ETS-INSULIN-BOLUS CALCULATION PROMOTES TIGHTER GLYCAEMIC CONTROL FOR TYPE 1 DIABETICS

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ABSTRACT

Title: Ets-Insulin-Bolus-Calculation Promotes Tighter Glycaemic Control for Type 1 Diabetics.

Key Terms: Blood glucose profiles; control performance; ets-insulin-bolus calculator; hypo- & hyperglycaemia; tight glycaemic control & type 1 diabetics.

Type 1 Diabetes is a dangerous and life-long disease for which its prevalence is global. Research has shown that tight glycaemic control of this disease significantly reduces the risks of developing several life threatening diabetic complications.

The Ets-Insulin-Bolus Calculator (EIBC), inspired by the Ets concept (**E**quivalent **T**easpoon **S**ugar), was primarily designed to assist type 1 diabetics in improving their blood glucose control. The EIBC has shown to improve the average blood glucose level of type 1 diabetics. The need for this study however is to determine whether the EIBC promotes tighter glycaemic control for type 1 diabetics based on a more-in-depth numerical analysis.

With the use of the latest technology in blood glucose monitoring, the CGMS from Medtronic, mathematical models expressing and rating blood glucose control have been proposed and derived in this study. A clinical trial with type 1 diabetics has also been conducted.

The use of the models together with the clinical trial results have shown that the EIBC does in fact promote tighter glycaemic control for type 1 diabetics.

SAMEVATTING

Titel: Ets-Insulin-Bolus Calculation Promotes Tighter Glycaemic Control for Type 1 Diabetics.

Sleutel Terme: Mate van beheer; bloedglukose profile; ets-insulien-bolus rekenaar; hypo-& hyperglycaemia; streng bloedglukose beheer & tipe 1 diabetes.

Tipe 1 Diabetes is `n ernstige kroniese siekte wat algemeen wêreldwyd voorkom. Navorsing het al bewys dat streng bloedglukose beheer by hierdie betrokke siekte die risiko van verskeie lewensgevaarlike diabetiese komplikasies aansienlik verminder.

Die Ets-Insulien-Bolus Rekenaar (EIBC), geïnspireer deur die Ets konsep (**E**kwivalente **T**eelepel **S**uiker), is primêr ontwikkel om tipe 1 diabetes te help hul bloedglukose beheer te verbeter. Hierdie produk het al bewys dat dit die gemiddelde bloedglukose vlak van tipe 1 diabetes kan verbeter. Die behoefte van die studie is egter om te bepaal of die EIBC strenger bloedglukose beheer kan promoveer vir tipe 1 diabetes, gebasseer op `n meer-in-diepte numeriese analise.

Met die gebruik van die nuutste tegnologie in bloedglukose monitor, die CGMS van Medtronic, is wiskundige modelle voorgestel en afgelei tydens hierdie studie. Die doel van hierdie modelle is om bloedglukose beheer te kan uitdruk en te gradeer op `n numeriese wyse. Verskeie kliniese toetse saam met tipe 1 diabetes was ook uitgevoer.

Die gebruik van die modelle tesame met die kliniese toets resultate het egter bewys dat die EIBC kan strenger bloedglukose beheer meebring vir tipe 1 diabetes.

ACKNOWLEDGEMENTS

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Lastly and most importantly, I forever thank my Godly Father in heaven and saviour Jesus Christ.

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NOMENCLATURE

ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
ABCM	Area Between Curve and the Mean
ADA	American Diabetes Association
AUC	Area Under the Curve
CDA	Canadian Diabetes Association
CGMS	Continues Glucose Monitoring System
CHO	Carbohydrate(s)
DCCT	Diabetes Control and Complications Trail
DKA	Diabetic Ketoacidosis
EIBC	Ets Insulin Bolus Calculator
ETS	Equivalent Teaspoon Sugar
HNS	Nonketotic Hyperosmolar Coma
IDF	International Diabetes Federation
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
PIC	Patient Informed Consent
RDA	Recommended Daily Allowance
TGC	Tight Glycaemic Control
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organisation

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CHAPTER 1

INTRODUCTION

Millions of people suffering from type 1 diabetes struggle daily to control their blood glucose levels. A newly discovered idea, known as the Ets concept, has been designed which may ultimately improve the blood glucose control of type 1 diabetics. This study will focus on the tightness of glycaemic control for type 1 diabetics, using the Ets concept.

1.1 Background of the Study

Type 1 Diabetes

Diabetes mellitus is a well known and very serious chronic disease – a health condition that occurs when a person's blood glucose level is too high due to the body's inability to utilise glucose effectively. Types 1 and 2 diabetes are characterised by insufficient production of insulin or a resistance to insulin or a combination of both. This prevents efficient blood glucose control.

Type 1 diabetes, formerly known as "insulin-dependent diabetes", results from a destruction of the pancreatic islet β-cells, resulting in insulin deficiency [1, 5]. Medical experts have not yet discovered what it is that triggers this reaction in the immune system [2]. The life of persons living with type 1 diabetes therefore solely depends on the external administration of insulin in order to control their blood glucose level. Type 1 diabetes develops most often in children or young adults, but according to research can occur at any age [3].

Prevalence of Diabetes

The prevalence of diabetes is globally reaching epidemic proportions. In 2000 the total number of people with diabetes in all age groups was estimated to be 171 million. It is predicted that this number will increase to almost 366 million by the year 2030 [4]. Figure 1 illustrates the prevalence estimates of diabetes for 2007 according to the International Diabetes Federation (IDF) [5]:

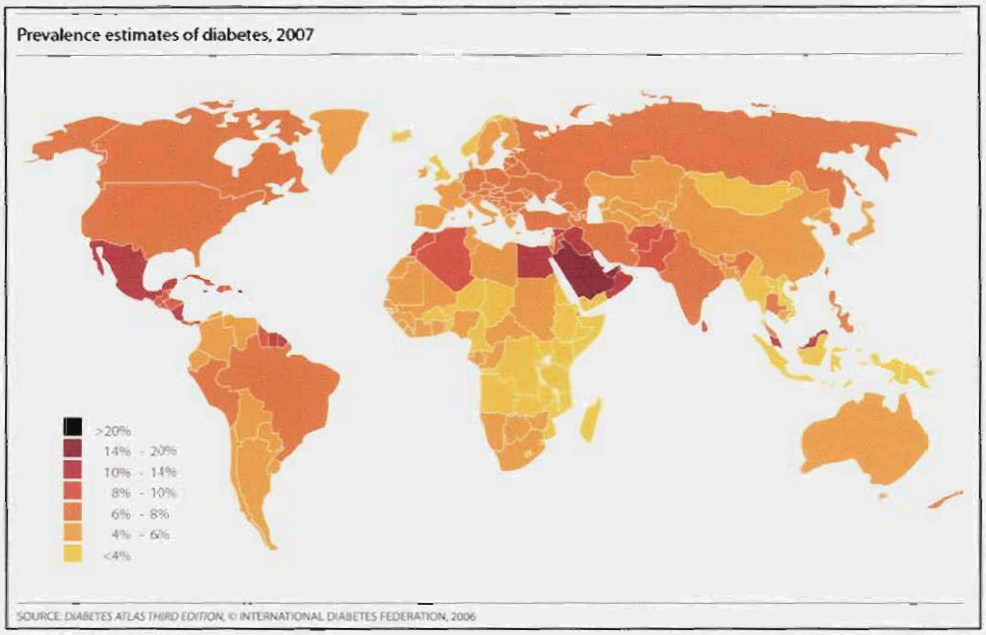

Figure 1: Estimated global prevalence of diabetes, 2007.

According to the World Health Organisation (WHO) more than 814 000 South Africans suffer from diabetes and this figure could rise to 1 286 000 by the end of 2030 [6].

Carbohydrate Counting

At present as many as 70% of all type 1 diabetics use the method known as carbohydrate counting to manage their blood glucose levels. Carb counting is a fairly old concept, dating back to the 1920s. This method is a meal-planning approach used by diabetic persons which focuses on the carbohydrate content of meals as the primary nutrient affecting blood glucose levels [8]. Diabetics then administer a certain amount of insulin according to the amount of carbohydrates ingested during main meals.

Scientific studies using modern research methods have shown, firstly, that carbohydrates are the main factor affecting postprandial blood glucose excursions. Secondly, carbohydrates are converted to glucose within the first two hours after eating and appear in the systemic circulation within 15 minutes after conversion [9, 10]. According to Marilyn [7] the results of their studies suggested that the estimates concerning carbohydrate content of meals from type 1 diabetes (n = 184) were quite inaccurate, even among individuals who regularly use the carb counting method.

The Ets concept

From an engineering point of view is it possible to visualise the human body as a complex energy system which is able to receive and utilise energy, in order to accomplish our daily tasks. The foods we ingest can be compared to the fuel fed into a car's engine, which is then converted into mechanical energy to produce useful output power. The human body functions pretty much on the same basis as a car's engine, in that the person's blood glucose level is the indicator of the energy available to the body. In this scenario carbohydrates are the main source of energy for the human body.

Although the carbohydrates in a meal are directly metabolised into blood glucose after digestion, it is possible that the energy available from different carbohydrates can vary by a substantial amount, even when the portion sizes of the carbohydrates are equal.

A fairly new concept, known as the Ets concept (**E**quivalent **t**easpoon **s**ugar), developed by Mathews [11] is a simpler and theoretically more accurate model for representing the energy available to the human body from different types of foods. This concept also represents a more accurate effect of the different foods on the blood glucose concentration by introducing several metabolic efficiency factors which the carb counting method does not account for. Previous calculations conducted by Botha and Mathews also proved the Ets concept to be a better predictor of insulin response by non-diabetic test subjects than the carb counting model [12, 14]. Figure 2 and Figure 3 illustrate the proof of this conclusion:

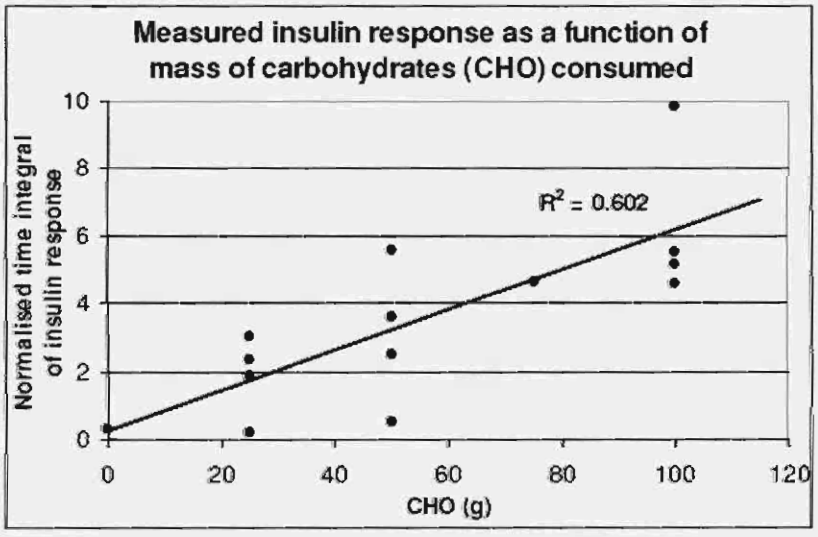

Figure 2: Measured insulin response as a function of mass of carbohydrates (CHO) consumed.

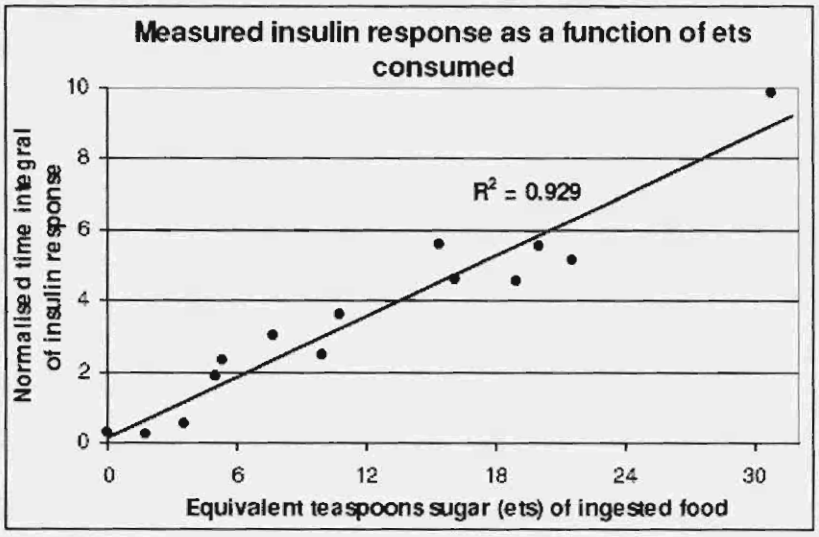

Figure 3: Measured insulin response as a function of ets consumed.

From figures 2 and figure 3 we can clearly see that the linear trend fit is better for the insulin response as a function of Ets than the insulin response as a function of carbohydrates (CHO). An analysis of data conducted by Wolever and Bolognesi [41], taken from 15 test subjects, revealed similar results for this insulin response experiment.

A further development of the Ets concept is the simulation of the human energy system by Botha [13]. Figure 4 presents an example of one of the whole-day simulations that was performed for one of the diabetic test subjects:

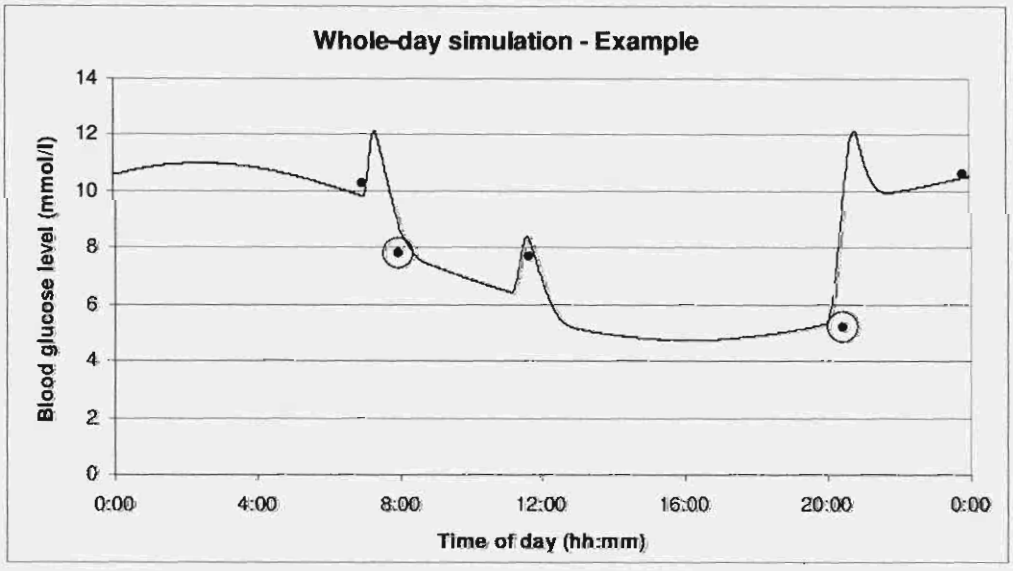

Figure 4: An example of one whole-day simulation for a diabetic subject.

The solid line on the graph is the simulated blood glucose profile, while the dots are the actual blood glucose measurements taken by the diabetic subject. This model not only showed that simulation of the glycaemic response is possible, but also proved more than 70% accurate for long-term simulations and more than 80% accurate for short-term simulations. These simulations laid the foundation for developments of novel products initially inspired by the Ets concept.

Figure 5: Nokia cellphone with the Ets-Insulin-Bolus Calculator.

One of these products is a cellphone-based application (Figure 5) called the Ets-insulin-bolus calculation system (EIBC) developed by Pelzer [14]. This system is a unique cellphone program designed to help type 1 diabetics control their blood glucose. The diabetic person enters into the program the time, type and amount of any foods or drinks ingested during the day, as well as any finger-stick blood glucose values. The EIBC uses this information, together with the Ets theory, to calculate the amount of bolus insulin the diabetic needs to administer in order to manage the blood glucose level at a certain target level.

Clinical trials were previously performed on several type 1 diabetic subjects, using the Ets-insulin-bolus calculator. This system not only received good qualitative feedback from diabetics, but also conclusively proved that it lowered the HbA1c levels of the test subjects who used it. The theory behind the Ets concept is thoroughly explained in the literatures of Mathews [11], Botha [13] and Pelzer [14].

Tightness of Glycaemic Control

The hemoglobin A1c (HbA1c) is a relatively simple lab test that shows the average amount of sugar (also called glucose) that has been present in a person's blood over the past three months [15]. The mapping between HbA1c and blood glucose average is shown in Table 1 [16] below:

Table 1: Relationship between HbA1c and mean blood glucose levels.

HbA1c (%)	Average Blood Sugar (mmol/L)
4	3.6
5	5.6
6	7.5
7	9.4
8	11.4
9	13.3
10	15.3
11	17.2
12	19.2

According to the DCCT [17] the HbA1c goal for people with diabetes should be less than 7%. Their findings showed that diabetics who keep their HbA1c levels close to 7% have a better chance of delaying or even preventing serious diabetic complications.

Although a person with type 1 diabetes can maintain a healthy HbA1c level, this does not necessarily indicate that good glycaemic control was simultaneously achieved. A person's actual day-to-day blood glucose profile can display several hypo- and hyperglycaemic events (too low or too high blood glucose excursions), and still portray a healthy average blood glucose value. Tightness of glycaemic control is per definition the degree of consistency achieved by a person's blood glucose level. This study will focus on the tightness of glycaemic control achieved by type 1 diabetics using the EIBC. The reduction in hypo- and hyperglycaemic events will also be considered for diabetic subjects using the EIBC.

1.2 Objective of the Study

The main purpose of the study is to verify the performance of the Ets-insulin-bolus calculation system. Clinical trials will be performed in which a number of type 1 diabetic subjects will make use of the Ets-insulin-bolus calculator to help control their blood glucose levels. The study will focus on the tightness of glycaemic control achieved by the subjects, as well as the reduction in hypo- and hyperglycaemic events during the clinical trails.

The scope of this study consists of the following:

- The characterisation of the tightness of glycaemic control for type 1 diabetics
- The execution of the clinical trials on type 1 diabetics
- Analysis of the clinical test results for determination of glycaemic control and frequency of hypo- and hyperglycaemic events, and relating this to the EIBC system.

1.3 Outline of the Study

This study document consists of seven chapters.

Chapter 2 discusses the importance of tight glycaemic control for type 1 diabetics. The need for this study will be explained in this chapter.

Chapter 3 is used to derive equations that will characterise the blood glucose control in a numerical fashion. Calculation of the tightness of glycaemic control as well as the frequency of hypo- and hyperglycaemic events will be discussed in this chapter. Monitoring blood glucose control by means of a CGMS (continuous glucose monitoring system) will also be discussed briefly.

Chapter 4 will give an explanation of the clinical trial protocol in which diabetics make use of the EIBC to control their blood glucose. A discussion of the EIBC's main features is also held within this chapter.

Chapter 5 reveals the results of the clinical trial, as well as a short discussion of the results.

Chapter 6 shall serve as the closure of this study.

1.4 Contribution of this Study

The Ets concept was initially inspired and developed by Mathews. Botha [13] made use of the Ets concept to develop the simulation model of the human energy system. A further development was the Ets-insulin-bolus calculation system by Pelzer [14].

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

- The derivation of several equations to calculate the tightness of glycaemic control achieved by type 1 diabetics, as well as the algorithm for calculating the frequency of hypo- and hyperglycaemic occurrences. The new proposed measure of glycaemic tightness is a novel approach and is very useful since the alternatives do not provide holistic results.
- The planning and execution of the clinical trial on several type 1 diabetics were done in conjunction with the medical practice of Dr L. Johnson at Montana Hospital in Pretoria, South Africa.

1.5 Summary

Diabetes mellitus is a chronic disease which affects millions of people worldwide. At present many type 1 diabetics use the carbohydrate counting method to help control their blood glucose levels. A remarkable new idea known as the Ets concept has been developed which theoretically gives a better indication of the effect of different foods on a person's blood glucose level. A cellphone-based application known as the Ets-insulin-bolus calculator has been designed. The goal of this study is to determine from a numerical point of view whether the Ets-insulin-bolus calculator contributes to tighter glycaemic control for type 1 diabetics.

CHAPTER 2

TIGHTNESS OF GLYCAEMIC CONTROL IN TYPE 1 DIABETICS

Type 1 diabetes is a chronic disease that causes several types of severe complications. Tighter glycaemic control effectively reduces the risk of these complications. However, the Ets concept was designed to help diabetics achieve tighter blood glucose control, and there exists a need at present to determine whether the Ets-insulin-bolus calculator can promote tighter glycaemic control for type 1 diabetics.

2.1 Introduction

Type 1 diabetes, also known as "juvenile onset" diabetes, are less common than type 2 diabetes and approximately 1 out of 10 diabetics suffers from the former type of this disease. Type 1 diabetes usually develops at an early age among people who, in most cases, have a family history of type 1 diabetes. Unfortunately no proven cure has yet been found for type 1 diabetes, although diabetes, in contrast with many other illnesses, is a self-managed disease involving both a doctor's diagnosis and the patient's co-operation in managing the disease.

Proper management of type 1 diabetes is crucial in order to minimise the chances of several life-threatening diabetic complications. Research has shown that good glycaemic control decreases the risk of diabetic complications, ultimately extending the diabetic's lifespan [18].

In this chapter we will emphasise the importance of tight glycaemic control for diabetics as well as discuss the need for this study.

2.2 Importance of Tight Glycaemic Control

2.2.1 Basics of the blood glucose system

Like many other control systems the human body is a complex biological system which receives and burns energy in order to stay alive and produce useful work. But what type of energy does the human body use? The answer is **glucose**. Glucose is an ubiquitous fuel in biology and is the human body's key source of energy [19]. This glucose is transported via the bloodstream which makes it possible for body cells to absorb this type of energy. Blood sugar is the medical term used to refer to levels of glucose concentration in the bloodstream.

