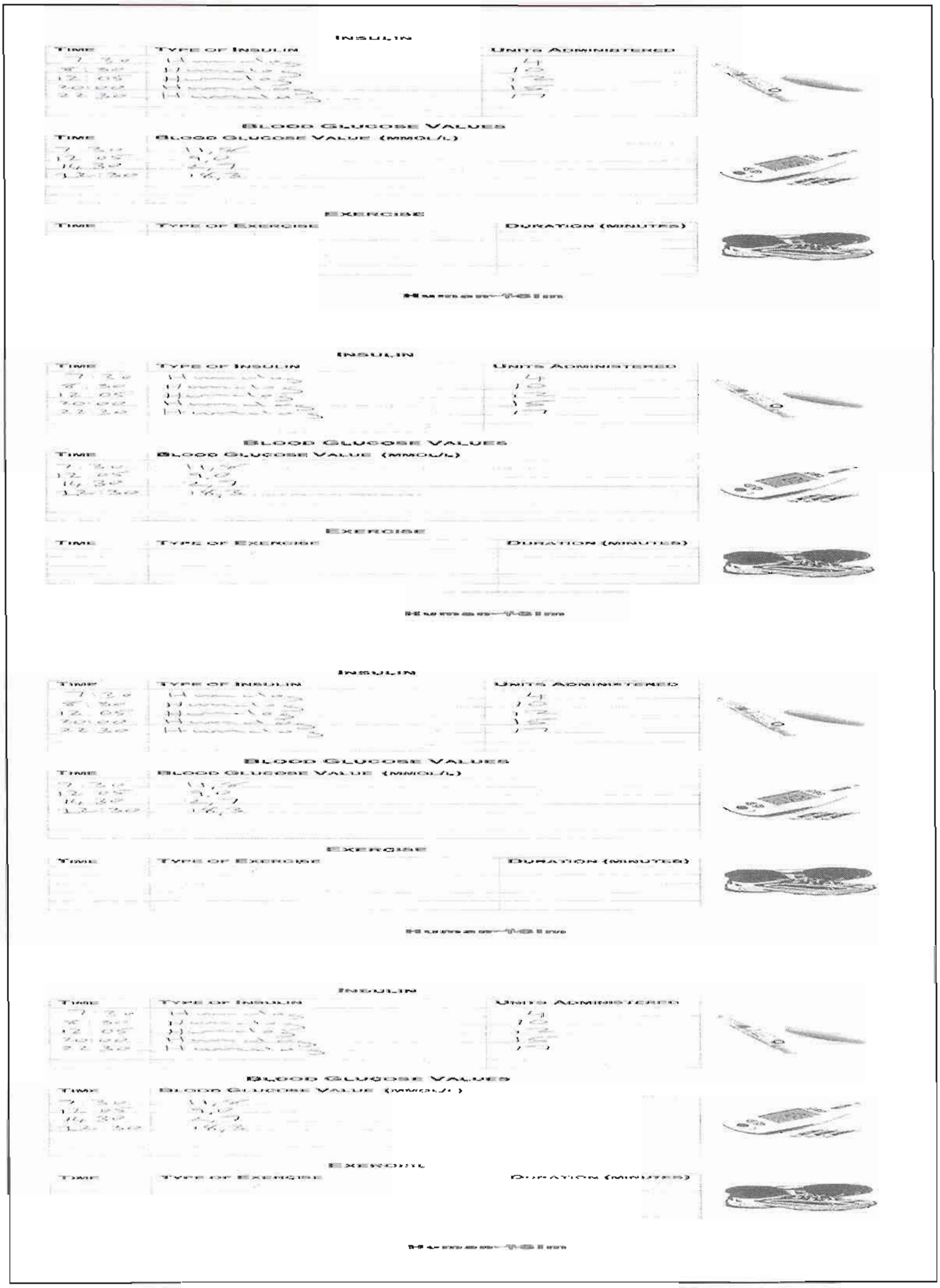

Figure 44 - Insulin regime paper diary page 4/6

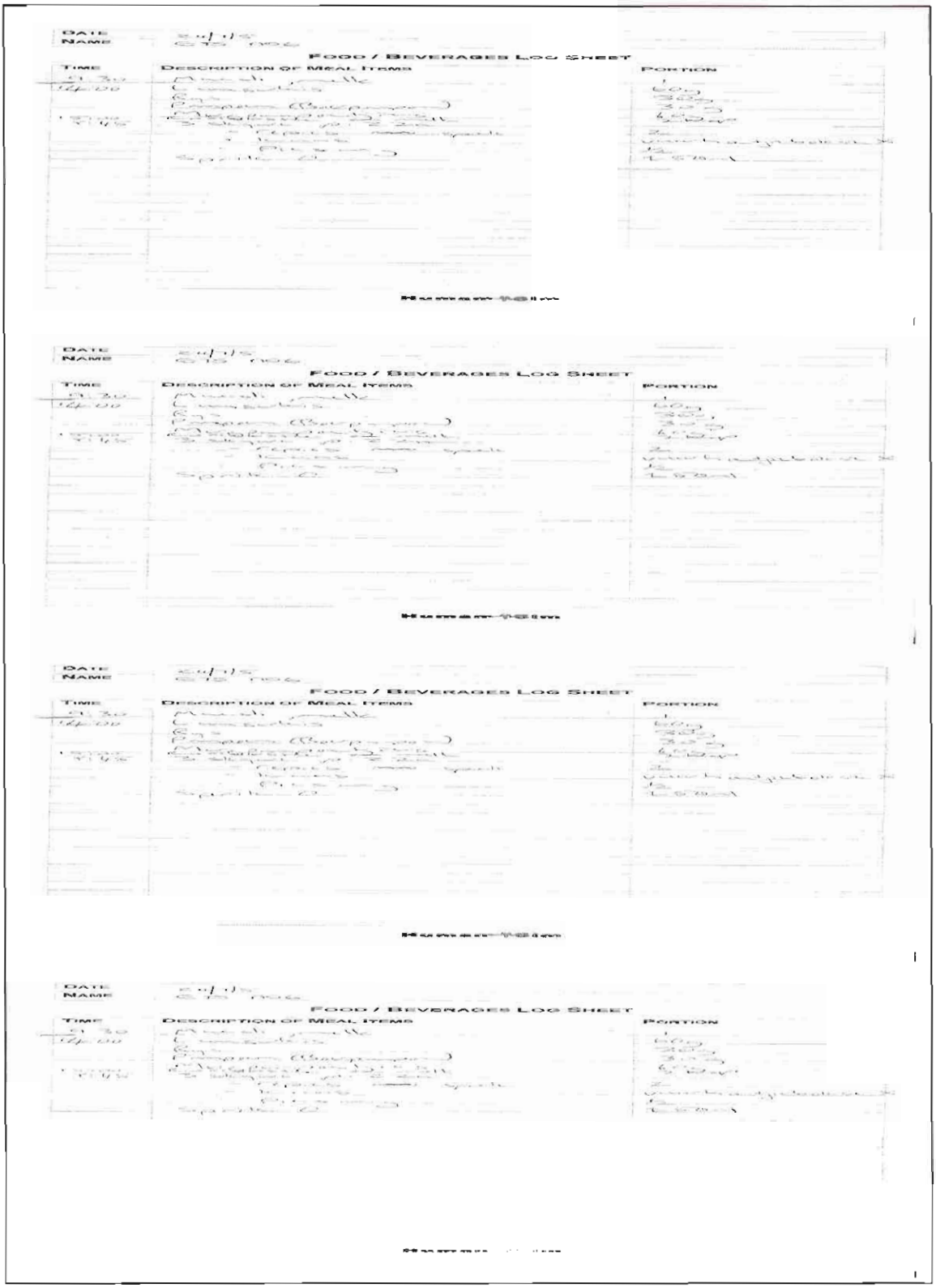

Figure 45 - Insulin regime paper diary page 5/6

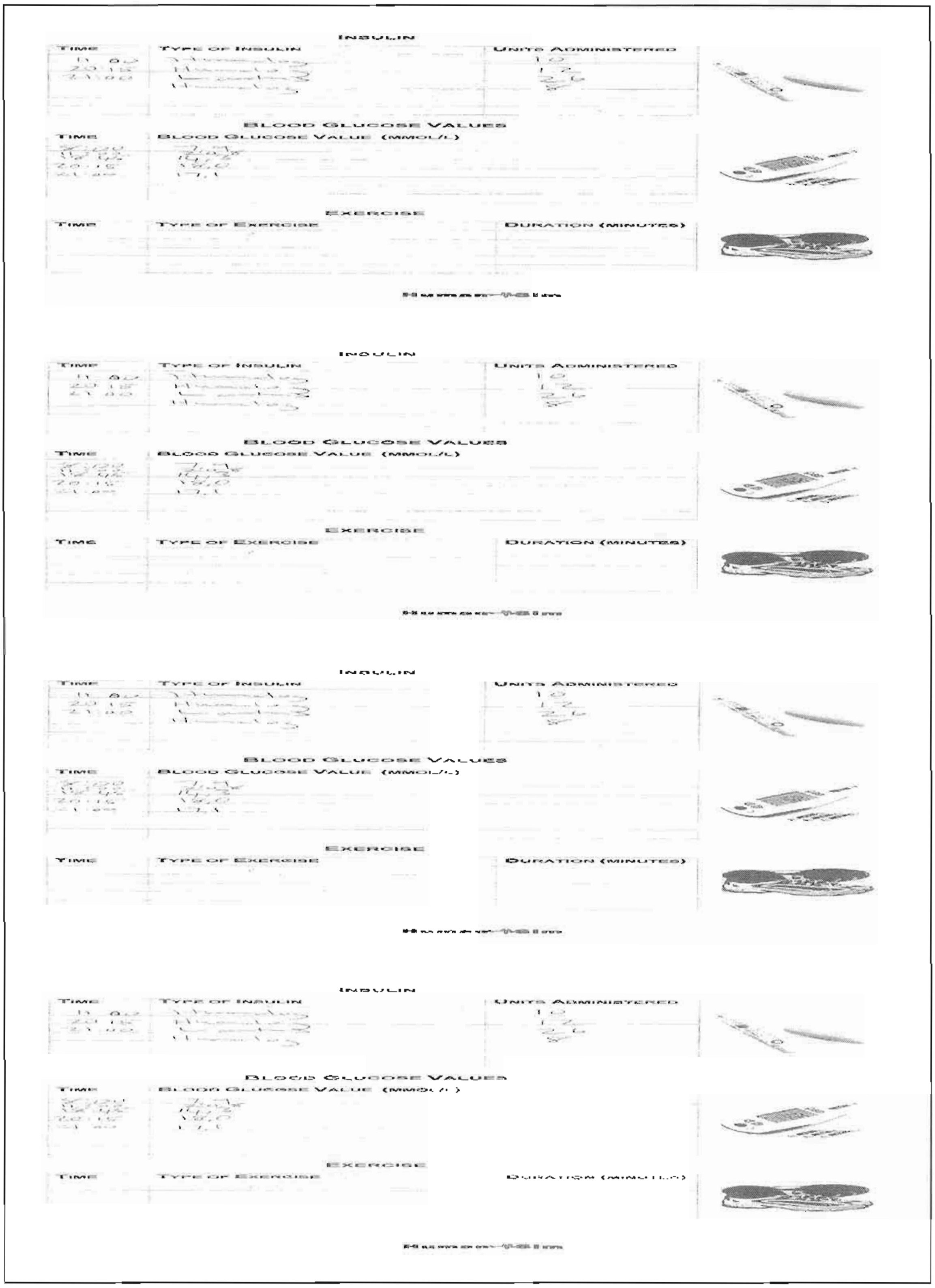

Figure 46 - Insulin regime paper diary page 6/6

Date and Time	Description	Value	Unit
2007-10-25 12:30	Food	0	ets
2007-10-25 12:30	Blood glucose	8.4	mmoll
2007-10-25 13:25	Food	6.4	Ets
2007-10-25 13:25	Blood glucose	7.3	mmoll
2007-10-25 13:25	Insulin	2	u
2007-10-25 16:00	Food	7	ets
2007-10-25 16:00	Blood glucose	8.1	mmoll
2007-10-25 19:00	Exercise	-7.4	ets
2007-10-25 19:00	Exercise	-5.5	ets
2007-10-25 20:00	Blood glucose	3.8	Mmoll