The blood glucose concentration (the unit used is mmol/ℓ or mg/dℓ) is tightly regulated in order to keep the human body in homeostasis. The levels of glucose in the blood are continuously monitored by cells in the pancreas. If the blood glucose level falls too low (due to excessive exercise or lack of food for extended periods), the alpha cells of the pancreas release a hormone called glucagon, which acts on the liver cells.

These cells in turn convert glycogen storage into glucose which is then released into the bloodstream, increasing the blood glucose levels. Other causes of an increase in blood glucose levels are "stress" hormones such as cortisol and adrenalin, as well as elements such as infections, trauma and ingestion of food.

When levels of blood glucose rise, a different hormone is released from the beta cells found in the islet of Langerhans in the pancreas. This hormone, called insulin, causes the liver to convert more glucose into glycogen. (This process is known as glycogenesis.) This forces about two-thirds of the body cells (primarily muscle and fat tissue cells) to take up glucose from the blood, thus decreasing blood glucose levels [20].

2.2.2 Difference between diabetic and non-diabetic blood glucose.

Referring to the previously mentioned metabolic processes these processes are functioning normally and without any external help in non-diabetic persons. In contrast diabetes is caused when there exists a dysfunctioning of these processes, mainly the process of decreasing blood glucose. Type 1 diabetes is caused by insufficient or non-existent production of insulin, due to the destruction of the islet's beta cells in the pancreas [4]. Type 2 diabetes is primarily due to a decreased response to insulin in the tissues of the body ("insulin resistance").

Both types of diabetes, if untreated, result in too much glucose remaining in the bloodstream (hyperglycaemia), causing in most cases long-term diabetic complications. Too much insulin and/or exercise without enough corresponding food intake also result in low blood glucose (hypoglycaemia).

In this study we will specifically focus on type 1 diabetes.

2.2.3 Diabetic complications

Abnormal blood glucose levels in most cases result in several long- and short-term diabetic complications. The risk of developing these complications can be drastically reduced by means of proper blood glucose management. Let us first discuss the several diabetic-related conditions.

Acute

Diabetic ketoacidosis (DKA) is an acute (short-term) and dangerous complication that can cause hypotension and shock. Inadequate treatment can lead to a coma or even death [21].

Non-ketotic hyperosmolar coma (HNS) is the osmotic effect of high glucose levels combined with a loss of water which can ultimately progress to a coma [21].

Hypoglycaemia or abnormally low blood glucose may develop if the glucose intake does not match the treatment. The patient may become agitated, sweaty, feeling weak and displaying many symptoms of sympathetic activation of the autonomic nervous system, resulting in feelings similar to dread and immobilised panic. Severe hypoglycaemia may result in loss of consciousness, coma and even death. Frequent hypoglycaemic events therefore reduce the patient's quality of life, for example leading to loss of employment or the ability to drive a car [22, 23].

According to research, Figure 6 illustrates how the body typically reacts when the blood glucose decreases past a certain glycaemic threshold [24]:

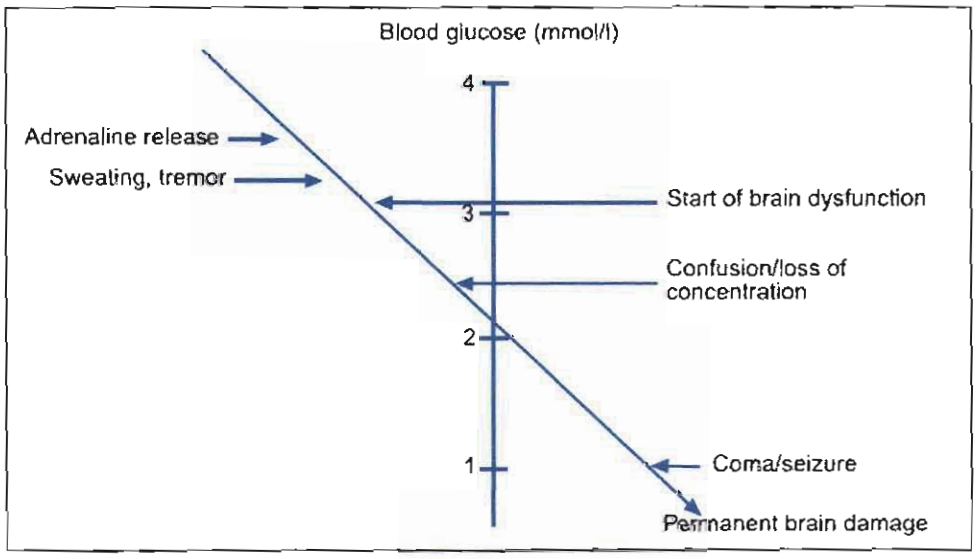

Figure 6: Glucose threshold for the activation of the physiological defence to hypoglycaemia.

Chronic

Chronic (long-term) elevation of blood glucose causes damage to blood vessels. In diabetes the resultant problems are grouped under "microvascular disease" (damage to small blood vessels) and "macrovascular disease" (damage to the arteries).

Microvascular diseases

Retinopathy is the growth of friable and poor-quality new blood vessels in the retina of the eye, which can lead to severe loss of vision or blindness [25].

Neuropathy is the effect of abnormal and decreased sensation due to damage to small vessels that supply nerves. Abnormal high blood glucose is one of the major risks for developing neuropathy, which in severe cases may necessitate amputation of feet and legs [26].

Nephropathy *is* damage to the kidneys which leads to chronic renal failure. Hyperglycaemia increases the risk of developing diabetic nephropathy [27].

Macrovascular diseases

Macrovascular disease leads to cardiovascular disease, mainly by accelerating the following diseases:

- ***Coronary artery disease***, leading to heart attacks
- ***Stroke***
- ***Peripheral vascular disease***, which contributes to diabetic foot
- ***Diabetic myonecrosis.***

Diabetic foot is characterised by skin ulcers and severe foot infections. In serious cases this disease leads to amputation of toes or feet [28]. According to Learch and Gentili approximately 25% of the 14 million diabetics in the USA will develop foot problems and 6% to 10% of these people will undergo amputations [29].

Mortality

The number of deaths attributed to diabetes in national mortality statistics is likely to be a huge underestimate of the actual number of deaths caused by diabetes. This is because other diseases caused by diabetes – such as CVD (cardiovascular disease) – are normally given as the cause of death on the death certificates of people with diabetes.

Various studies have sought to determine the total number of deaths attributable to diabetes. The best known study is that of the World Health Organisation's Global Burden of Disease Project. This study suggests that in established market economies such as in the UK there are about five times as many deaths indirectly attributable to diabetes as are directly attributable. This would mean that there are about 33 000 deaths per year attributable to diabetes – about one in seven of all deaths [30].

CVD is by far the most common cause of death amongst people with diabetes. For example, in the British Diabetic Association's cohort study – a study of 23 752 patients under the age of 30 years diagnosed with type 1 diabetes throughout the UK – 63% of deaths in men aged 40–59 with diabetes were from CVD compared with 35% of men in the general population. For women aged 40–59 with diabetes, 52% of deaths were from CVD compared with 20% in the general population [31].

In the British Diabetic Association's cohort study men aged 40–59 with diabetes were three times more likely to die of any cause, and five times more likely to die of CVD than people without diabetes. Women with diabetes were four times more likely to die of any cause, and eight times more likely to die of CVD [32].

Morbidity

Diabetes causes severe morbidity. Complications of diabetes can be divided into three categories:

- Metabolic complications of low blood glucose levels (hypoglycaemia) and of high blood glucose levels (hyperglycaemia). Diabetic coma is one such metabolic complication of a particularly severe nature.

- Damage to small blood vessels (microvascular complications) leading in turn to damage to the retina (retinopathy), kidneys (nephropathy) and nerves (neuropathy).

- Damage to the larger arteries leading to the brain (leading to stroke) or to the heart (leading to coronary heart disease) or to the legs and feet (leading to peripheral vascular disease) (macrovascular complications).

The World Health Organisation's Global Burden of Disease Project estimates that in established market economies such as in the UK 3% of years of life lost in disability are due to diabetes. This is only slightly less that the 4% of years of life lost in disability due to cancer [33].

The UK Prospective Diabetes Study (UKPDS) – a multicentre prospective randomised intervention trial where the subjects are people with newly diagnosed type 2 diabetes – has found that nearly half of the people with diabetes recruited to the trial had one or more micro- or macrovascular complication, and also showed that about a quarter already had CVD [34].

2.2.4 Economical burden

The complications of diabetes not only have an impact on the individual's social, health and psychological behaviour, but also carry an enormous burden for the economy in general. Diabetes creates loss in work productivity and disability, and results in high utilisation of health care resources.

A report from the ADA concluded that direct medical and indirect expenditures attributable to diabetes in the USA in 2002 were estimated at $132 billion! When adjusting for differences in age, sex and race, people with diabetes had medical expenses that were 2,4 times higher than expenses that would occur for the same group in the absence of diabetes [35].

The World Health Organisation estimates that over the next 10 years (2006–2016), China will lose $558 billion in foregone national income due to heart disease, stroke and diabetes alone [36].

2.2.5 Tight Glycaemic Control

As of 2006 no proven cure has yet been discovered for diabetes. Although many pancreas transplantations have been done over the past few years with increasing success rates over time, it is still not recognised as a regular medical practice [37]. However, diabetes is a manageable disease which can be controlled within healthy blood glucose levels. Glycaemic control can be defined as the management of a diabetic's blood glucose with the goal of maintaining the blood glucose within certain target levels. Type 1 diabetics manage their blood glucose by means of their diet, exercise and external administration of insulin. Most diabetics find it difficult to administer just the right amount of insulin to stay within a good glycaemic range.

Because blood glucose levels fluctuate throughout the day, the haemoglobin A1c test (as previously discussed) is currently used as a proxy measure of long-term glycaemic control in research trials. This test reflects the average glucose concentration that was present in the bloodstream over the preceding 2–3 months. A non-diabetic's blood glucose is typically between 4% and 6% [38].

Table 2 shows again the relationship between HbA1c values and the corresponding blood glucose values:

Table 2: Relationship between HbA1c and mean blood glucose levels.

HbA1c (%)	Average Blood Sugar (mmol/L)
4	3.6
5	5.6
6	7.5
7	9.4
8	11.4
9	13.3
10	15.3
11	17.2
12	19.2

Most diabetics tend to control their blood glucose at higher levels than the suggested healthy target level. The HbA1c values of these diabetics, when tested, are significantly higher than the proposed 7% [39]. The reason for this poor control is the diabetic's fear of hypoglycaemia (hypos for short) and its immediate response of bad symptoms. Thus the lowering of a diabetic's HbA1c is in most cases beneficial to the diabetic on the long-term, up until the point where the HbA1c value is indeed inside the ideal blood glucose range.

Several international diabetic organisations have established healthy blood glucose ranges for diabetics. Guidelines from these organisations, including the American Diabetes Association (ADA), European Diabetes Policy Group, Canadian Diabetes Association (CDA), American Association of Clinical Endocrinologists (AACE), Latin American Diabetes Association and the Asian-Pacific Type 2 Diabetes Policy Group recommend that the HbA1c target for diabetes should be less than 6–7%. These guidelines emphasise the impact of improved glycaemic control on most diabetic complications [39, 40, 41, 42, 43, 44].

When it comes to the lower limit of the ideal target range, a blood glucose level less than 3,6 mmol/ℓ (HbA1c < 4%) is usually described as abnormal low blood glucose, and is called a hypoglycaemic attack or a "hypo" [38].

Thus good glycaemic control means maintaining the blood glucose level between 9,4–3,6 mmol/ℓ, which is an acceptable range for most of the diabetic organisations. "Perfect or tight" glycaemic control would mean that the glucose levels were almost always normal (3,9–7,2 mmol/ℓ) and indistinguishable from those of a non-diabetic person [38]. In another study tight glycaemic control (TGC) in the intensive care unit (ICU) was defined as the maintenance of blood glucose between 4,4 and 6,1 mmol/ℓ [45]. It can therefore be seen that the exact glycaemic threshold varies between several different post-studies and diabetic associations. In this particular study we define the normal glycaemic range as **9,4–3,6** mmol/ℓ.

The process of achieving tight glycaemic control is, however, not without risk. In particular, the need for frequent, accurate blood glucose measurements and the possibility of prolonged, unrecognised hypoglycaemia are of concern.

A number of studies have been undertaken since 2001 which addressed the implementation and effectiveness of TGC within the ICU. In one particular study, the objective was to introduce the process of TGC within the ICU, whilst maintaining patients' safety on critically ill patients [46]. Fifty patients were enrolled in this evaluation for seven days, which equated to 7 189 hours of insulin administration and 6 424 blood glucose measurements. The data were transcribed onto an Excel spreadsheet for each patient.

It is interesting to note the illustration that was used in this study for describing the tightness of glycaemic control that was achieved. Figure 7 describes the percentage of time TGC was maintained for the group of diabetic patients.

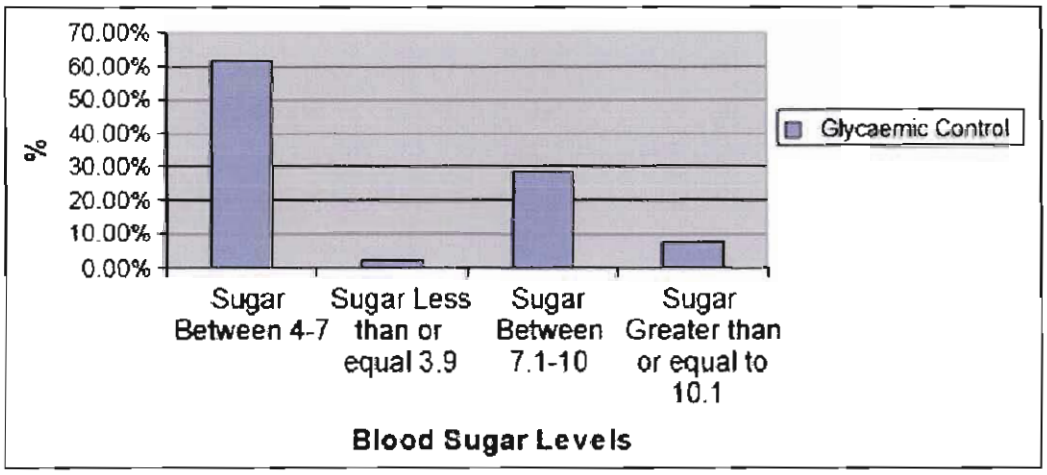

Figure 7: Illustration of TGC by means of time percentage factor.

During this study 3 965 (61,6%) blood glucose measures were within the 4–7 mmol/ℓ range and TGC achieved within a median time of 5 hours. This study used the time percentage factor for illustrating the tightness of glycaemic control achieved by a diabetic patient.

2.2.6 Benefits of tighter glycaemic control

The Diabetes Control and Complications Trial (DCCT) was the largest, most comprehensive diabetes study ever conducted at the time. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducted this study of 1 441 volunteers with type 1 diabetes at 29 medical centres in the USA and Canada between 1983 and 1993. The purpose of the study was to determine whether intensive treatment (with the goal of achieving tight glycaemic control) could decrease the risks of developing several diabetic complications.

These were the results of the DCCT:

- Tight glycaemic control reduced the risk of retinopathy by 76%.
- Tight control reduced the risk of albuminuria by 54%.
- Clinical neuropathy was reduced by 44%.
- Kidney disease risk was lowered by 50%.

The findings of this study definitely indicate that improving and tightening blood glucose control substantially lower the risks for developing these diabetic problems [17, 47, 48, 49, 50].

Studies by Van den Berghe have also demonstrated the effects of tight glycaemic control in reducing mortality and improving morbidity in surgical ICU patients [51].

2.3 Need for the study

It will be clear from the previous section that tightening of blood glucose control leads to a decreased risk of developing long-term diabetic complications. Tightening of glycaemic control also simultaneously implies that a decrease in short-term problems should occur, thus improving the diabetic's overall quality of life.

This is concluded from the fact that tightened glycaemic control means that the blood glucose levels remain inside the healthy target range for a longer period than before. This means that the frequency and/or intensity of hypos and hypers should be less.

In chapter 1 the Ets concept by Mathews [11] was mentioned and previous studies by Pelzer [14] have shown that the Ets-insulin-bolus calculator can lower the HbA1c levels of diabetics using it. Although a diabetic can maintain a healthy HbA1c level, it does not necessarily mean that a tight glycaemic control is achieved at the same time.

The HbA1c test only gives an approximation of the *average* amount of blood glucose that was present in the bloodstream over the preceding 2–3 months. Figure 8 shows an example of the typical blood glucose curve of a type 1 diabetic:

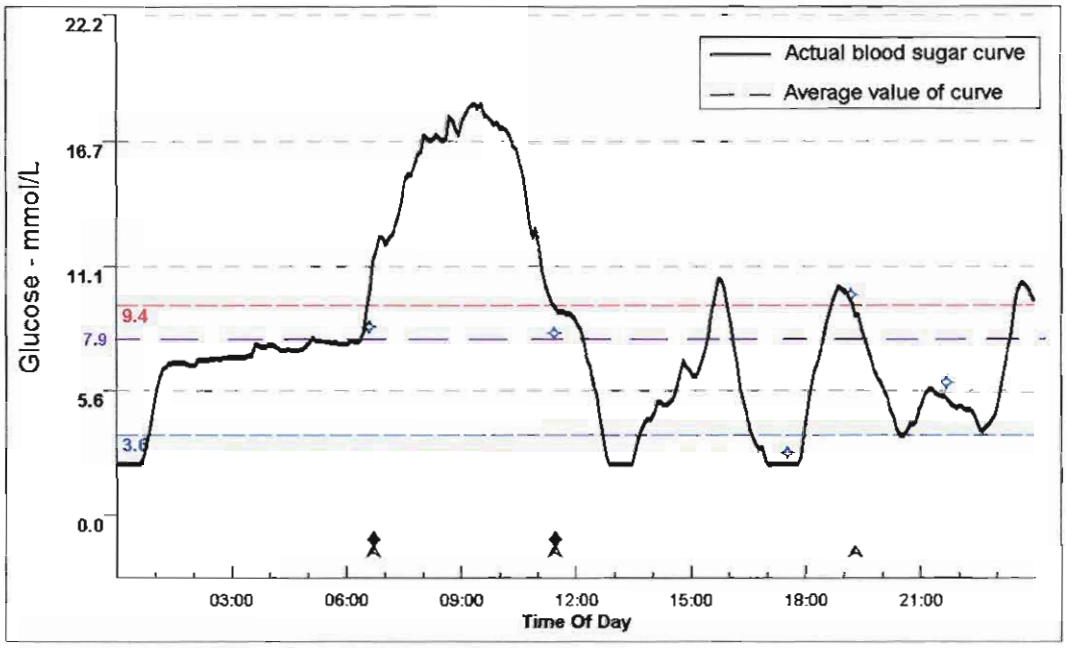

Figure 8: Typical blood glucose curve of a type 1 diabetic.

Looking at Figure 7 it is clear that it is possible for a diabetic to experience several hypos and hypers on a daily basis while achieving a mean blood glucose value within the healthy range. The goal of this study, however, is to determine whether the Ets concept can tighten the glycaemic control of a type 1 diabetic using the EIBC. Figure 9 illustrates the meaning of tightening the blood glucose control:

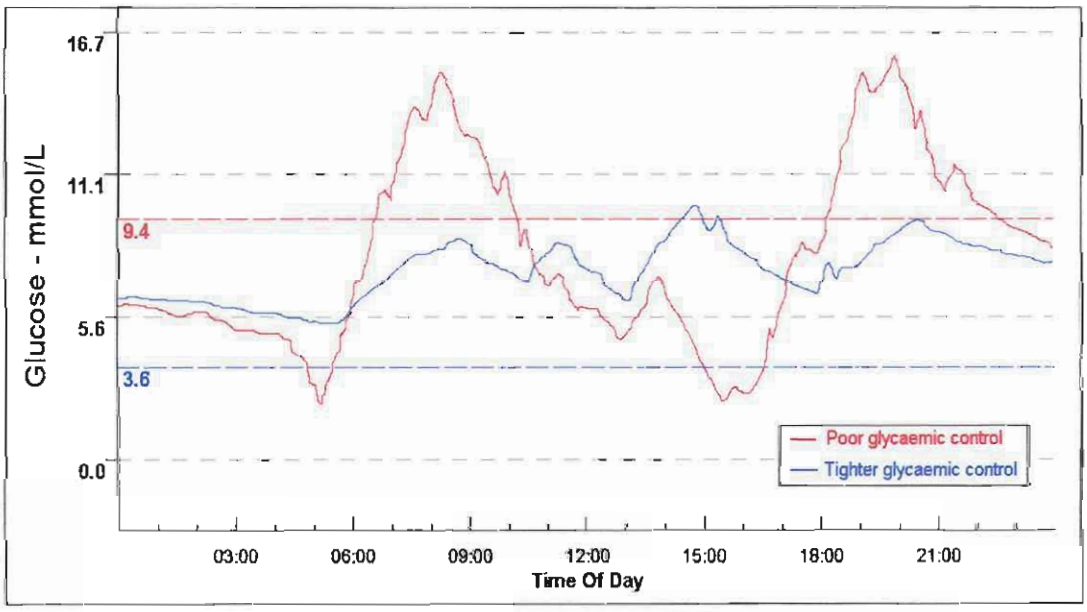

Figure 9: A blood sugar curve: poor control VS tighter control.

Tightening of the blood glucose control literally means to achieve a "smoother" blood glucose curve, thus maintaining the blood glucose level for longer periods between the hypo- and hyperglycaemic limits. This study will also determine whether the use of the EIBC reduces the frequency of hypo- and hyperglycaemic events. In the next chapter we will discuss the methods for determining these changes in blood glucose control.

2.4 Summary

During this chapter we firstly discussed the basics of the human blood glucose system, as well as the long- and short-term health complications due to poor glycaemic control. According to research the tightening of glycaemic control reduces the risks for developing several serious health hazards. There is, however, a huge demand for methods to help improve diabetic blood glucose control. The EIBC, based on the Ets concept, was specifically designed to help type 1 diabetics improve their blood glucose control. The need for this study is to observe whether the EIBC can promote tighter glycaemic control for type 1 diabetic.

CHAPTER 3

CHARACTERIZATION OF GLYCAEMIC CONTROL

The traditional HbA1c lab test is currently the only method for rating a diabetic's average blood glucose control. With the introduction of the CGMS system deeper insight into blood glucose control is now possible. This leads to the need for proposing and constructing a new concept for expressing blood glucose control in type 1 diabetics.

3.1 Introduction

Up until this point the conclusion was drawn that diabetes is a serious health concern in many countries, and that tightening of blood glucose control for type 1 diabetics will definitely promote a positive impact in managing this disease and its complications. The EIBC was initially designed to assist type 1 diabetics in achieving an improved glycaemic control, thus attempting to fulfil a huge demand in the global health sector.

The purpose of this chapter is to discus the methods necessary to calculate the blood glucose control of diabetics using the EIBC. In the first part of this chapter we will discuss the latest technology available that will be used during this study to monitor glycaemic control of the diabetic subjects. This will be followed by proposing a new concept for rating blood glucose control. This is the point where the engineering part of this study is introduced in order to quantify blood glucose control. Several mathematical models will be derived and the link between blood glucose monitoring and quantifying of blood glucose control will be explained.

3.2 Monitoring of Glycaemic Control

3.2.1 Determination of blood glucose control

Once again it is necessary to state here that the main objective of this study is to determine whether the Ets concept promotes tighter glycaemic control for type 1 diabetics. Tightness of glycaemic control is defined in this study as the degree of consistency achieved by the diabetic's blood glucose level – in other words, the "smoothness" of the diabetic's blood glucose profile. This blood glucose profile is, however, required in the first place to calculate the tightness of the diabetic's glycaemic control. We will now explore the latest technology in blood glucose monitoring which records the diabetic's blood glucose profile on a daily basis.

3.2.2 Continues Glucose Monitoring System (CGMS)

The CGMS from Medtronic is a state-of-the-art diagnostic tool used by physicians to track continuous blood glucose patterns in people with diabetes.

Comprehensive information provided by the CGMS system can identify erratic blood glucose fluctuations and trends which often go unnoticed when standard HbA1c tests and finger-sticks are used [52]. This system provides additional insight to healthcare professionals, enabling them to work with their patients to make therapy, dietary and lifestyle adjustments with the goal of improving diabetic management. The CGMS system is shown in Figure 10 with all of the system's basic components:

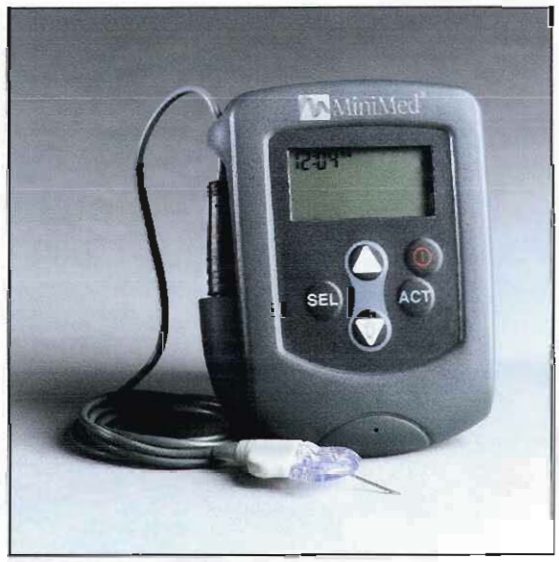

Figure 10: Continuous Glucose Monitoring System.

The monitor is worn discreetly like a pager on the patient's belt or in the pocket. A sensor is placed into the skin, usually on the anterior abdominal wall, where it stays for three consecutive days. The sensor is connected by a wire to the monitor. The glucose sensor is a microelectrode with a thin coating of glucose oxidase beneath several layers of biocompatible membrane.

The sensor continuously converts glucose from the person's interstitial fluid (liquid found between the cells of the body) into an electronic signal, the strength of which is proportional to the amount of glucose present. Blood glucose and interstitial fluid glucose levels are essentially equal when blood glucose is not changing rapidly [53].

Every five minutes the CGMS records a blood glucose value and stores this data on the system. This provides 288 glucose measurements each day, and the glucose sensor is to be used for a maximum of three days.

The CGMS is, however, intended for occasional rather than everyday use, and is a supplement to the standard method of blood glucose monitoring.

The CGMS system needs several input parameters in order to monitor the diabetic's glycaemic profile. Firstly, the patient enters into the monitor the time of several daily events such as when food is ingested, insulin taken or when any exercises are done by the patient. Secondly, the regular finger-stick values are also entered into the CGMS. The system uses a minimum of four external (finger-stick) blood glucose values per day for calibration purposes.

After using the CGMS, the sensor can easily be removed from the skin, and the recorded data downloaded via the ComStation from the monitor to a computer. CGMS Solutions Software then simplifies analysis by organising all the data into charts, graphs and tables. This is the useful output of the system. Figure 11 and Table 3 illustrate the data analysis of the CGMS Software after downloading the data from the monitor [54]:

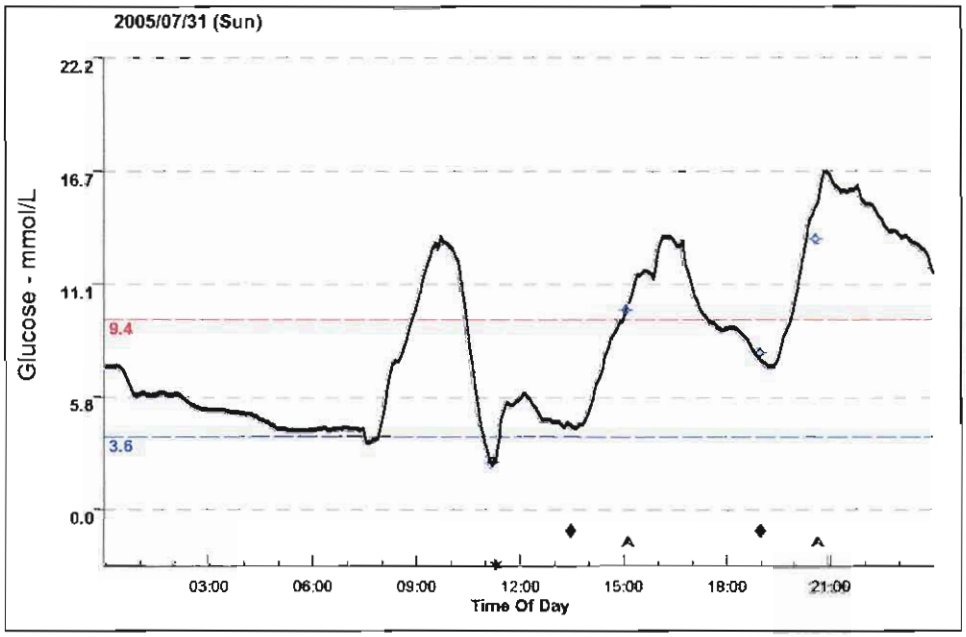

Figure 11: Daily blood glucose graph from the CGMS.

Table 3: Summary of CGMS results.

Date		2006/08/22	2006/08/23	2006/08/24	2006/08/25	Totals
Sensor	# of Sensor Values	48	288	288	166	788
	Average (mmol/L)	4.3	7.6	8.8	8.5	7.6
	Min - Max (mmol/L)	3.3-8.3	2.4-13.1	4.8-11.1	3.2-9.3	2.4-13.1
	STDev (mmol/L)	1.2	3.3	1.3	1.7	2.6
Meter	# of Meter Values	1	4	3	2	10
	Average (mmol/L)	4.9	8.5	8.0	9.2	8.1
	Min - Max (mmol/L)	4.9-4.9	6.9-10.1	6.2-9.2	3.3-15.1	3.3-15.1
Optimal Accuracy Criteria	Designation	X: Use Clinical Judgment			X: Use Clinical Judgment	
	# of Paired Readings	1	4	3	1	9
	Mean Abs. Diff. [MAD%]	35.7	13.7	11.7	2.8	14.3
	Correlation Coeff. [R]	n/a	n/a	n/a	n/a	0.83
Excursions High > 9.4mmol/L Low < 3.6mmol/L	# of Excursions*	1	2	6	1	10
	# of High Excursions*	0	1	6	0	7
	# of Low Excursions*	1	1	0	1	3
	Duration Above High Limit	00:00 (0%)	05:10 (38%)	06:55 (29%)	00:00 (0%)	16:05 (25%)
	Duration Within Limits	02:10 (54%)	12:10 (51%)	17:05 (71%)	12:05 (93%)	43:30 (67%)
	Duration Below Low Limit	01:50 (46%)	02:40 (11%)	00:00 (0%)	00:55 (7%)	05:25 (8%)
	Pie Chart Red: Above Limits Green: Within Limits Blue: Below Limits					
	Glucose Area Above High Limit (mmol/L*Day)	0.0	0.8	0.2	0.0	0.4

The comprehensive data provided by the CGMS system have been shown to assist healthcare professionals in optimising treatment programs for diabetics based on detailed glycaemic profiles. It is also a useful educational tool that can improve motivation and collaboration with patients [55]. Several metabolic efficiency factors used in the EIBC are calculated from the CGMS glycaemic profiles.

In the next section we will discuss how these blood glucose profiles will be used to calculate the tightness of glycaemic control in type 1 diabetes.

3.3 Derivation of Glycaemic Control Equations

3.3.1 New concept for defining glycaemic control

Currently the HbA1c lab test is the only standard reference for rating a diabetic's blood glucose control. HbA1c test results reveal only an average value of the blood glucose concentration of the preceding 2–3 months [15].

Most type 1 diabetics tend to control their blood glucose levels at higher than normal ranges out of fear for striking hypoglycaemia. These higher than normal HbA1c values increase the changes for developing many long-term health hazards. Lowering of the mean blood glucose level is beneficial in most scenarios.

However, from Figure 8 we have learned that the diabetic's actual daily blood glucose profile can reveal several hypo- and hyperglycaemic events and still portray a healthy average blood glucose value. The latest technology in blood glucose monitoring has made this more in-depth view of the actual blood glucose response possible. The following factors can now be indicated from the CGMS blood glucose profiles:

- Average blood glucose value
- Amount, time and intensity of hypos and hypers
- "Smoothness" of the actual blood glucose profile.

It is now possible, with the above added information, to optimise the definition for glycaemic control and define a new concept for rating a diabetic's blood glucose control. This study now proposes a new concept for looking at glycaemic control with the support of the CGMS system. Refer to Figure 12:

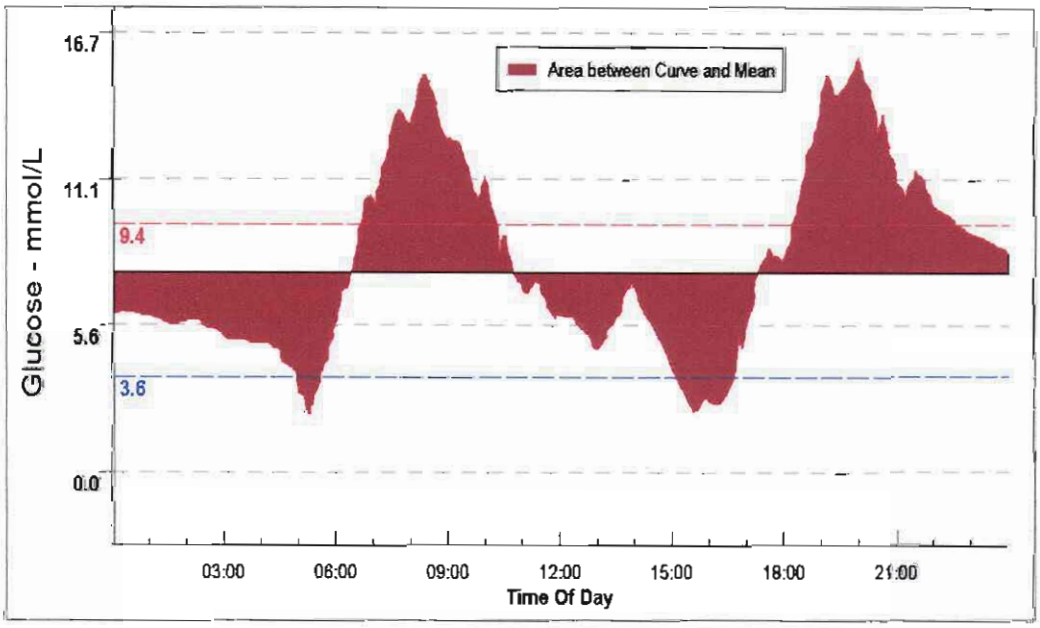

Figure 12: Area between Curve and Mean of the blood glucose curve.

From any continuous curve such as the curve in figure 11 which is bounded with a start and end point, an area can be calculated from the graph. Areas are simple and effective methods for illustrating blood glucose control, and can easily be calculated from the CGMS profiles. In the above figure the area between the curve and the mean is shown, for this area can be used to give an indication of the tightness of the actual blood glucose profile.

This study also now proposes that the performance of a diabetic's blood glucose control should not only be influenced by the average blood glucose value (HbA1c), but should rather be a function of the HbA1c value, occurrences of hypos and hypers, as well as tightness (or smoothness) of the actual blood glucose profile. Thus:

$$\text{Control performance} = f(\text{HbA1c, hypos, hypers, tightness of profile}) \qquad (1)$$

in terms of areas.

3.3.2 Area Between Curve and Mean (ABCM)

Now that the different variables for the blood glucose control have been proposed, the first element in the control performance formula can be derived and explained. Firstly, the tightness of the blood glucose profile gives an indication of the "smoothness" of the diabetic's blood glucose profile. Also called the tightness control, the intensity of this variable will be determined by means of the area between the curve and the mean (ABCM) of the blood glucose profile (refer to Figure 12).

On a mathematical basis there are several methods for determining the area under a continuous curve. This study, however, will make use of one of the simplest methods which is defined by the following theorem [56]:

The area A of the region S that lies under the graph of the continuous function f the limit of the sum of the areas of approximating rectangles:

$$A = \lim_{n\to\infty} R_n = \lim_{n\to\infty} [\, f(x_1).\Delta x + f(x_2).\Delta x + \ldots + f(x_n).\Delta x \,] \qquad (2)$$

Consider the following figure:

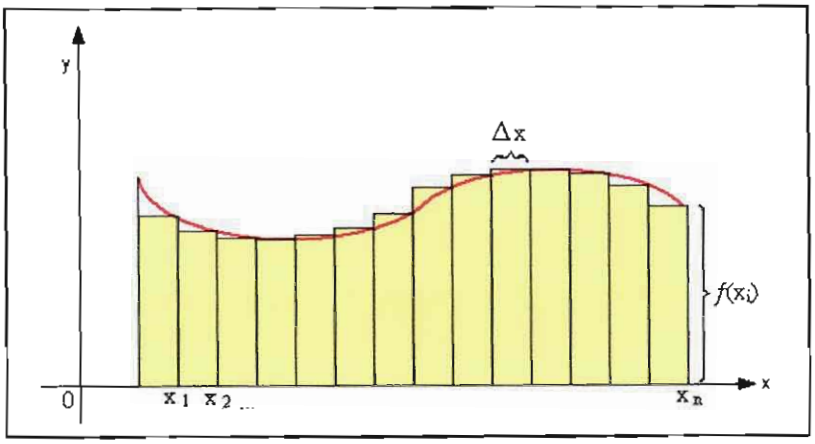

Figure 13: Definition of the Area Under the Curve.

In this scenario of blood glucose control the blood glucose profile is defined by the function $f(x)$ which describes the change in blood glucose concentration over time. The CGMS records a blood glucose value every five minutes of the day, resulting in 288 blood glucose values per day (if the profile is continuous for the whole day). Thus $n = 288$ in the theorem for each one day period, $\Delta x = 5$ minutes and $f(x_i)$ is the blood glucose value at the i^{th} – time increment.

Yet the tightness control defined in this study is the area between the curve and the mean. Considering the mean value of the curve and the theorem, the calculation of the ABCM is as follows:

$$\text{ABCM} = \sum | (BS(t) - M) \times 5 | \qquad (3)$$

Where: BS(t) = blood glucose value as a function of the time

M = mean value of the blood glucose curve.

Consider Figure 14 :

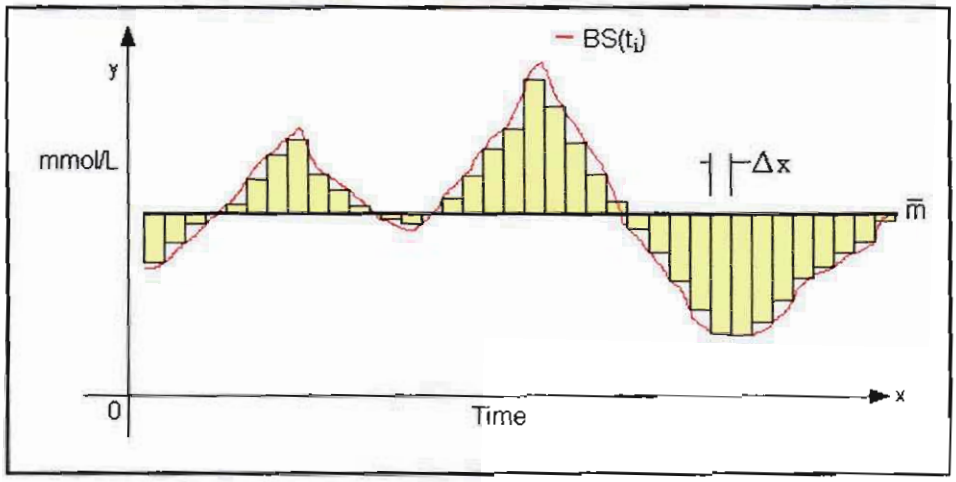

Figure 14: Calculation of the ABCM from the blood sugar profile.

The unit for the ABCM is mmol.min/ℓ. During this study the ABCM is calculated for each patient for a certain time period (2–3 days). Two ABCM values will be determined:

- ABCM $_{CHO}$
- ABCM $_{ETS}$

ABCM $_{CHO}$ is for the time period in which diabetics use the traditional carbohydrate counting method for controlling their blood glucose levels. The ABCM $_{ETS}$ is calculated for the time period when patients are using the EIBC to control their blood glucose levels.

Both ABCM values will be compared to each other and in the next chapter the two methods will be discussed in order to verify the change in tightness control for each of the diabetic subjects.

It can be seen from Figure 14 that the smaller the total ABCM value, the smoother the overall blood glucose profile becomes, thus improving tightness control for the patient. The smallest ABCM values will be the average value calculated from a typical non-diabetic's blood glucose profile. Over a 24-hour period this value has been calculated from this to be 771,93 mmol.min/ℓ (n = 2). This effect of reducing the ABCM will indirectly reduce the occurrence and/or intensities of hypos and hypers as well.

3.3.3 Hypo- and Hyperglycaemic events

Abnormal blood glucose levels in diabetics fall into two categories, namely hypoglycaemia and hyperglycaemia. Hypoglycaemia (hypos) is characterised by an abnormal low blood glucose concentration which is combined with immediate symptoms of tiredness, sweating, dizziness and nausea. According to research in the literature study, when the diabetic's blood glucose falls below 3,6 mmol/ℓ (HbA1c < 4%), the diabetic goes into a state of hypoglycaemia [38]. Although there are minor differences in the exact hypoglycaemic threshold among the many different diabetic associations, a universal limit of 3,6 mmol/ℓ will be used in this study.

It has further been noticed from the CGMS Software [53] that each hypoglycaemic event is only counted as an occurrence when the blood glucose level remains under 3,6 mmol/ℓ for more than 30 minutes. Furthermore, the end of one such occurrence is proclaimed only when the blood glucose level has returned to the normal range and remains in this range for at least 30 minutes. This rule of counting is also applicable to the occurrence of hyperglycaemia, and shall be used as the norm for measuring the hypo- and hyperglycaemic events in this study. Figure 15 illustrates this definition for hypo- and hyperglycaemic events:

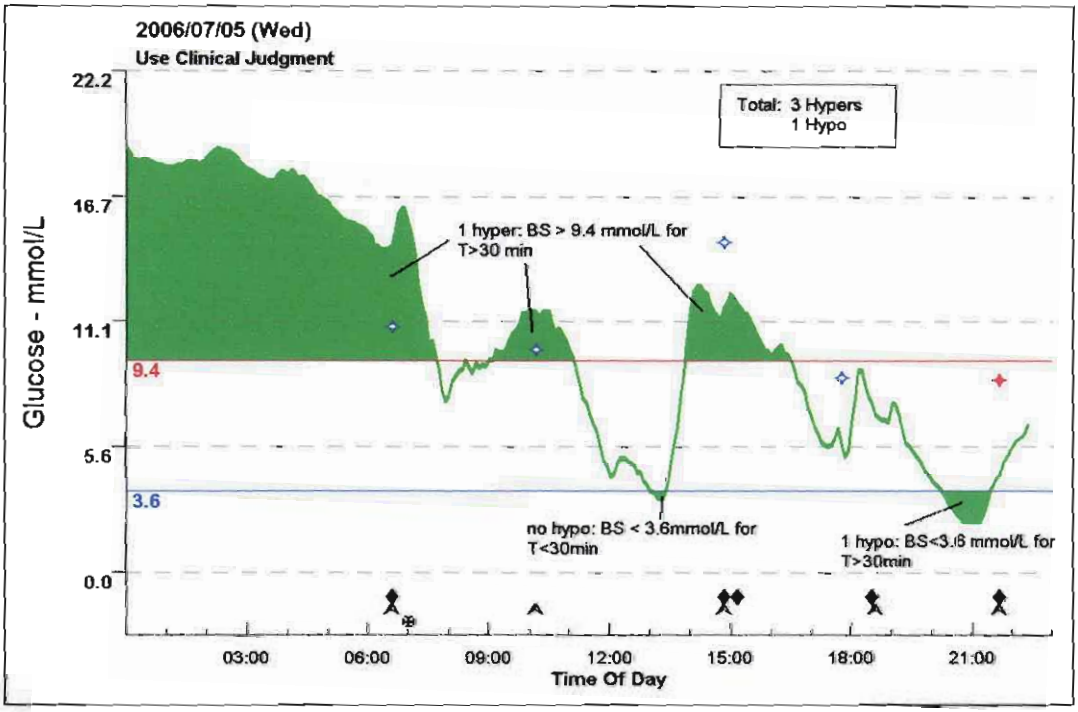

Figure 15: Measurement of Hypo's and Hypers from BS profile.