2007-10-25 20:00	Blood glucose	3.8	mmoll
2007-10-25 20:00	Insulin	0	u
2007-10-25 20:15	Food	5.1	ets
2007-10-25 20:15	Food	2	ets
2007-10-25 21:30	Blood glucose	5.2	mmoll
2007-10-26 09:00	Food	5.2	ets
2007-10-26 09:00	Blood glucose	14.6	mmoll
2007-10-26 09:00	Insulin	14	u
2007-10-26 11:00	Blood glucose	17.8	mmoll
2007-10-26 13:30	Food	0.2	ets
2007-10-26 13:30	Blood glucose	8.7	Mmoll
2007-10-26 13:30	Insulin	14	u
2007-10-26 15:30	Food	6	ets
2007-10-26 15:30	Blood glucose	2.3	Mmoll
2007-10-26 19:00	Food	3.8	ets
2007-10-26 19:00	Blood glucose	14.6	Mmoll
2007-10-26 19:00	Insulin	14	u
2007-10-26 19:00	Insulin	22	u

2007-10-26 21:00	Food	3.8	ets
2007-10-26 21:00	Blood glucose	10.9	mmoll
2007-10-27 05:00	Food	2.3	ets
2007-10-27 07:45	Food	5.2	ets
2007-10-27 07:45	Blood glucose	13.3	mmoll
2007-10-27 07:45	Insulin	14	u
2007-10-27 09:30	Food	3.2	ets
2007-10-27 13:00	Food	12.8	ets
2007-10-27 13:00	Blood glucose	10.7	mmoll
2007-10-27 13:00	Insulin	14	u
2007-10-27 15:00	Blood glucose	5.8	mmoll
2007-10-27 17:00	Food	8	ets
2007-10-27 19:00	Blood glucose	7.9	mmoll
2007-10-27 19:00	Exercise	-7.4	ets
2007-10-27 19:00	Exercise	-5.5	ets
2007-10-27 20:00	Blood glucose	5.2	mmoll
2007-10-27 20:45	Food	5	ets
2007-10-27 22:15	Blood glucose	11.7	mmoll
2007-10-27 22:15	Insulin	12	u
2007-10-27 22:15	Insulin	22	u

Table 12 - Captured data for insulin regime clinical trial