Hyperglycaemia (hypers) on the other hand is abnormal high blood glucose concentrations causing several long-term diabetic complications. According to the research, a state of hyperglycaemia is reached when the blood glucose rises above an HbA1c value of 7% or 9,4 mmol/ℓ [39, 40, 41, 42, 43, 44]. This study will use 9,4 mmol/ℓ as the hyperglycaemic threshold for the clinical trials.

From the CGMS results obtained from the clinical trials, the total hypo- and hyperglycaemic events will be measured for each patient before and while using the EIBC. If, indeed, the CGMS results show a reduced amount of such hypos and/or hypers for a patient using the EIBC, then clearly the use of the EIBC reduces the chances for a diabetic to experience hypos and/or hypers. The method for expressing the improvement or degradation of this particular issue of blood glucose control will be explained in the next chapter.

3.3.4 Area Under the Curve (AUC)

Most of the type 1 diabetics, being more afraid of hypos than hypers, control their blood glucose in a higher blood glucose range than the normal or "healthy" range. Thus most medical experts encourage diabetics to control their blood glucose level at a lower range, which in turn means lowering their average blood glucose levels. This average blood glucose level is linked to the traditional HbA1c values.

A similar value based on the theory of equation (2) can be calculated using the area under the blood glucose curve (AUC). The AUC is calculated by equation (4) as follows:

$$\text{AUC} = \sum (BS(t) \times 5) \tag{4}$$

Where: BS(t) = blood glucose value as a function of the time.

The AUC value for the first and the second CGMS test for each diabetic patient will be calculated and afterwards compared to each other. The value calculated from the first test is known as the AUC_{CHO} while the value calculated from the second test is known as the AUC_{ETS}.

If the AUC_{ETS} is less than the AUC_{CHO}, it can be deduced that the mean blood glucose value from the second CGMS test is lower than the value in the first CGMS test, thus indirectly imposing a reduced HbA1c value for the test subject using the EIBC.

3.3.5 Overall Control Performance

Since the different blood glucose control variables have now been derived, the link between these control variables can be established in order to construct an overall blood glucose control equation. This equation is known as the Overall control performance and is a function of the different control variables such as in equation (1).

This section shall also be used to discuss the newly proposed methods for expressing blood glucose control. First, let us discuss the main form of the Overall control performance. This is a function of the four different variables and is the combined (added) effect of these blood glucose control effects, thus:

$$\text{Overall control performance} = ABCM_{Fac} + HYPO_{Fac} + HYPER_{Fac} + AUC_{Fac} \qquad (5)$$

in which the different factors are in units of percentages or fractions of 1.

It has further been proposed that each variable should be multiplied with several **weight factors.** The reason for these weight factors is that hypos in general cause short-term complications while hypers cause long-term complications. This means that the hypoglycaemic events cause a larger negative effect on the immediate blood glucose control of the diabetic than the effect from the occurrences of hypers. Most type 1 diabetics are more fearful of hypos than of hypers, and of all the diabetic-related hospitalisations most are caused by acute symptoms from severe hypos.

Yet both hypo- and hyperglycaemia affects the diabetic's daily blood glucose control. It is now proposed from this study that the exact initial values of these variable weight factors should be as follows:

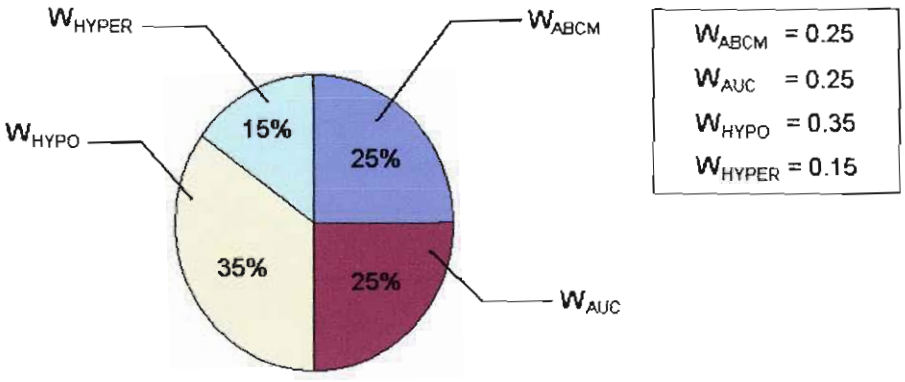

Figure 16: Weight factors for the variable control factors.

Thus the equation for the Overall control performance changes as follows:

$$\text{Overall control performance} = (W_{ABCM} \times ABCM_{Fac}) + (W_{HYPO} \times HYPO_{Fac}) + (W_{HYPER} \times HYPER_{Fac}) + (W_{AUC} \times AUC_{Fac}) \quad (6)$$

Since the definition for the Overall control performance has now been discussed, the methods for expressing the rating of the Overall control performance can now be proposed. Remember that the main purpose of the study is to determine whether the Ets concept improves or deteriorates the overall blood glucose control compared to the carb counting method.

Two methods will now be proposed for rating the change in overall control performance.

A. Group method

In the *group method* the Overall control performance is calculated for the group of test subjects as a whole. The calculation remedy is as follows:

Step 1: Determine the ABCM, AUC, hypos and hypers for each patient before and while using the EIBC.

Step 2: Determine the average value for each of the different control variables.

Step 3: Determine the different control variable factors as follows:

$$ABCM_{Fac} = \left[\frac{Avg(ABCM_{CHO})}{Avg(ABCM_{ETS})}\right]$$

$$HYPO_{Fac} = \left[\frac{Avg(HYPO_{CHO})}{Avg(HYPO_{ETS})}\right]$$

$$HYPER_{Fac} = \left[\frac{Avg(HYPER_{CHO})}{Avg(HYPER_{ETS})}\right]$$

$$AUC_{Fac} = \left[\frac{Avg(AUC_{CHO})}{Avg(AUC_{ETS})}\right]$$

In this method the overall control performance measurement is called the Overall Ets performance and is calculated by the following equation (7):

$$\text{Overall Ets performance} = (ABCM_{Fac} \times 0{,}25) + (HYPO_{Fac} \times 0{,}35) + (HYPER_{Fac} \times 0{,}15) + (AUC_{Fac} \times 0{,}25) \quad (7)$$

The meaning of the final value of the Overall Ets performance is as follows:

Overall Ets performance < 1 : The group on average experienced a deteriation in blood glucose control while using the EIBC.

Overall Ets performance = 1 : On average the overall blood glucose control remained unchanged for the whole group while using the EIBC.

Overall Ets performance > 1 : The whole group experienced on average an improvement in blood glucose control while using the EIBC.

B. Individual method

The *individual method* proposes to calculate the different control variables and the overall control performance for each individual test subject. This will be done by comparing the control values of the patients with the control values calculated for a typical non-diabetic. Thus the variable factors and the overall control performance are expressed in percentages, and the non-diabetic's blood glucose control values represent 100% control.

The procedure of the *individual method*:

Step 1: Determine the ABCM, AUC, bypos and hypers for each patient before and while using the EIBC.

It should be noted that the time period of the CGMS data for each patient differs in most cases.

Step 2: Determine the **24-h factor**:

$$\text{24-h factor (each patient)} = \frac{Time_{MONITOR}[h]}{24} \tag{8}$$

Step 3: Calculate for each patient (both CHO and Ets periods) the control variables **per day** by dividing the values calculated in step 1 with the 24-h factors calculated in step 2:

$$\text{ABCM/day} = \frac{ABCM}{24h.factor}$$

$$\text{HYPOS/day} = \frac{HYPO'S}{24h.factor}$$

$$\text{HYPERS/day} = \frac{HYPERS}{24h.factor}$$

$$\text{AUC/day} = \frac{AUC}{24h.factor}$$

Step 4: Determine the same values as in step 3 for several non-diabetic patients and calculate the average of these values. Initial standard values are calculated and proposed from this study.

Step 5: a.) Initial calculation of the **max. hypo/hyper factor** :

Determine the max. value from all of the HYPOS/day and HYPERS/day column. Now round off this value to the next integer, e.g. 2,41 → 3.

b.) This study proposes to use this newly calculated max. hypo/hyper factor to calculate any futuristic individual control performance.

Step 6: Calculate the tightness control of the individual patient by means of the following equation (9):

$$\mathrm{ABCM_{Perf}} = \left(\frac{ABCM\,/\,day_{NON-DIABETE}}{ABCM\,/\,day_{INDIVIDUAL}} \right) \times 100 \qquad (9)$$

Step 7: Calculate the hypo and hyper performance of the individual patient with the following equation (10) and (11):

$$\mathrm{HYPO_{Perf}} = \left(1 - \frac{HYPO'S\,/\,day_{INDIVIDUAL}}{Max.Hypo\,/\,Hyper.Factor} \right) \times 100 \qquad (10)$$

$$\mathrm{HYPER_{Perf}} = \left(1 - \frac{HYPERS\,/\,day_{INDIVIDUAL}}{Max.Hypo\,/\,Hyper.Factor} \right) \times 100 \qquad (11)$$

Step 8: Calculate the AUC performance of the individual patient with equation (12):

$$\mathrm{AUC_{Perf}} = \left(\frac{AUC\,/\,day_{NON-DIABETE}}{AUC\,/\,day_{INDIVIDUAL}} \right) \times 100 \qquad (12)$$

Step 9: Finally the overall control performance for the individual patient is calculated as follows:

$$\text{Overall control performance} = (ABCM_{Perf} \times 0{,}25) + (HYPO_{Perf} \times 0{,}35) + (HYPER_{Perf} \times 0{,}15) + (AUC_{Perf} \times 0{,}25) \quad (13)$$

In addition for this study the overall control performance for each patient will be calculated for both the time periods before and while using EIBC.

Both the control performance – Ets and the control performance – CHO will be determined and deducted from each other to conclude the change in overall blood glucose control for each patient. Afterwards the average value of the control performance – Ets and the control performance – CHO for the group will be calculated and compared to each other.

3.4 Summary

In this chapter the main goal was to propose and discuss a new concept for characterising blood glucose control. The CGMS System® from Medtronic has reached new frontiers in glycaemic monitoring, and brought with it several new opportunities for analysing and rating blood glucose control. After discussing the main features of the CGMS System, a new calculation remedy for expressing blood glucose control was established.

With the use of the CGMS output data, several new equations and blood glucose control variables have been derived. Finally, two new methods have been proposed and explained for rating a diabetic's overall blood glucose control in a numerical and scientific fashion.

CHAPTER 4

CLINICAL TRIAL PROTOCOL

In order to conduct medical research on human beings, several ethical guidelines need to be addressed. A clinical trial protocol needs to be in place to ensure the safe and orderly execution of the trials. A comprehensive discussion of the EIBC is also held within this chapter.

4.1 Introduction

The thesis of this study started off with chapter 1 which stated the main objective of the study. Chapter 2 was used to explain the reasons for conducting the study. In chapter 3 the characterisation models of glycaemic control were derived which formed part of the study's methodology.

In this chapter we continue with an explanation of the method of this study by firstly discussing the main features of the EIBC. Secondly, the clinical trial protocol will be explained in further detail.

4.2 Ets-Insulin-Bolus Calculator (EIBC)

As stated previously the EIBC, a derivation of the Ets concept, is a cellphone-based application with the main goal of assisting type 1 diabetics in achieving better glycaemic control. Figure 17 once again shows a picture of the EIBC:

Figure 17: Nokia cellphone with EIBC application.

Type 1 diabetics control their blood glucose level by means of their diet, insulin dosages and exercises. This task is, however, a complex task for most diabetics.

Currently most diabetics make use of either of two different methods regarding their insulin dosages. One method is a fixed amount of bolus (short-acting) insulin after every main meal. The diabetic's physician calculates an initial value for the required insulin dosages, and this value is optimised as time goes by. This method is not very efficient since not every meal affects the blood glucose level in the same way.

The second method is that of carbohydrate counting and at present as many as 70% of all type 1 diabetics use this method [8]. This method definitely requires more attention from the diabetic, yet is substantially more efficient than the first-mentioned method.

A "third" method is the newly found Ets concept, in which the different foods, together with their GI-values and portion sizes are expressed in units of Ets. We will now discuss the basic principles of the EIBC. Consider Figure 18 :

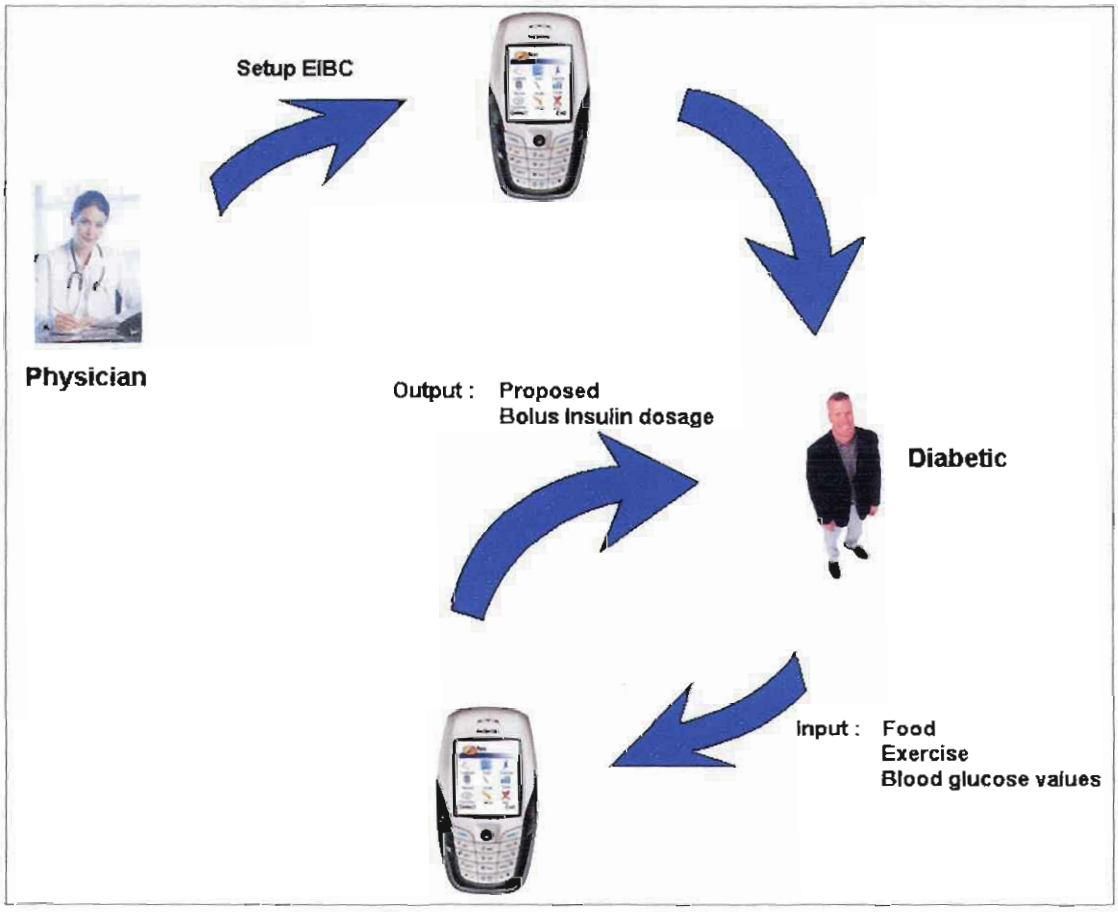

Figure 18: Input/Output cycle of the EIBC.

The main function of the EIBC is to calculate the required amount of bolus insulin for the diabetic in order to stabilise the blood glucose level at a healthy target level. More information can also be found in the EIBC user guide [57] and in appendix C.

The calculation is based on the Ets concept and takes into account the food consumption, exercises and finger-stick blood glucose values. The EIBC's calculation model is a simplified mathematical equation which represents the human blood glucose level. However, not every diabetic's blood glucose system behaves in the same way as any other diabetic's blood glucose system. The EIBC has made provision for this issue by introducing several metabolic efficiency factors into the equation. Thus, before the diabetic receives the calculator, his/her physician individually customises the EIBC for each diabetic.

The EIBC needs the following information regarding the diabetic in order to set up the calculator:

1. Length and weight
2. Age and gender
3. Activity level (low, medium or high)
4. Total daily long- and short-acting insulin
5. Ets sensitivity and insulin sensitivity factors
6. Target blood glucose value
7. Maximum Ets value per meal
8. Maximum insulin value per dosage
9. Ets recommended daily allowance.

The information in numbers 1, 2 and 3 above is primarily used to calculate the RDA in terms of Ets for the specific diabetic. The RDA feature is mainly used for dietetic purposes. Input of the total daily bolus and basal insulin are mostly for reference calculation. The metabolic Ets and insulin sensitivity factors are, however, important input variables into the EIBC, and the calculation of these variables is explained in the next section.

Number 6 from the list is the target blood glucose value. This value is normally in the range of 5–8 mmol/ℓ and is used as the set point in the equation.

The EIBC also includes several safety variables in the set-up process. The purpose of these safety buffers is to warn the diabetic when the current food portion will cause dangerously high blood glucose elevations. Part of these safety variables is also to prevent the diabetic from administering too much insulin which will in most cases lead to severe hypoglycaemic attacks. The following are a list of other beneficial features of the EIBC [14]:

- Easy-to-use and practical device
- Improved visibility of device
- Complete food database and predefined meals
- Complete exercise database
- Educational tool.

The main purpose of the EIBC, using the efficiency factors together with all of the other input variables, is to calculate an accurate proposed insulin requirement. This will lead to a smoother blood glucose profile, thus improving overall glycaemic control for the diabetic.

4.3 Clinical Trial Protocol

Before any research can be conducted on human beings there are several issues that need to be addressed first. Any research conducted on human beings is subject to certain ethical guidelines [58, 59]. Approval should be obtained from an ethical committee within the country.

In order to achieve a successful clinical trial within this study, it is necessary to follow a specific trial protocol. The clinical trial protocol describes the phases and processes of the trial. The protocol consists of the following main outcomes:

- Patient's informed consent (PIC) form
- Pre-trial questionnaire
- First three-day CGMS test
- Use of the EIBC
- Second three-day CGMS test

Apart from the trial protocol, the final data analysis is done at the end of the trials.

4.3.1 Patient Informed Consent form

The purpose of the PIC form is to inform the diabetic patient of the following:

- Purpose of the study
- Methodology of the study
- Possible benefits from the study
- Possible risks from the study
- Information regarding the termination of the study

The PIC serves as an agreement between the trial subject and the trial coordinator, and sets out the terms and conditions of participation in the clinical trial. Note that the PIC is shown in appendix A.

It should also be noted that any trial subject may at any time withdraw from the clinical trial. In case of certain adverse events happening, the trial coordinator and/or trial doctor may terminate a trial subject's participation in the trials.

4.3.2 Pre-Trial Questionnaire

After signing the PIC form the trial subject needs to complete the pre-trial questionnaire. This questionnaire is used to obtain the following information regarding the diabetic subject:

- Age
- Gender
- Weight at onset of trial
- Height
- Daily activity level
- Type and amount of daily bolus insulin dosage
- Type and amount of daily basal insulin dosage
- Frequency of hypo- and hyperglycaemic occurrences
- Type of insulin therapy
- Brand and model of blood glucose monitor
- Medical history regarding diabetes or other chronic diseases

- Target blood glucose level
- HbA1c as measured

The pre-trial questionnaire serves as a baseline examination and is reviewed by the trial coordinator and the trial doctor.

* An example of the pre-trial questionnaire is shown in the appendices.

4.3.3 First 3-day CGMS Test

After the diabetic subject completes the pre-trial questionnaire, the monitoring process of the diabetic's blood glucose starts. The diabetic makes use of the CGMS for 3–4 consecutive days to monitor and record his/her typical daily blood glucose profile.

On completion of setting up and initiating the CGMS for the patient, the subject follows his/her typical daily routine for the first two days. It is, however, very important that the patient follows his/her normal daily routine and not be intimidated by the CGMS. The blood glucose profile obtained from the first two days serves as the baseline profile, and comparisons will be made to this baseline. On the third day the patient is asked to follow the rule below:

Administer the typical required amount of bolus insulin 90 minutes after each main meal.

The purpose of this rule is to create the opportunity from which the Ets and insulin sensitivity factors can be successfully calculated. Refer to Figure 19 on the calculation of these factors:

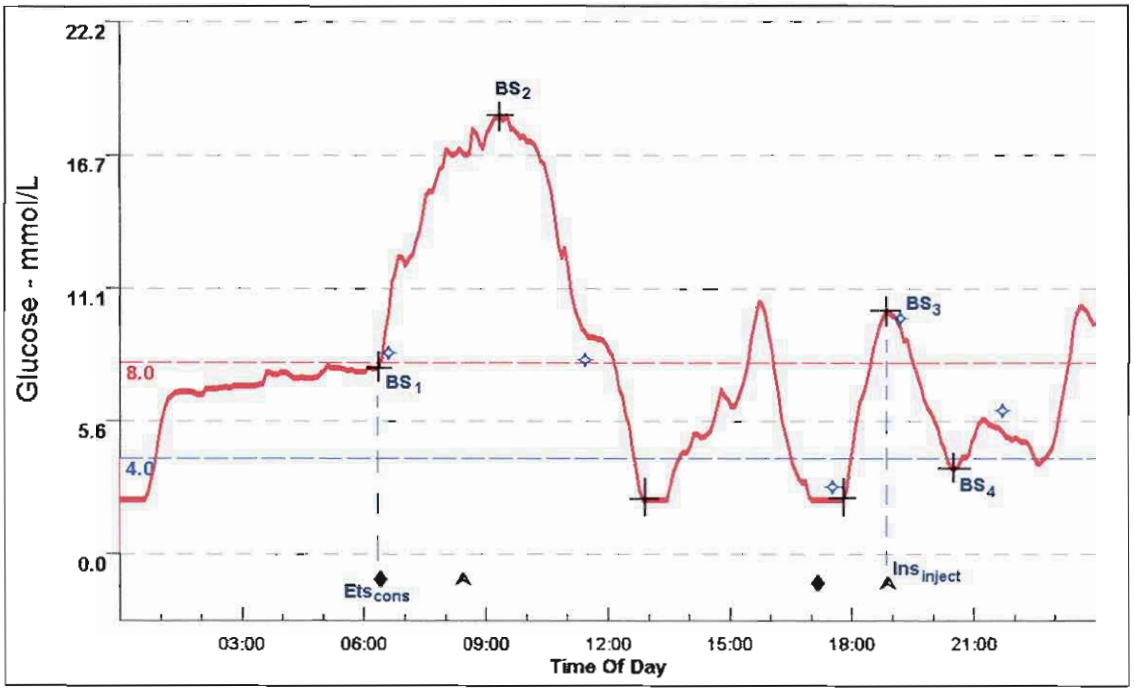

Figure 19: Calculation of the Ets- and Insulin sensitivity factors.

The Ets and insulin sensitivity factors are calculated with the following equations:

Ets sensitivity :

$$E_S = \frac{BS_2 - BS_1}{ETS_{CONS}} \qquad \left[\frac{mmol.L^{-1}}{Ets}\right] \tag{14}$$

Where: BS_1 = blood glucose value at the start of the meal.

BS_2 = peak blood glucose value after 90 minutes from start of meal.

ETS_{CONS} = total food in units of Ets ingested during the meal.

After determining the E_S factor, this value can be multiplied with the amount of Ets ingested at any other instance to calculate the increase in blood glucose that the food ingested shall cause.

Insulin sensitivity :

$$I_S = \frac{BS_3 - BS_4}{INS_{INJECT}} \qquad \left[\frac{mmol.L^{-1}}{U}\right] \tag{15}$$

Where: BS_3 = peak blood glucose value after 90 minutes from start of meal

BS_4 = lowest blood glucose value after 90 minutes after bolus insulin dosage

INS_{INJECT} = units of insulin injected.

When the I_S factor is multiplied with the amount of bolus insulin injected at any other instance, the total decrease in blood glucose concentration can be calculated. Both the E_S and the I_S factors are calculated at two or three instances in the last day's profile, from which an arithmetic average is calculated for each factor.

In addition the diabetic patient writes down on the given trial log sheets the precise amount, time and type of all meals, exercises and measured finger-stick blood glucose values. After the third day the CGMS is carefully removed and the data from the trial is downloaded onto a computer.

4.3.4 Use of EIBC

The information from the CGMS is then used by the physician and the trial coordinator to determine the various set-up variables as mentioned in section 4.2. After customising the EIBC for the specific diabetic, the trial subject then receives the EIBC and starts to use the EIBC for its intended purpose.

The trial subjects will use the EIBC for approximately three months. This three months period allows enough time to reflect a possible change in the average blood glucose level (HbA1c). During this period the trial coordinator is continuously in contact with the trial subject. The patient gives feedback regularly on the status of the trial. Optimising of the sensitivity factors may occur during this period.

4.3.5 Second 3-day CGMS Test

At the end of the three-month period a second and final three-day CGMS test is conducted with each of the trial subjects. During this test the diabetic still uses the EIBC to control his/her blood glucose level.

The purpose of this second CGMS test is to record the updated typical blood glucose profile while the patient is using the EIBC. This second profile is compared with the previous baseline profile, and the necessary calculations are being done as described in the previous chapter.

During this particular test the subjects do not need to write down on log sheets the same information as was required in the previous CGMS test.

Figure 20: Illustration of diabetic person using the CGMS.

4.4 Summary

During this chapter a brief discussion was held on the features of the EIBC. The EIBC is a novel device and its performance will be tested in this study based on the mathematical models. The clinical trial protocol was also thoroughly laid out in this chapter. Chapters 3 and 4 conclude the methodology of the study.

CHAPTER 5

EIBC PERFORMANCE VERIFICATION

In order to verify the mission statement of this study, clinical trials with several type 1 diabetics are needed. The control equations derived from the previous section are implemented in this chapter to give verification of the EIBC's performance on type 1 diabetics.

5.1 Introduction

As previously mentioned the EIBC, a development from the Ets concept, was primarily designed to assist type 1 diabetics in improving their daily blood glucose control. Clinical trials are, however, important to determine whether the use of the EIBC by type 1 diabetics improves overall blood glucose control. Verification of the EIBC's performance will now be made, using the principles and equations derived from the previous chapter. This chapter shall be used to expose the results of the clinical trials.

5.2 Clinical Trial Overview

This section illustrates a quick overview of the clinical trial process. Figure 21 illustrates this overview:

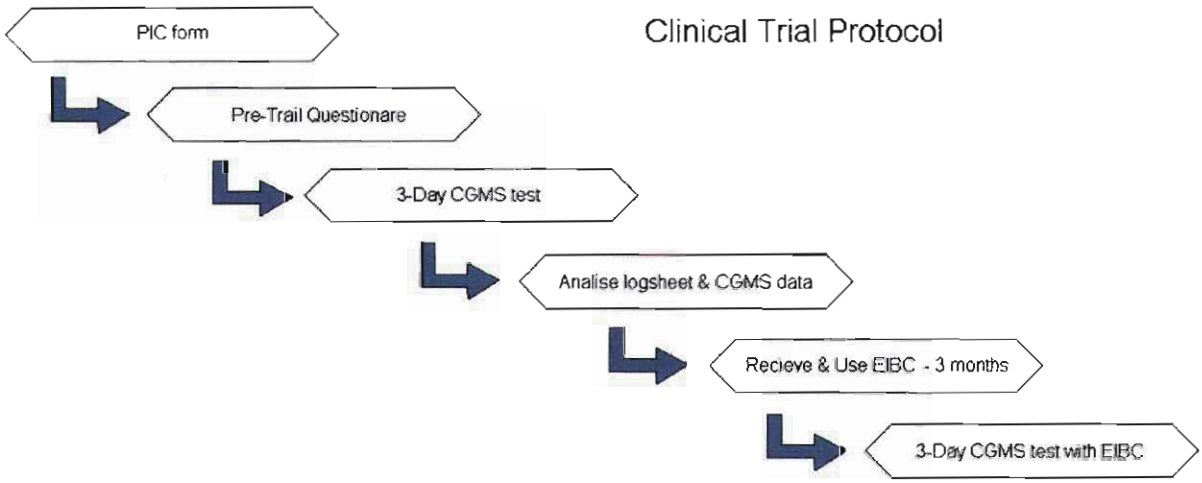

Figure 21: Layout of Clinical Trial Procedure.

It should, however, be noted that if the diabetic person experiences severe hypo- or hyperglycaemic events during any stage of the trial, the subject should temporarily abort the test procedure in order to take correctional steps to improve blood glucose control. Any test subject also has the right to abort the trial at any given time.

5.3 Trial Subject Description

In Table 4 general information of the test subjects participating in the clinical trial is given:

Table 4: Trial subjects information.

Subject	Gender	Age	Height [m]	Weight [kg]	Activity Level
1	Female	21	1.69	60	Medium
2	Male	54	1.80	75	Medium
3	Female	45	1.60	93	Medium
4	Male	23	1.68	61	High
5	Female	26	1.70	74	Medium
6	Male	53	1.80	67	Medium
7	Female	18	1.66	75	Medium
8	Female	50	1.75	66	Medium
9	Female	34	1.60	52	Medium

5.4 Trial Results

In this section the main results of the trials are shown, followed by short discussions of the results. Two of the nine test subjects have done an additional CGMS test.

5.4.1 Tightness Control (ABCM)

Group method

In Figure 22 the trial results regarding the tightness control achieved with the CHO method and the Ets concept (EIBC) for each of the test subjects are shown:

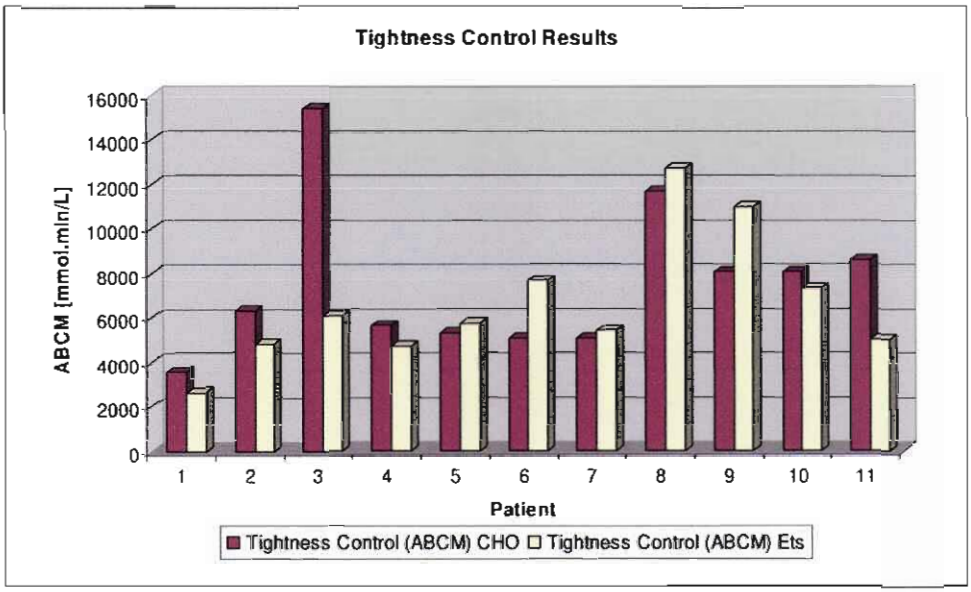

Figure 22: Tightness Control achieved with CHO and ETS method.

The calculated average ABCM values for the group are:

$ABCM_{CHO}$ = 7 537 mmol.min/ℓ

$ABCM_{ETS}$ = 6 637 mmol.min/ℓ

This indicates an average improvement of the tightness control with the Ets concept by a factor of **1,14**.

Individual method

Table 5 shows the results of the tightness control as calculated with the *individual method* for each patient:

Table 5: ABCM results for each patient with Individual Method.

	Tightness Control		
	ABCM_cho	*ABCM_ets*	*Δ ABCM*
Subject	%	%	%
1	**40.64**	**55.68**	15.03
2	**23.41**	**30.68**	7.27
3	**14.19**	**36.03**	21.85
4	**23.97**	**28.70**	4.74
5	**35.78**	**33.13**	-2.64
6	**27.86**	**18.45**	-9.41
7	**27.86**	**26.20**	-1.65
8	**16.20**	**14.91**	-1.29
9	**23.85**	**17.58**	-6.26
10	**23.85**	**26.37**	2.53
11	**13.80**	**23.76**	9.96

From Table 5 can it be calculated that the EIBC improved the Tightness Control on average by **3.65 %**.

5.4.2 Hypo- and Hyperglycaemic Occurrences

Group method

An illustration of the hypo- and hyperglycaemic occurrences during the trial is shown in Figure 23 and Figure 24 respectively:

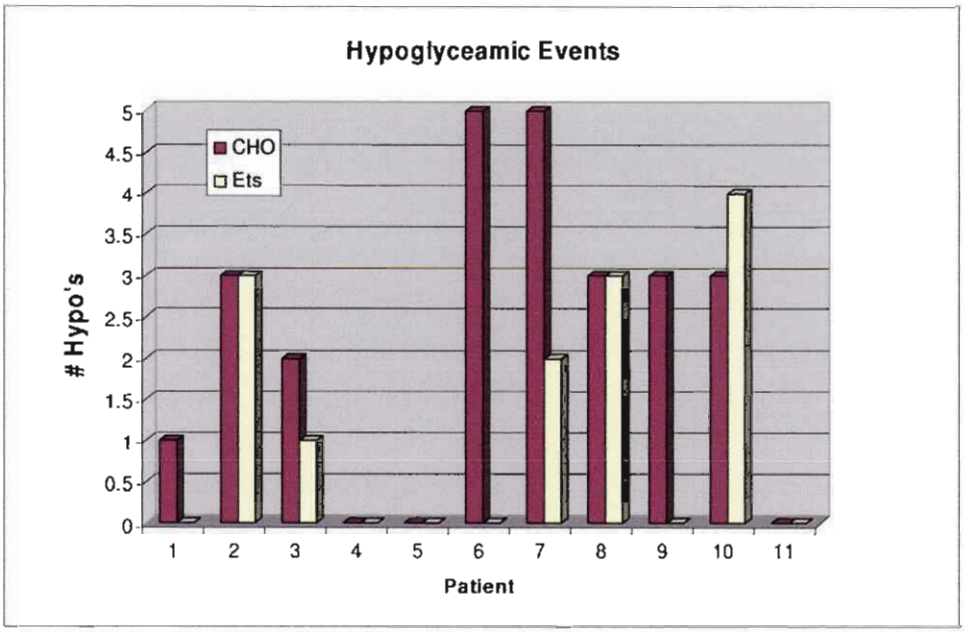

Figure 23: Amount of Hypo's experienced during trials.

From Figure 23 it is found that the average number of hypos from the CHO period was 2,27 and 1,18 for the Ets period. This shows that the Ets concept improved hypoglycaemic occurrences by a factor of **1,92**.

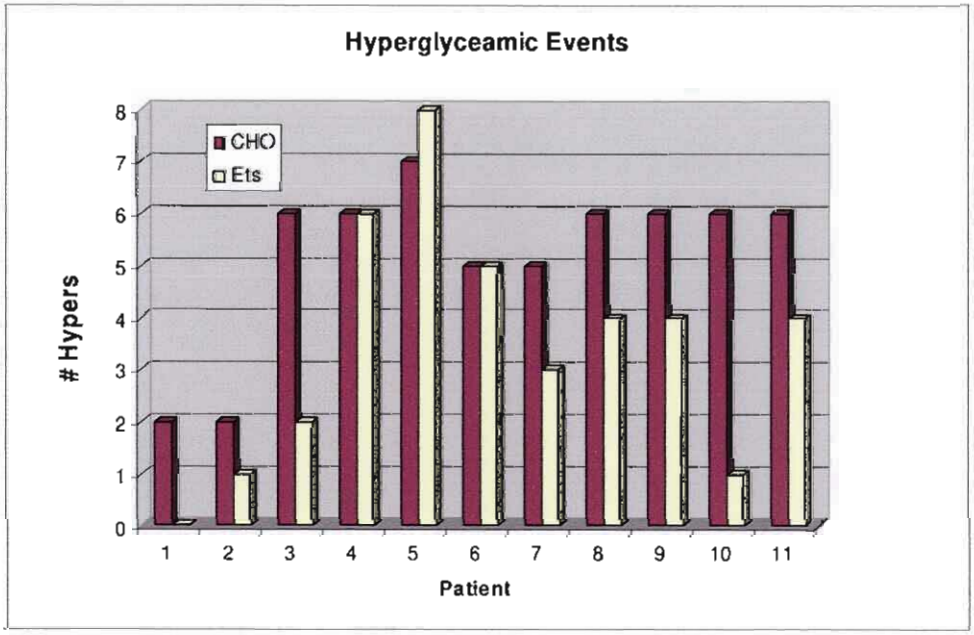

Figure 24: Amount of Hypers experienced during trials.

The average number of hypers for the CHO period is 5,18 and for the Ets period 3,45. The hyperglycaemic occurrences were improved by a factor of **1,50** by means of the Ets concept.

Table 6: Hypoglycaemic results for each patient with Individual Method.

	Hypoglycaemic Events		
	HYPO_cho	HYPO_ets	Δ HYPO
Subject	%	%	
1	**86.67**	**100.00**	**13.33**
2	**60.87**	**60.87**	**0.00**
3	**82.35**	**91.18**	**8.82**
4	**100.00**	**100.00**	**0.00**
5	**100.00**	**100.00**	**0.00**
6	**31.82**	**100.00**	**68.18**
7	**31.82**	**72.73**	**40.91**
8	**69.49**	**69.49**	**0.00**
9	**70.00**	**100.00**	**30.00**
10	**70.00**	**60.00**	**-10.00**
11	**100.00**	**100.00**	**0.00**

The average value calculated for the change in hypoglycaemic occurrences is **13.75%**. Thus the EIBC improved the issue of hypoglycaemia.

Table 7: Hyperglycaemic results for each patient with Individual Method.

	Hyperglycaemic Events		
	HYPERS_cho	HYPERS_ets	Δ HYPER
Subject	%	%	
1	**73.33**	**100.00**	**26.67**
2	**73.91**	**86.96**	**13.04**
3	**47.06**	**82.35**	**35.29**
4	**14.29**	**14.29**	**0.00**
5	**28.81**	**18.64**	**-10.17**
6	**31.82**	**31.82**	**0.00**
7	**31.82**	**59.09**	**27.27**
8	**38.98**	**59.32**	**20.34**
9	**40.00**	**60.00**	**20.00**
10	**40.00**	**90.00**	**50.00**
11	**2.70**	**35.14**	**32.43**

The Ets concept also improved hyperglycaemic events with an average value of **19.53 %.**

5.4.3 HbA1c (AUC)

Group method

The following results regarding the AUC values from the trial are shown in Figure 25:

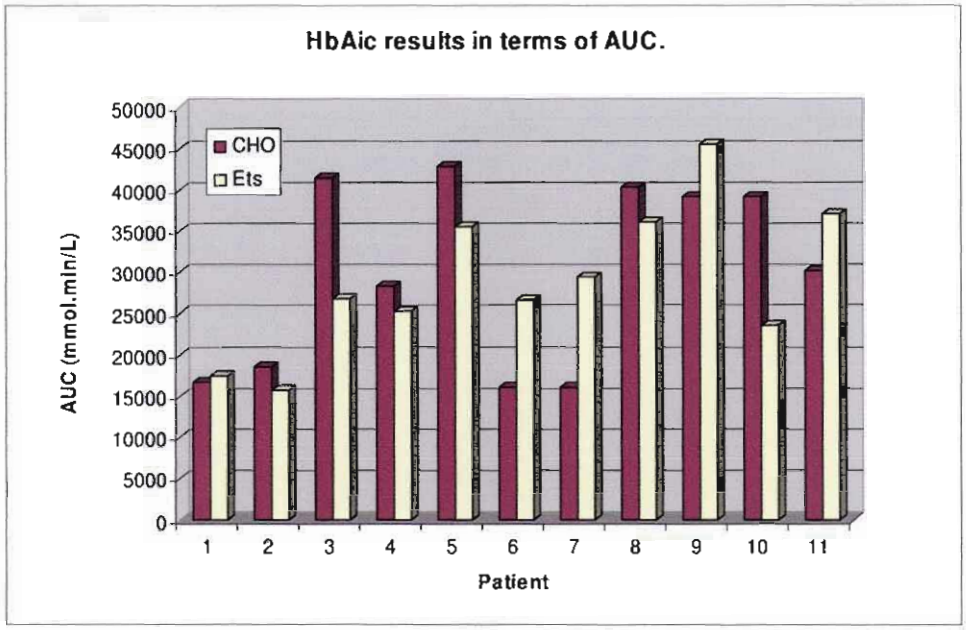

Figure 25: AUC results for the group during CHO and ETS period.

As in the ABCM category, a reduction in AUC value relates to an improvement in HbA1c level. From the above figure, six of the 11 trial results showed improvements in AUC values with the use of the EIBC. In a three-month period the Ets concept on average slightly improved the AUC (HbA1c) with a factor of **1,03**.

Individual Method

Table 8: AUC results for each patient with Individual Method.

	AUC (HbA1c)		
	AUC_cho	AUC_ets	Δ AUC
Subject	%	%	%
1	**87.65**	**83.80**	-3.85
2	**80.59**	**94.68**	14.09
3	**53.25**	**82.61**	29.36
4	**47.99**	**53.86**	5.86
5	**44.67**	**53.95**	9.29
6	**88.23**	**53.65**	-34.58
7	**88.23**	**48.46**	-39.77
8	**47.49**	**52.87**	5.38
9	**49.73**	**42.80**	-6.93
10	**49.73**	**83.00**	33.27
11	**39.79**	**32.36**	-7.44

The average value in change of AUC calculated for Table 8 is **0,42%**. The use of the EIBC leads to a relatively small improvement in AUC for the test subjects.

5.4.4 Overall Control Performance

Group method

If we combine the above blood glucose control elements using equation (6), we then calculate the Overall Ets performance to be **1,44**. According to the equation it shows that the average overall blood sugar control for the group of test subjects was improved by 44% for subjects using the EIBC.

Individual method

Lastly, in Table 9 the results for the overall control performance are shown for each patient as well as the change in overall control performance between the CHO and Ets periods:

Table 9: Overall Control Performance for each patient with Individual Method.

	Overall Control Performance		
	Control Performance_cho	Control Performance_ets	Improvement Control
Subject	%	%	%
1	**73.41**	**84.87**	**11.46**
2	**58.39**	**65.69**	**7.30**
3	**52.74**	**73.92**	**21.18**
4	**55.13**	**57.78**	**2.65**
5	**59.43**	**59.57**	**0.13**
6	**44.93**	**57.80**	**12.87**
7	**44.93**	**52.99**	**8.05**
8	**46.09**	**50.17**	**4.07**
9	**48.89**	**59.10**	**10.20**
10	**48.89**	**61.84**	**12.95**
11	**48.80**	**54.30**	**5.50**

Looking at the above figures in Table 9 we can see that all patients improved their overall blood sugar control with the use of the EIBC. The average value calculated for the above improvement figures for the group is **8,76%**.

5.5 Summary

In this chapter we firstly discussed the clinical trial procedure. The trial period for each patient is three months, for which two CGMS tests per patient are performed at the beginning and at the end of the three-month period.

Secondly, we investigated the end results from the clinical trial in which the performance of the EIBC was tested on a numerical basis. Several performance factors and control percentages were calculated, using the control equations.

If the value of these factors in the *group method* were less than one, this implied a deterioration of that specific glycaemic element. If the factor were greater than one, it implied an improvement.

The average values of the clinical trial results showed that the patients using the EIBC experienced improvements in tightness control (**1,14**), hypo occurrences (**1,92**) and hyper occurrences (**1,50**). On average the AUC value remained almost the same with an end factor of **1,03**. The Overall Ets performance factor calculated for the 11 trial results is **1,44**. meaning that on average the group's blood glucose control were improved when using the Ets concept.

When using the *individual method* the blood sugar control values were compared with the values calculated for a typical non-diabetic and expressed in percentage value, 100% being perfect control. The average improvements calculated for the group with the *individual method* was **3,65%** in tightness control, while hypoglycaemia improved by **13,75%**, hyperglycaemia improved by **19,53%** and HbA1c in terms of area improved by **0,42%**. On average the whole group's overall control performance was increased with **8,76%** after using the EIBC.

CHAPTER 6

CLOSURE

Chapter 6 serves as the closure of this study. The final conclusion regarding this study's objective is made, and recommendations are made for further work in this particular field of study.

6.1 Introduction

Now that the final task in the performance verification process has been completed, a conclusion can be drawn regarding the glycaemic control of diabetics using the EIBC. In this chapter the overall findings of the study will be mentioned, and recommendations for further work will also be made. Chapter 6 shall serve as the closure for this study.

6.2 Conclusion of the Study

The overall conclusion of the study will start off by once again referring to the mission statement of the study. The main objective of this study was to determine whether the Ets concept by means of the Ets-insulin-bolus calculator (EIBC) promotes tighter blood glucose control for type 1 diabetics. Tighter glycaemic control means improving the control remedy in such a way that the actual daily blood glucose profile is tighter or "smoother". This enhancement automatically reduces the occurrences and/or intensity of hypo- and hyperglycaemic events, thus improving the short- and long-term quality of the diabetic's lifestyle.

The secondary objective of the study was to propose and construct a mathematical model for expressing and rating blood glucose control. After discussing in chapter 3 the features of the CGMS System® from Medtronic, two new scientific models have been derived in order to verify the performance of the EIBC in a numerical fashion.

This was followed by performing the clinical trials with several type 1 diabetics under the controlled supervision of the diabetics' physician, Dr Louise Johnson. The output CGMS data from the trials, together with the derived control equations, formed the overall control performance figures of the diabetics before and while using the EIBC.

The final conclusion of the study is that the EIBC does in fact on average improve overall blood glucose control and thus promotes tighter glycaemic control for type 1 diabetics. The final figures from both the *group method* and the *individual method* support this conclusion.

6.3 Recommendations for Further Work

Experience gained from this study has shown several opportunities for future research. The following is a list of recommendations:

- Many of the diabetic trial patients had suggestions on improving the EIBC. It is recommended that these suggestions from the patients be investigated, which could lead to upgrading the EIBC.
- The development of an educational CD regarding the Ets concept and its products for diabetics could lead to improved co-operation from diabetics during clinical trials.
- Designing and developing a computer program that is capable of receiving all of the input data from the EIBC and analysing this data in the form of graphical blood glucose trends and figures. Diabetics could gain deeper insight into their blood glucose behaviour with the use of the EIBC.
- The trials in this study were performed over a relatively short-term period of three months. It is recommended that clinical trials monitoring the long-term performance of the EIBC be conducted.

CHAPTER 7

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APPENDIX A - PATIENT INFORMED CONSENT FORM

GLYCEMIC CONTROL OF TYPE 1 DIABETICS USING THE ETS CONCEPT

PROTOCOL HS_DIAB_004

Version 1.3 – 21 June 2005

PATIENT INFORMED CONSENT FORM

Human-Sim thanks you for your time and willingness to help us with this clinical trial. It is our company's goal to improve the health of diabetics by improving their blood glucose control. Without your help this would not be possible. In order for you to participate in our trial, we need your informed consent. Please read through this agreement and sign it on the last page if you agree to participate in this clinical trial. Please do not hesitate to ask should you have any questions.

RESEARCH

The purpose of this clinical trial is to determine whether ETS-counting (a concept developed from research done by Human-Sim, South Africa) as opposed to Carbohydrate-counting can improve blood glucose control for Type 1-diabetics. Data analysed of Canadian researchers Lee, Wollever and Bolognesi showed ETS to be a more accurate predictor of insulin response than carbohydrates. A cellular phone software application will be used to calculate boluses using ETS-counting. By entering a current blood glucose level, selecting the food and beverage items to be consumed and exercises to be performed, the program will suggest a bolus. This clinical trial will therefore investigate the ETS-counting concept in a practical environment by using a cellular phone application.

SELECTION PROCEDURE

Between 10 and 20 test subjects will participate in the clinical trial. Trial subjects were selected on a random basis from Dr. L. Johnson's practice (convenience samples) and had to meet certain inclusion requirements e.g. be at least 14 years old and need to be familiar with the carbohydrate counting concept. Participants in this clinical trial will not be allowed to plan to become pregnant. be pregnant or breastfeeding for the duration of the trial. Adequate contraception must be used for the duration of the trial. If a participant does however fall pregnant, the participant will be required to withdraw

from the clinical trial.

TRIAL PROCEDURES

The trial will be initiated by a briefing session at Dr. L. Johnson's practice at the Montana Hospital in Pretoria. The ETS-concept will be explained to all participants and demonstrations will be given on operating the cellular phone and the bolus insulin calculation software. Each participant will receive a cellular phone with the bolus calculation software. A blood sample will be taken to test Glycohemoglobin levels (HbA1c). This gives an indication of the quality of blood glucose control for the period of three months prior to the trial. A simple procedure will then be performed on test subjects to determine sensitivities to ETS and insulin. Blood glucose levels will be monitored while first ingesting a meal and then afterwards injecting short acting insulin. The calculated values will then be entered into each individual's cellular phone to customize it for the specific participant. Participants will then for three months calculate their boluses with the device. Technical support will be available to all participants. At the end of the trial Glycohemoglobin levels will be tested again and compared with the initial values. Participants will also receive a questionnaire at the end of the clinical trial. Participants will have to return the cellular phones at the end of the trial.

POSSIBLE BENEFITS TO PARTICIPANTS

Benefits of participating in this trial may include:

- improved blood glucose control,
- fewer occurrences of hypo- and/or hyperglycemia and
- a better understanding of blood glucose control.

These benefits can however not be guaranteed. Participation in this clinical trial also helps the international scientific community to further diabetic research and could eventually improve the lives of many diabetics.

PARTICIPATION

Participation in this clinical trial is voluntary. Participants may at any time decide to stop participating without supplying a reason. The research company strongly urges participants not to withdraw from the trial, as this will have an effect on the statistical significance of the research. There are however no foreseeable risks involved by withdrawing from the trial. The research institution or study doctor will inform

participants if new information becomes available that might influence their willingness to continue the study. The research company reserves the right to terminate the clinical trial at any stage on their discression, should it become necessary.

CONFIDENTIALITY

All records identifying participants will be kept confidential, to the extent permitted by the applicable laws and/or regulations and will not be made publicly available. If the results of this trial are published, the subject's identity will remain confidential. All participants have the right to see, copy and correct some of their personal health information related to the research as long as this information is held by the study doctor (Dr. L. Johnson) or research institution (Human-Sim (Pty) Ltd.). The participant agrees that the Monitors, Auditors, the Ethics Committee and the Regulatory Authorities be granted direct access to the participant's medical records for verification.

CONTACT INFORMATION

Should the participant require any help or assistance the following people could be contacted at any time:

Technical assistance, ETS-concept information etc.

Ruaan Pelzer	083 391 6672	012 809 1051
Henry Townsend	082 575 2336	012 809 1055

Medical emergencies

Dr. L. Johnson	082 821 9680	012 548 5409

I hereby declare that I am willing to participate in the clinical trial as discussed in this document. I am aware that participation will involve some changes to my insulin regime and that I may at any stage decide to withdraw from the clinical trial.

SIGNED

Name of participant, parent or guardian	Signature of participant, parent or guardian	Date signed
Name of investigator or designated person	Signature of investigator or designated person	Date signed

A signed copy of this document will be handed to you, the participant.

APPENDIX B - PRE-TRIAL QUESTIONAIRE

PRE CLINICAL TRIAL QUESTIONNAIRE- ETS BOLUS CALCULATOR

Please complete the following questionnaire. If you are not sure what is being asked, please consult one of the assistants or doctors. We appreciate your time and effort in helping us with this clinical trial.

Date:

YOUR DETAILS

Full name:

Contact numbers:

Home:	
Work:	
Mobile:	

Contact addresses:

Residential:	
Postal:	
Email:	

YOUR DAILY ACTIVITIES

How often do you exercise?	
What type(s) of exercise or sport?	
Typical duration of exercise?	
Typical daily activity level during week?	☐ Low ☐ Moderate ☐ High
Typical daily routine?	
At what time do you normally go to bed?	
At what time do you normally get up in the morning?	

YOUR MEALS AND SNACKS

How many meals do you have per day?

How many snacks do you have per day?

Do you count your calories? ☐ Yes ☐ No

YOUR BODY

Gender: ☐ Male ☐ Female **Age**: **Height**: **Weight**:

HbA1C: (Leave this space open)

IF YOU ARE USING AN **INSULIN PEN** OR **SYRINGE** AND NOT AN INSULIN PUMP
PLEASE COMPLETE THIS PAGE:

YOUR LONG-ACTING INSULIN (BASAL)

Type:	Eg. Lantus
Total daily dose:	U

At what time(s) do you inject? How many units?

Basal dosage 1	**Basal dosage 2**
Time:___ h___	Time:___ h___
Units:_____U	Units:_____U

SHORT-ACTING/MIXED INSULIN (BOLUS)

Type:	Eg. Actrapid
Total daily dose:	U

Please give us an indication of the typical dose and time of your boluses:

Bolus 1	**Bolus 2**	**Bolus 3**	**Bolus 4**	**Bolus 5**
Time:___ h___	Time:___ h___	Time:___ h___	Time:___ h___	Time:___ h___
Units:_____U	Units:_____U	Units:_____U	Units:_____U	Units:_____U

METHOD OF INSULIN ADMINISTRATION

☐ Pen ☐ Syringe ☐ Other, please specify _____

YOUR BLOOD GLUCOSE MONITOR (METER)

Type or brand of meter:	
How many times per day do you measure your blood glucose level?	

YOUR BLOOD GLUCOSE (SUGAR)

What is your target blood glucose level? Between ☐ mmol/l and ☐ mmol/l

How often do you get Hypo's (low blood glucose)? ☐

At what time(s) are you most likely to get a hypo?

☐ Early morning ☐ Morning ☐ Afternoon ☐ Early evening
☐ Late in the evening (before going to bed) ☐ While sleeping for a short while
☐ While sleeping for a long while

How often do you have a problem with high blood glucose levels?

☐

IF YOU ARE USING AN **INSULIN PUMP** PLEASE COMPLETE THIS PAGE:

YOUR INSULIN REGIME

Type of insulin:	Eg. Actrapid
Total daily basal dose:	U
Total daily bolus dose:	U = + + + +

Please give us an indication of the typical basal dosages and the times of your boluses:

Bolus 1	**Bolus 2**	**Bolus 3**	**Bolus 4**	**Bolus 5**
Time:___ h___	Time:___ h___	Time:___ h___	Time:___ h___	Time:___ h___
Units:_____U	Units:_____U	Units:_____U	Units:_____U	Units:_____U

YOUR BLOOD GLUCOSE MONITOR (METER)

Type or brand of meter:	
How many times per day do you measure your blood glucose level?	

YOUR BLOOD GLUCOSE (SUGAR)

What is your target blood glucose level? Between ☐ mmol/l and ☐ mmol/l

How often do you get Hypo's (low blood glucose)? ☐

At what time(s) are you most likely to get a hypo?

☐ Early morning ☐ Morning ☐ Afternoon ☐ Early evening
☐ Late in the evening (before going to bed) ☐ While sleeping for a short while
☐ While sleeping for a long while

How often do you have a problem with high blood glucose levels?

☐

- End of Questionnaire -

Thank you for your time

APPENDIX C - EIBC USER GUIDE

USER'S GUIDE FOR ETS-BOLUS CALCULATION CELLPHONE

Equivalent Teaspoons Sugar ets®

R PELZER

HELP / ASSISTANCE

DURING THE DURATION OF THIS CLINICAL TRIAL, YOU MAY AT ANY TIME CONTACT US FOR HELP OR ASSISTANCE. PLEASE DO NOT HESITATE TO CONTACT US SHOULD YOU EXPERIENCE ANY PROBLEMS OR HAVE ANY QUESTIONS.

FOR TECHNICAL ASSITANCE (E.G. PROBLEMS WITH THE PHONE OR SOFTWARE) CONTACT EITHER

- RUAAN PELZER, 083 391 6672 OR
- HENRY TOWNSEND, 082 575 2336

YOU CAN ALSO CONTACT US AT OUR PRETORIA OFFICE ON 012 809 1055.

IF YOU HAVE A MEDICAL EMERGENCY OR NEED MEDICAL ASSISTANCE PLEASE CONTACT DR. LOUISE JOHNSON ON ONE OF THE FOLLOWING NUMBERS:

- 012 548 5409 (PRACTICE AT MONTANA HOSPITAL)
- 082 821 9680

ALTERNATIVELY, YOU MAY ALSO PHONE YOUR GENERAL PRACTITIONER OR LOCAL HOSPITAL TO ASSIST YOU IN CASE OF A MEDICAL EMERGENCY

CONTENTS

1 - USING THE CELLPHONE

Here is a brief summary of the most important phone functions.

TURN THE PHONE ON

Press and hold top button, ...Wait a few seconds, Enter PIN (when asked) and press #

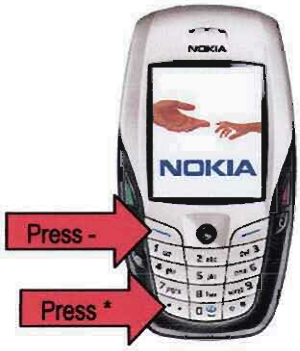
TURN THE PHONE OFF

Press and hold top button *

* Make sure the keypad is not locked

LOCK OR UNLOCK THE KEYPAD

First press "–" and then *



HOW TO MAKE A TELEPHONE CALL

Make sure the keypad is unlocked. Enter the telephone number and press the green button (left). Press the red button (right) to end the call.

...or...

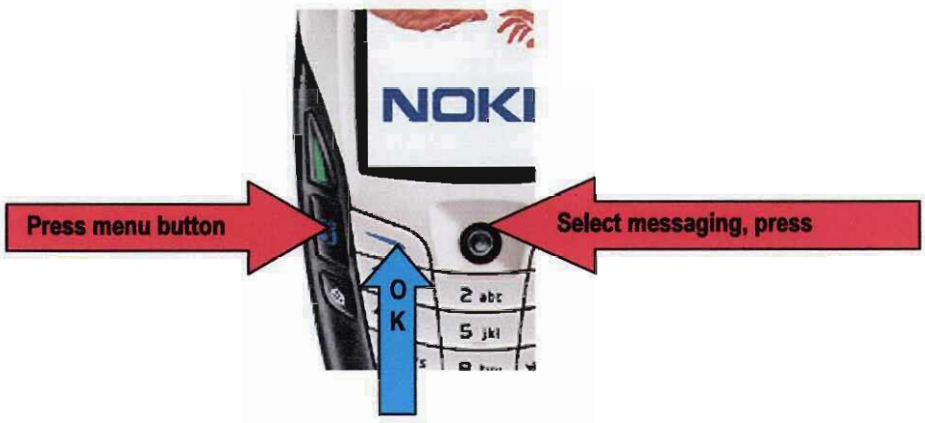
View your phone book by pressing "Contacts". Use the Main Key (also called the centre or navigation key to move up and down) to select the person to phone and press the green key to make the call.

HOW TO RECEIVE A TELEPHONE CALL

To answer a call, press the green button (left). To end the call, press the red button (right).

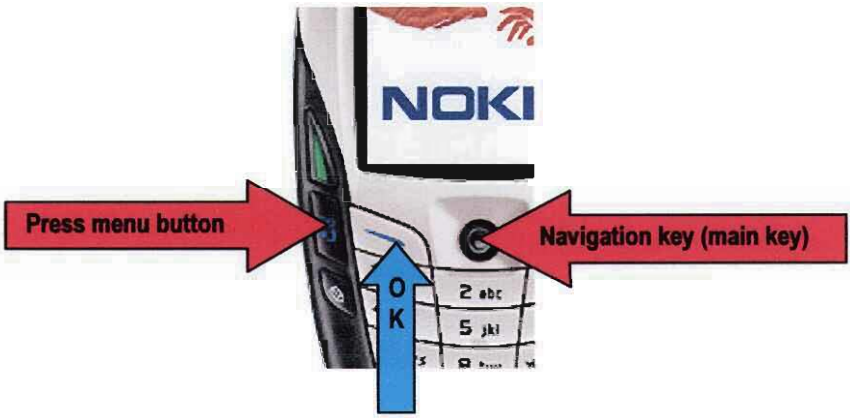
HOW TO SEND AN SMS

To create an SMS, press the menu button. Use the navigation key to move to messaging and then press the navigation key. Select "New message" by pressing the navigation key. Select Text message by pressing the navigation key. While in the "To" box, press the navigation key again to view your contact list. Select all the recipients by moving to them with the navigation key and then pressing the navigation key (to flag as a recipient). When you are done, press OK. Type your message in the message box. When you are finished, press "Options" and select "Send"

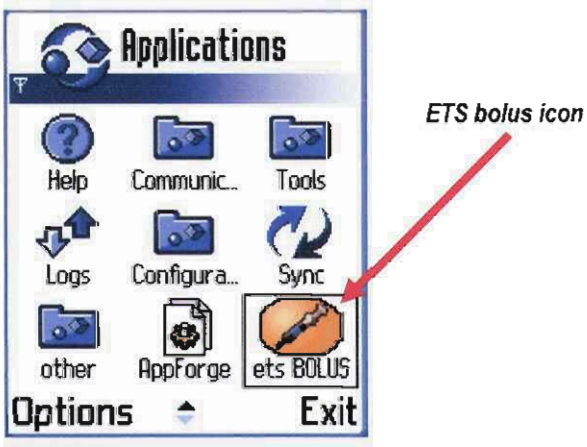


2 - OPENING THE ETS-BOLUS SOFTWARE

To start the ETS-bolus software, make sure that the phone is turned on and the keypad is unlocked. Press the menu button.



Use the navigation key to move to the ***ets Bolus Icon***. Press the ***MainKey*** to open the software program. You will have to browse down to see the icon.



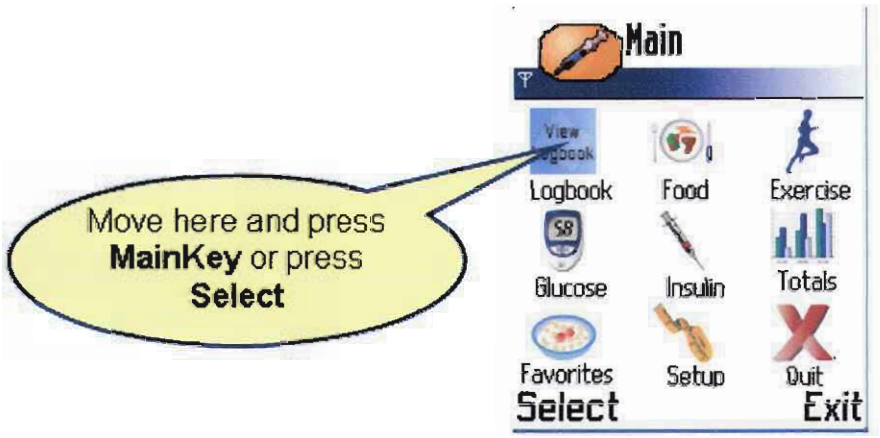
After a few seconds, the following screen will be displayed. You are now ready to use the bolus calculator.

The different program options will be discussed in the next sections.

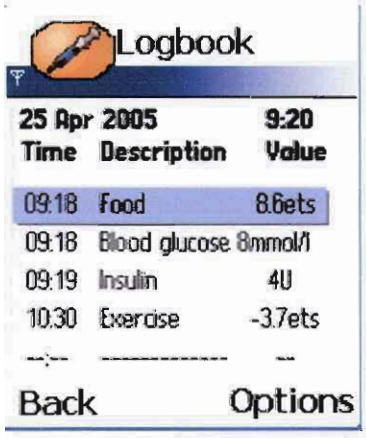
LOGBOOK

The logbook displays activities for the day entered into the cellphone. These activities include food intake, exercise, blood glucose measurements and insulin boluses.

TO VIEW THE LOGBOOK



WHAT'S IN THE LOGBOOK?



The **date and and time** are displayed on top - make sure that it is correct!

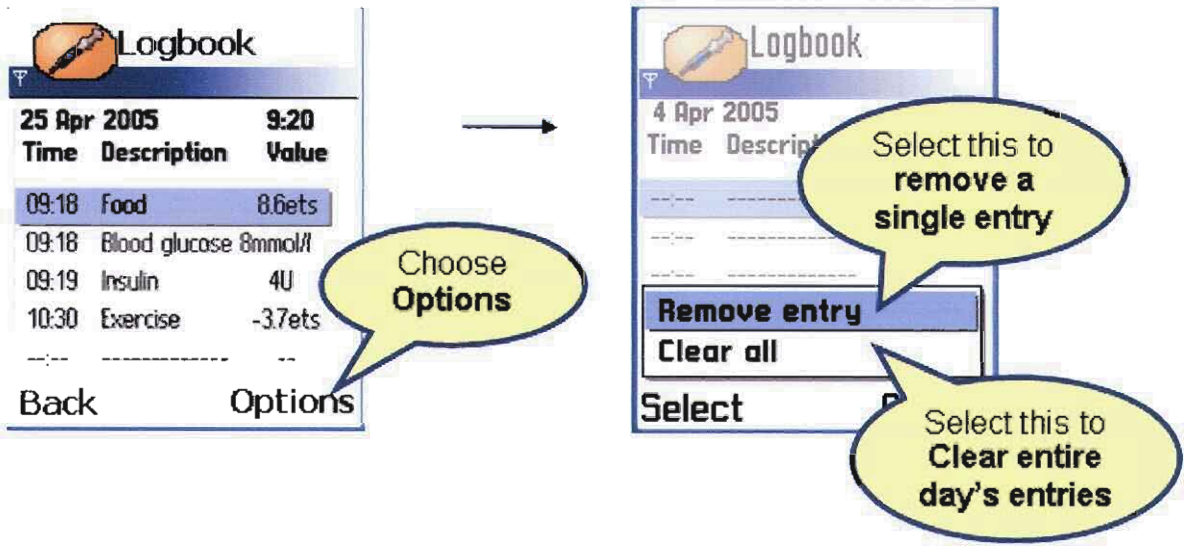
The **times of events** are shown in the left column, the *different actions* in the middle and the *magnitude* in the right hand column.

Food is measured in *ets* (**e**quivalent **t**easpoons **s**ugar that goes into the blood). **Exercise** is shown as negative ets (sugar is taken out of the blood). **Insulin** in Units (U) and **blood glucose values** in mmol/l.

The ***ets Bolus Calculator*** uses this information to calculate bolusses.

HOW TO REMOVE LOGBOOK ENTRIES

Move up or down to highlight the entry you want to remove. Then choose ***Options*** and select whether you want to ***remove entry*** (single entry) or ***Clear all*** (removes all the entries for the day).

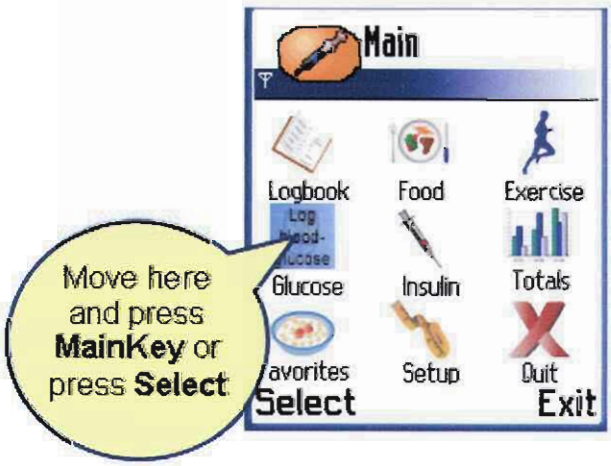


4 - BLOOD GLUCOSE MEASUREMENT

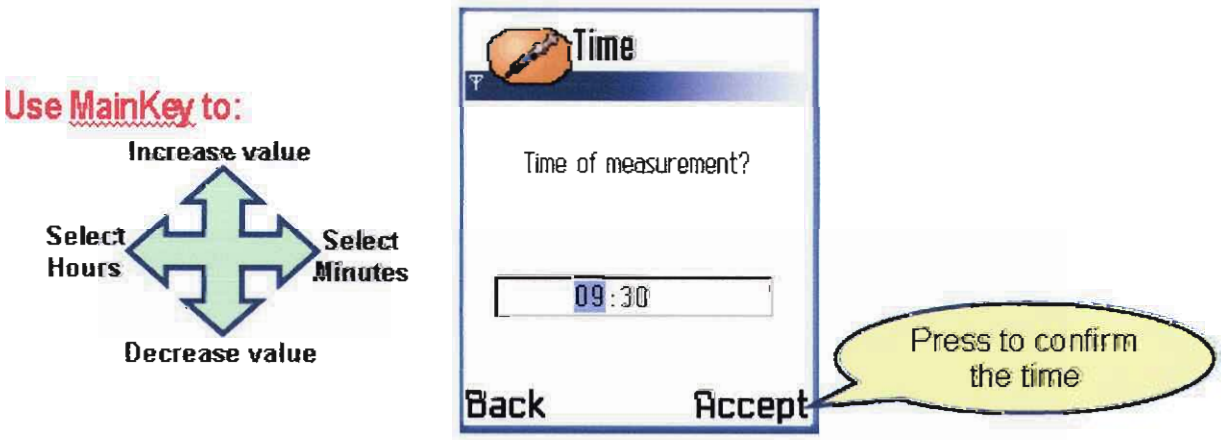
You can use the logbook to store measured blood glucose values. *If you are not going to administer an insulin bolus*, you can use this option to store your blood glucose value. *If you are going to take a bolus, go directly to* ***Insulin*** – you will be prompted there to enter your current blood glucose level.

TO ENTER A BLOOD GLUCOSE VALUE

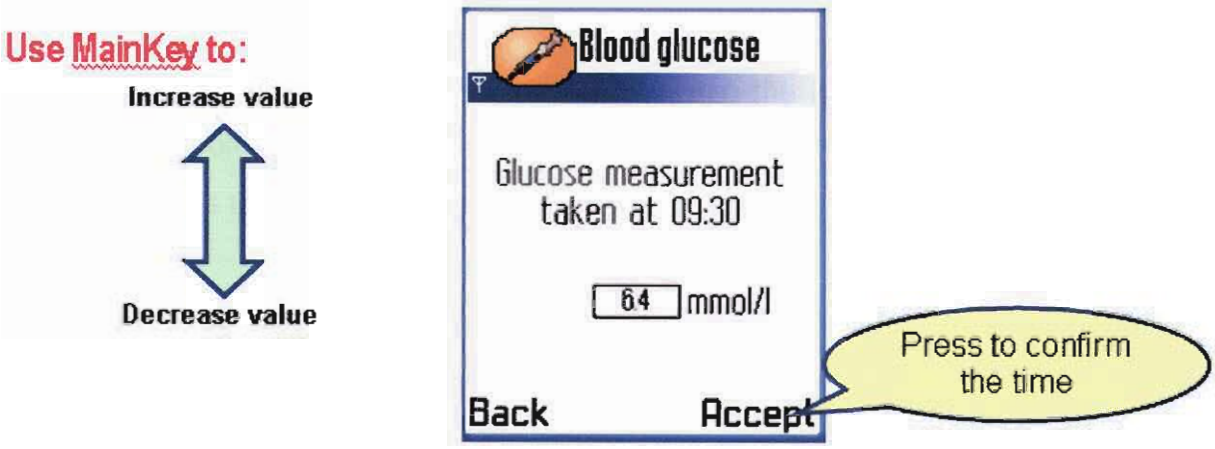
While in the Main menu, select **Glucose**



Enter or confirm the **time of the measurement**



Enter the **blood glucose value**



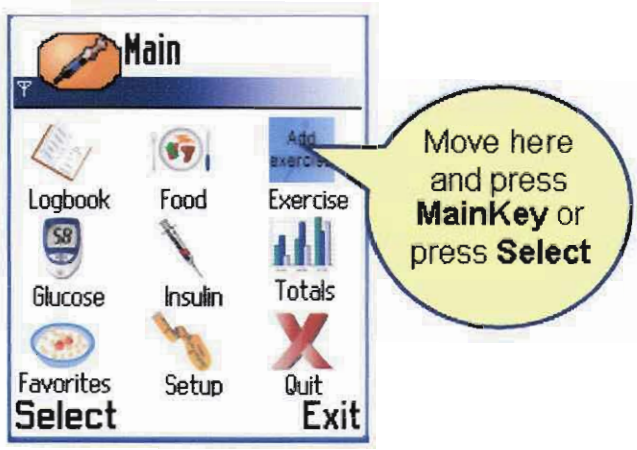
By pressing ***Accept*** the blood glucose value will be stored in the logbook.

5 - EXERCISE

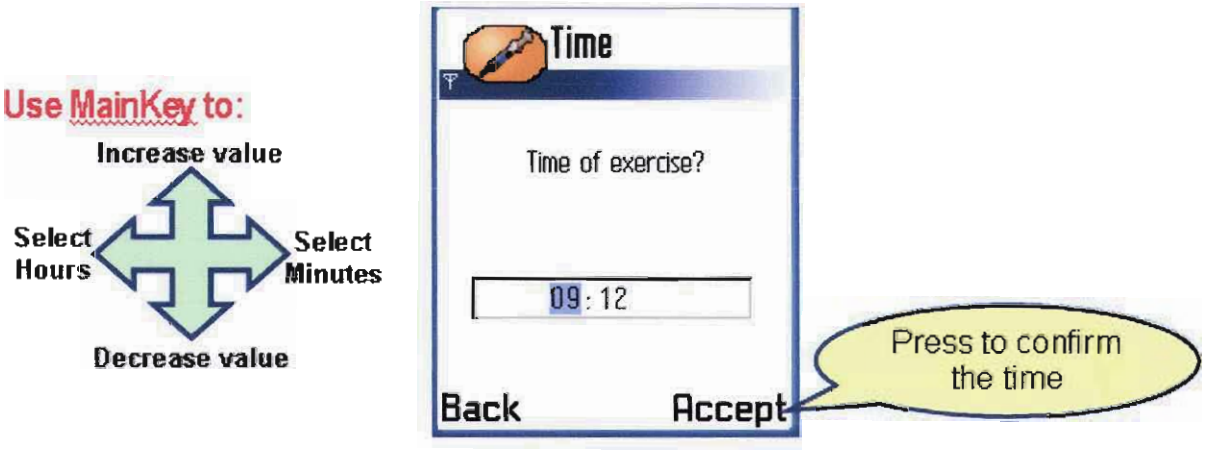
It is important to enter your exercises, if any, into the logbook. This will reduce your insulin bolus in order to reduce the risk of hypoglycemia. Bolus calculations take exercises up to six hours in advance into account.

TO ENTER AN EXERCISE

While in the Main menu, select **Exercise**



Enter or confirm the **time of the exercise.** Remember that exercises should be entered in advance before the bolus calculation preceding the exercise!!!



Select the type of exercise

Enter the duration of the exercise

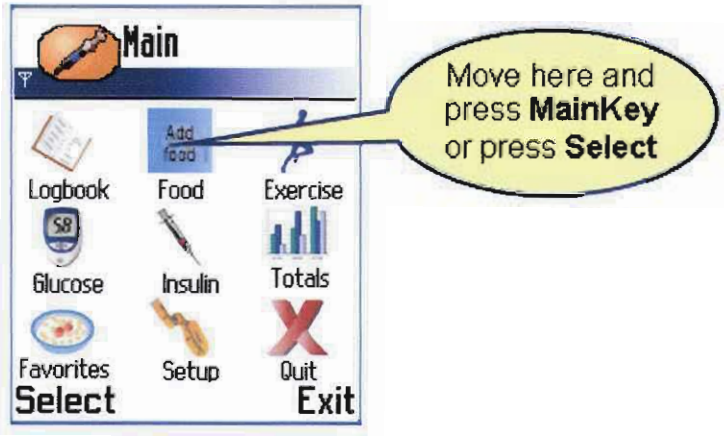
By pressing ***Accept*** the exercise will be stored in the logbook.

6 - Food

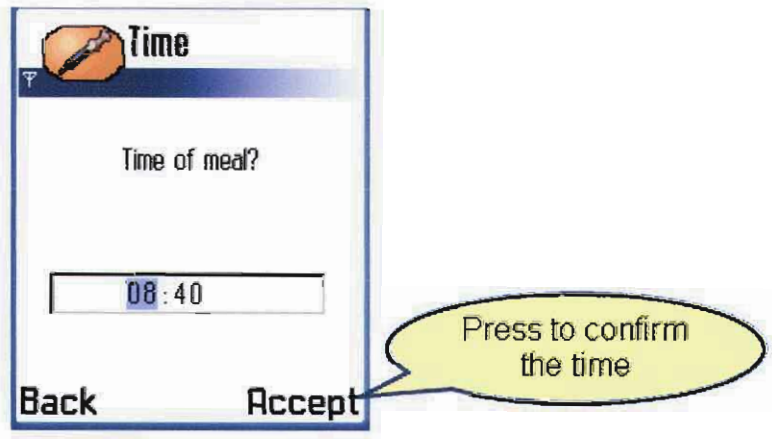
The ***ets Bolus Calculator*** has a database that contains more than 1500 food items.

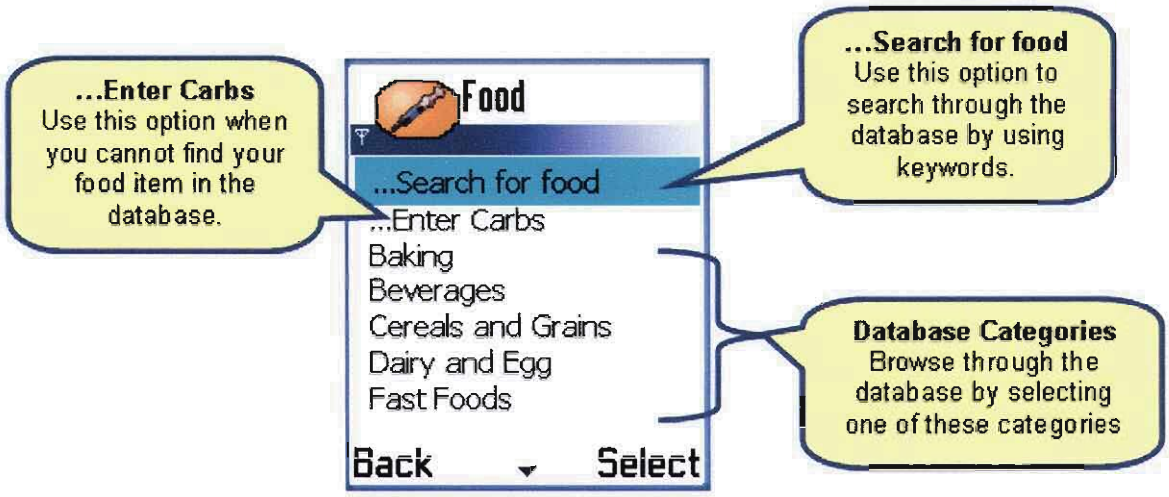
To View Food Options

While in the Main menu, **select Food**



Enter or confirm the **time of the meal**



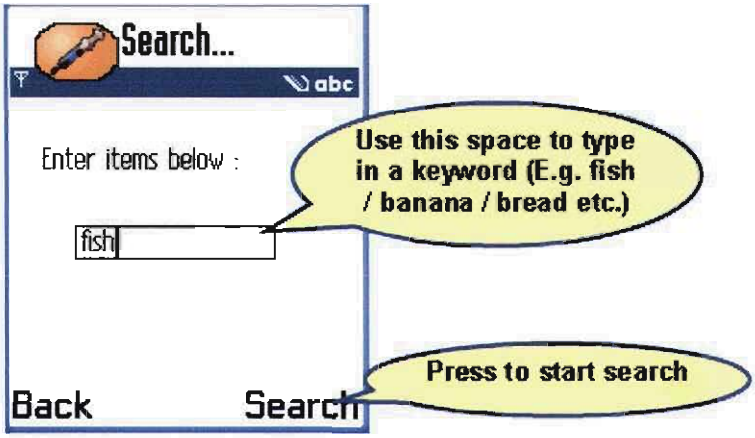


You now have three options. They are:

- **...Search for food:** This option allows you to enter keywords to search for. E.g. "chocolate" will return items such as "chocolate milk", "chocolate cake" etc.
- **...Enter carbs:** This is the carb counter. If you cannot find the food item in the database but know how many grams of carbohydrates there are in the food, you can use this option.
- **Browse through the database:** This option allows you to browse through the database, which is neatly categorized.

...SEARCH FOR FOOD

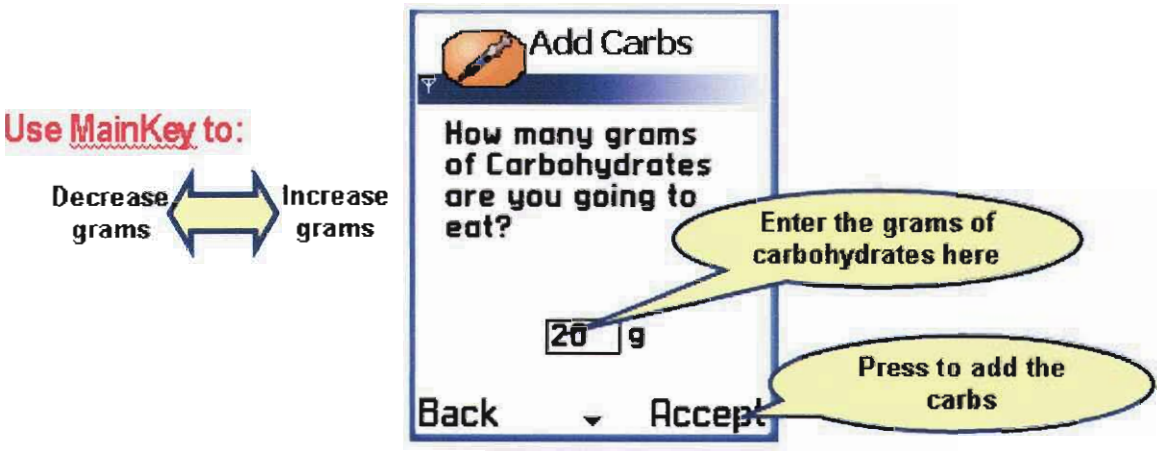
If you quickly want to find an item in the database select ...**Search for food.** The following screen will be displayed.



Your results will be displayed. Select the item you are looking for and press ***Accept*** to select the food item or press ***Back*** to search over again.

...ENTER CARBS

This is the carb counter. If you cannot find the food item in the database but know how many grams of carbohydrates there are in the food, you can use this option. The following screen will be displayed.



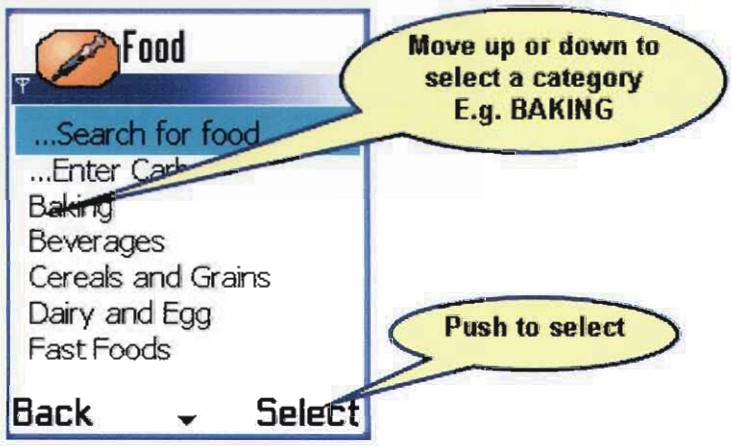
By pressing **Accept** the amount of carbohydrate grams will be converted to ets and added to your logbook. Remember to take the portion size into account when entering the grams of carbohydrates. Rather use the *...Search function* or *Browse through the database* to add food items to your logbook. These two methods will provide you with more accurate results.

BROWSE THROUGH THE FOOD DATABASE

If you want to add a specific food item, you can browse through the database to select it. Let say, for example, we want to add a hot cross bun. First select the Food option from the Main Menu.

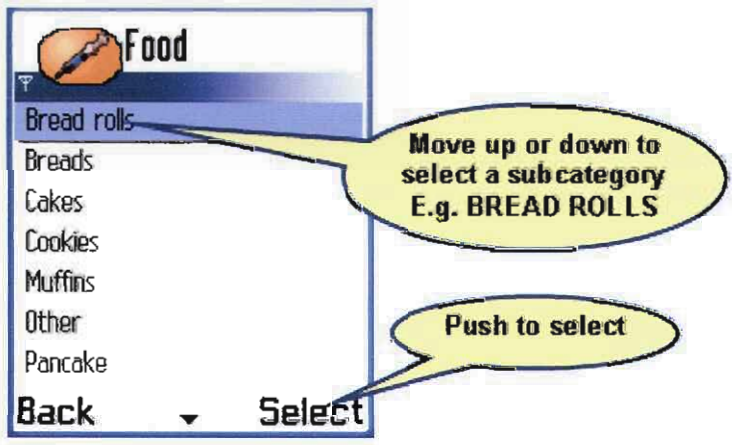
Step 1 – Select the main food category

For our example, select Baking



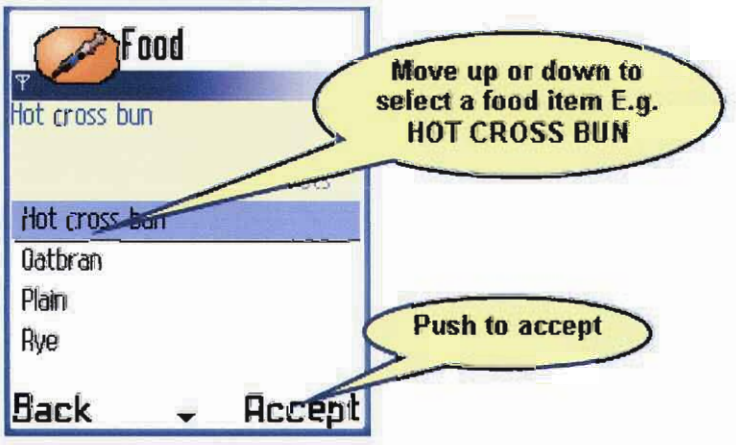
Step 2 – Select the food sub-category

For our example, select Bread rolls



Step 3 – Select the specific food item

For our example, select Hot cross bun



Step 4 – Specify the number of portions

For our example, lets say we are just going to eat a quarter Hot cross bun. Move the main key up and down to specify the number of portions.

By pushing ***Accept*** the specified number of portions will be added to the logbook.

7 – How to Calculate Insulin Boluses

In order to calculate your insulin bolus by using the cell phone – you must make sure that:

- You have entered all the food and beverage items you are about to eat into the logbook. When asked the time of the meal, please enter the time that you will be taking the meal.
- You have entered any exercises that you will be doing within six hours of the insulin bolus being calculated.

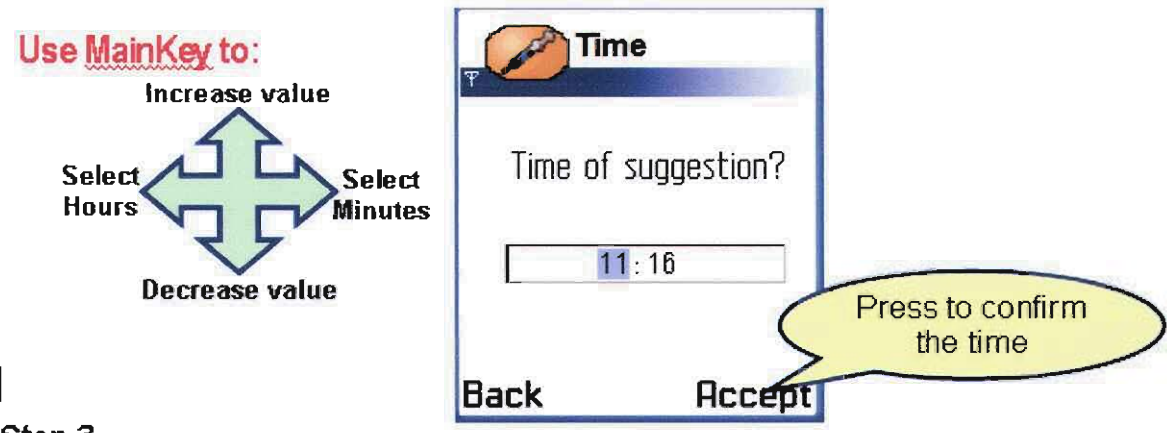
If you have entered your food, beverages and exercises correctly, it will be easy to calculate your insulin bolus.

Step 1

From the main menu, Move to ***Insulin*** and press ***Select*** (or press the ***MainKey***).

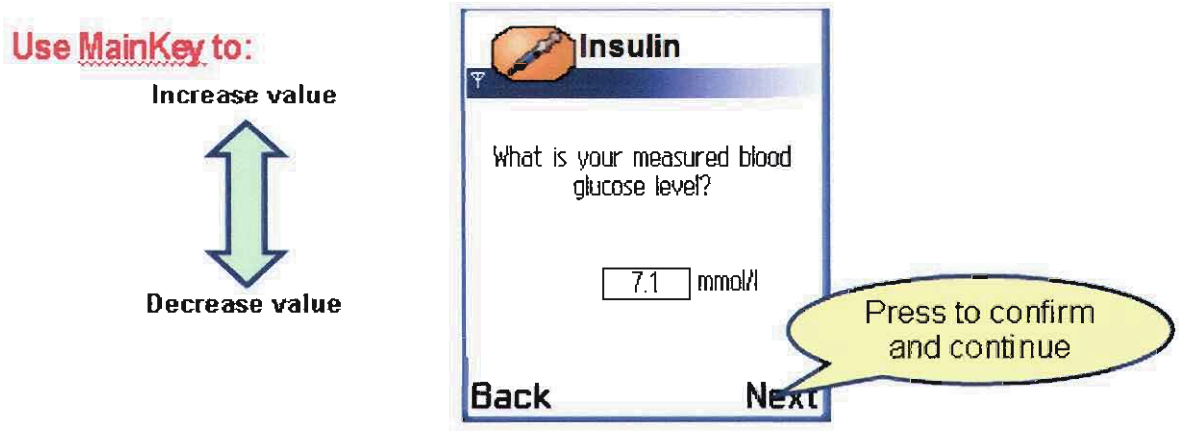
Step 2

Enter the time of the suggestion (insulin bolus) – usually the current time.



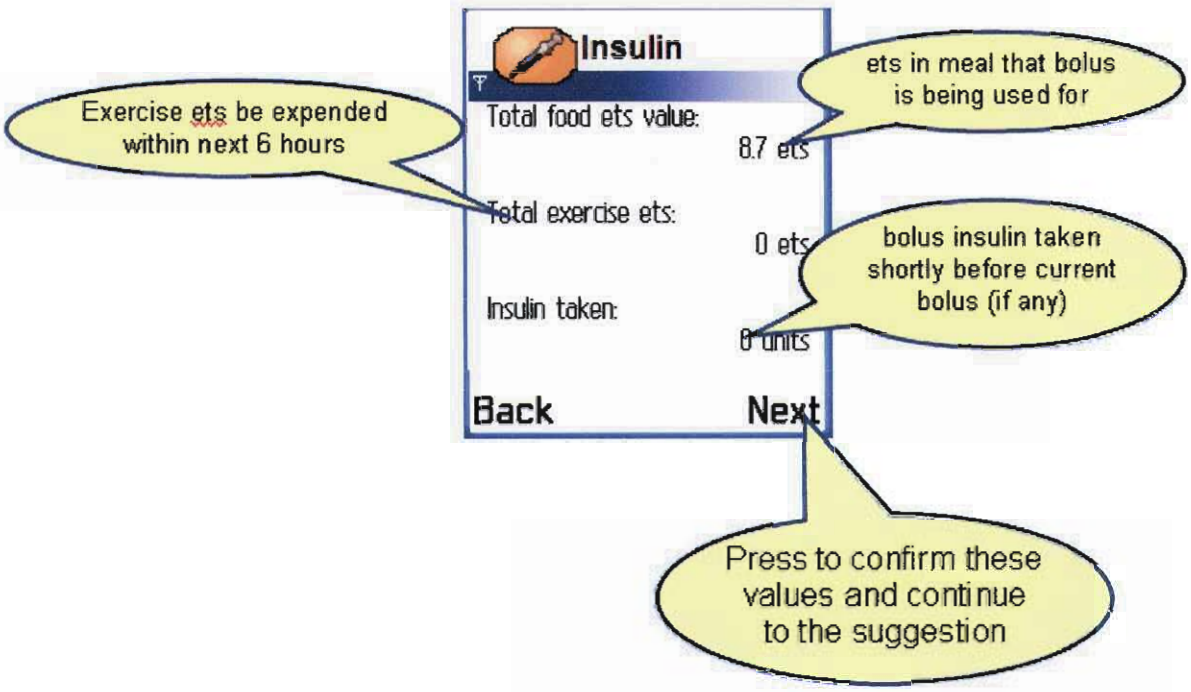
Step 3

Measure and enter your current blood glucose level. Press ***Next*** to continue.



Step 4

Check the food, exercise and insulin values. To confirm press ***Next***. If you do not agree, go back.



It is important that you check these values. If an extremely high or low ets count is shown for food, it is possible that the wrong time was used for the meal, or the number of portions was specified incorrectly etc. If you suspect these values not to be accurate, first remove the relevant meal items from the logbook and re-enter them. Make sure that you do not enter any items twice!

Step 5

Using the information from the logbook a suggestion will be made. There are four types of suggestions that can be made:

Bolus insulin suggestion If your predicted blood glucose level is too high a suggestion will be made for an appropriate insulin bolus. If you strongly disagree with this suggested bolus, you must use your own discretion.

Suggestion to eat additional ets If your predicted blood glucose level is too low, a suggestion will be made to eat additional ets (carbohydrate rich food) to raise your blood glucose level.

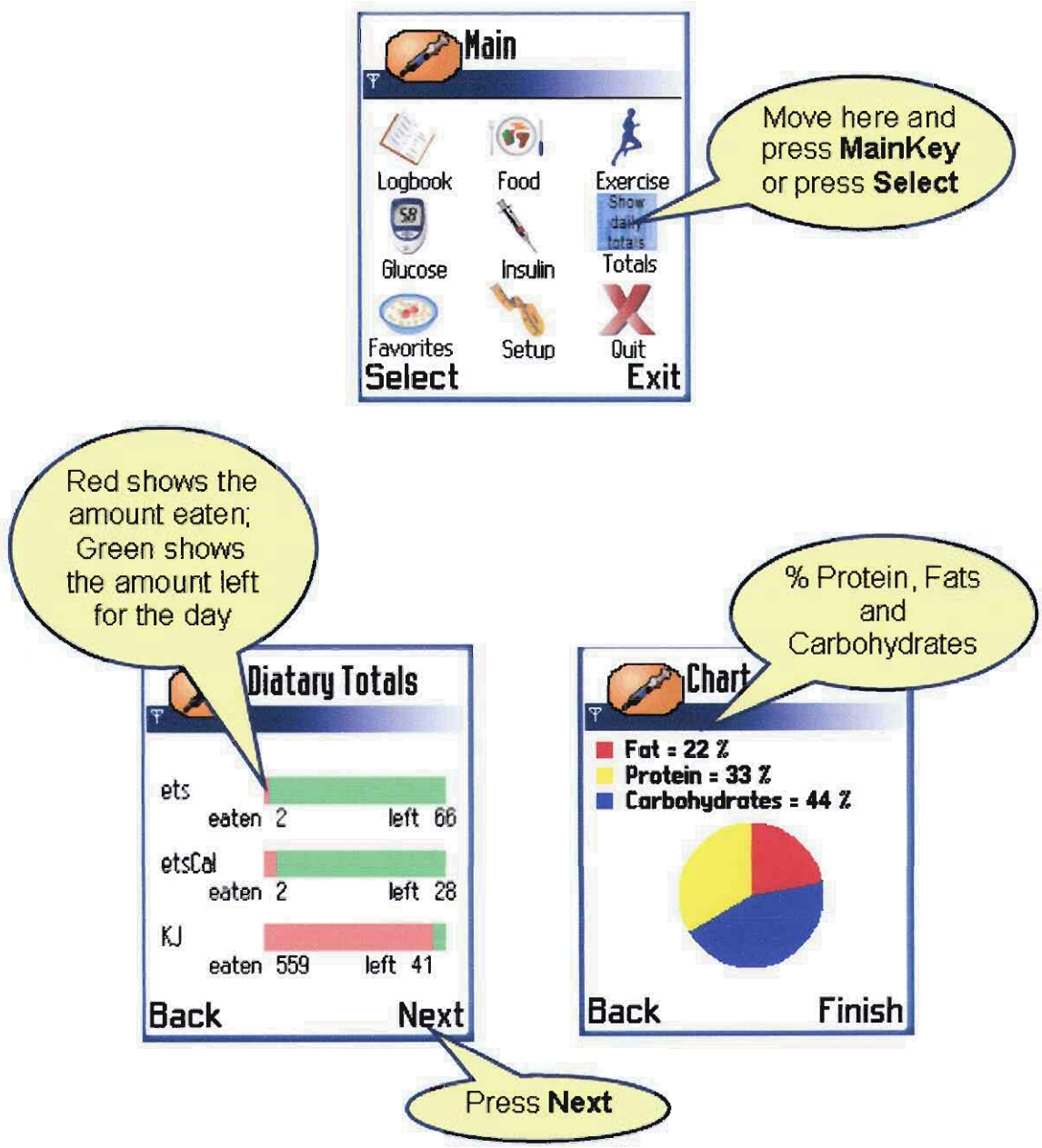
Suggestion to take no action If your predicted blood glucose level is close to your target blood glucose level, then a suggestion will be made to take no action (in other words – no bolus insulin or additional ets should be taken).

Suggestion cannot be calculated If your meal contains too much ets, or it is detected that a very large insulin bolus is needed, the suggestion will not be displayed. This safety feature is to prevent the system from making extremely high insulin boluses that could possibly result in a hypo when administrated. If you do get a message that the bolus could not be calculated – you will have to use your own discretion to determine your insulin bolus. There are ways to prevent this from happening: ensure that you do not consume a very high amount of carbohydrates (ets), especially when your current blood glucose level is already high.

8 - DAILY TOTALS

Daily totals give a summary of your food intake including ets, etsCal and calories. It also shows the composition of your daily food intake. Remember ets gives you an indication of how much glucose there is in your diet. You don't have to worry about these values for now, they are only here for your information.

TO VIEW THE DAILY TOTALS

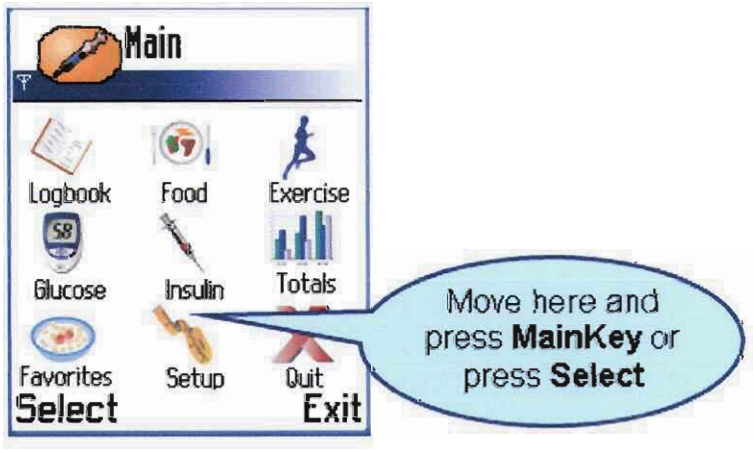


9 – SETUP (DON'T USE SETUP BY YOURSELF!)

It is very important that the values that are entered in the setup, are correct. The bolus calculator will not be able to make accurate calculations if these values are not correct. The setup values have to be set before the device can be used. One of the trial assistants will help you to enter the correct values. It is important that you do not change these values by yourself! You do not have to read through this section.

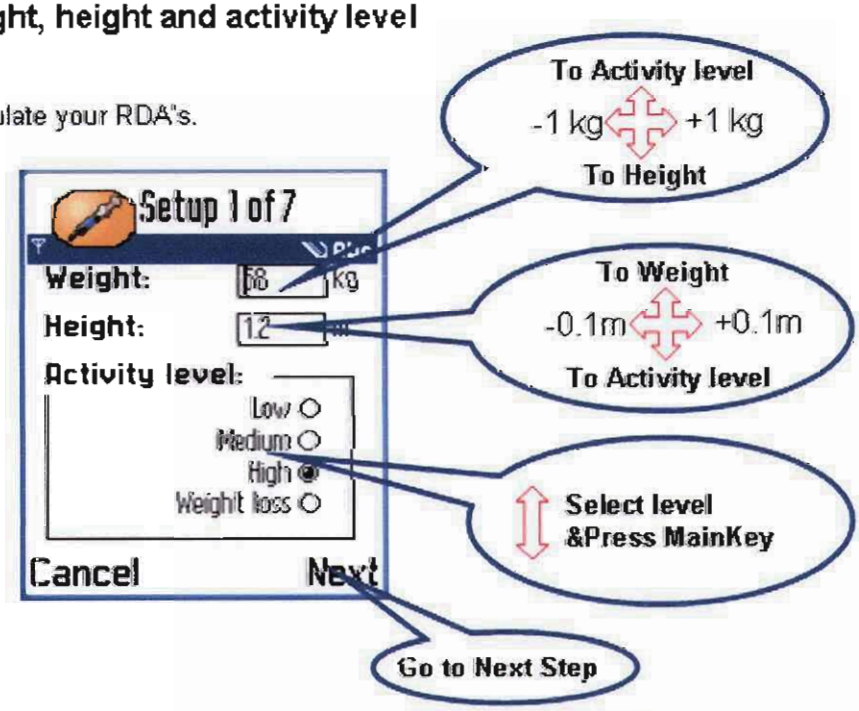
TO VIEW SETUP

Select **Setup**



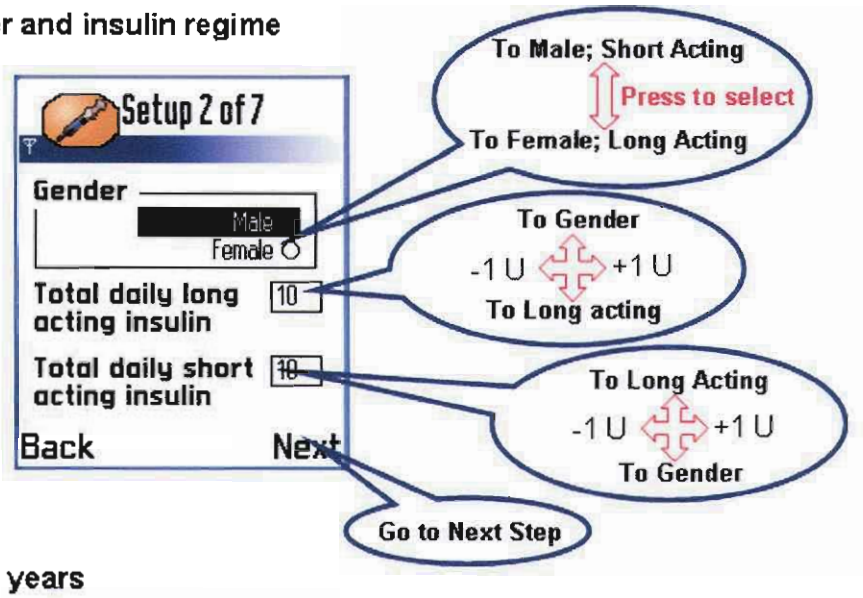
Step 1 – Enter your weight, height and activity level

These values are used to calculate your RDA's.

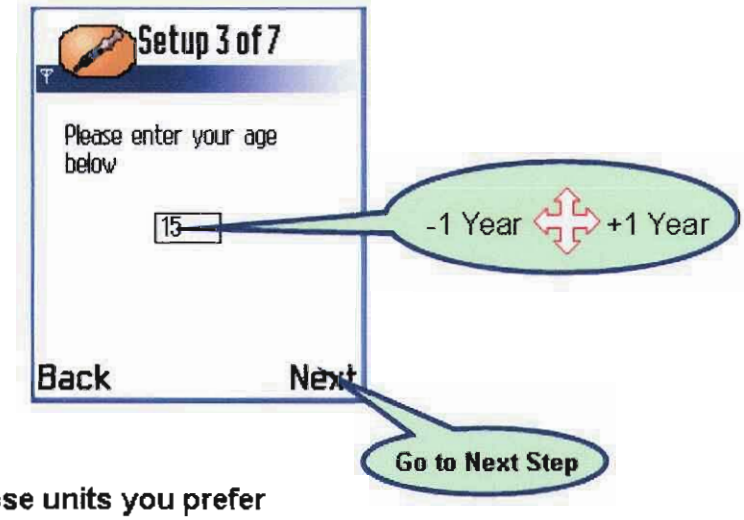


Step 2 – Enter your gender and insulin regime

If you are using an insulin pump, one of the research assistants will help you to determine your total daily long acting insulin (basal) dose.

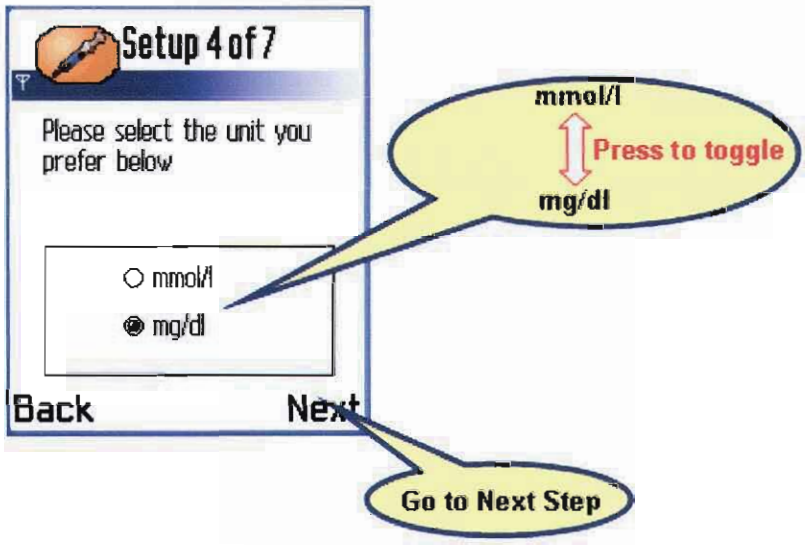


Step 3 – Enter your age in years



Step 4 – Select the glucose units you prefer

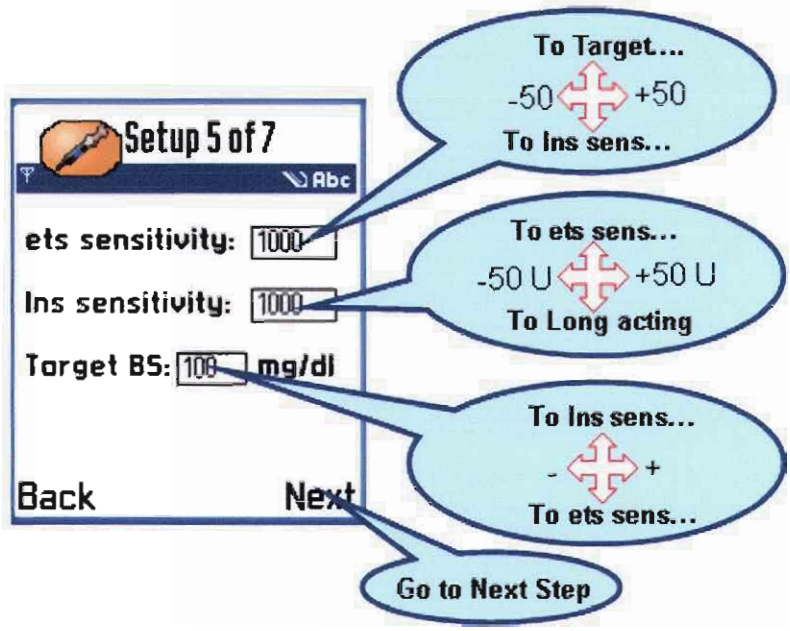
Blood glucose meters sold in South Africa are usually calibrated in mmol/l.



Step 5 – Enter your blood

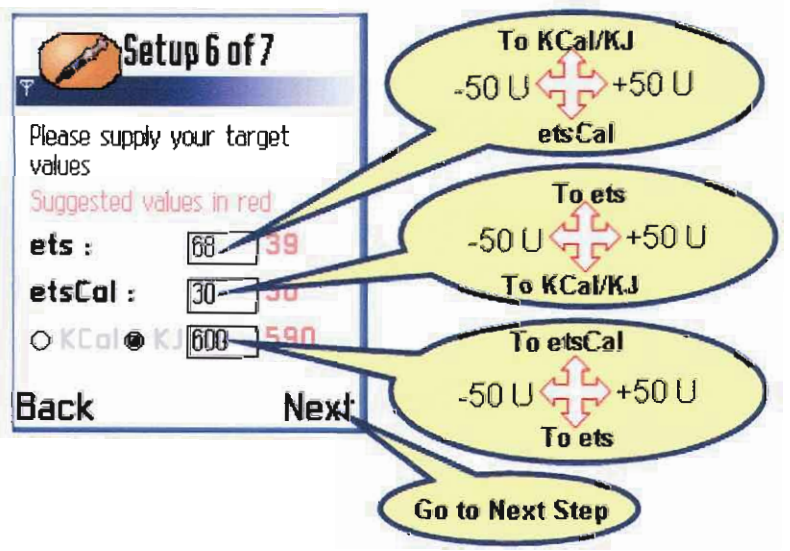
Step 5 – Enter your blood glucose setup

One of the research assistants will determine these values for you and enter them. **DO NOT CHANGE THESE VALUES BY YOURSELF!**



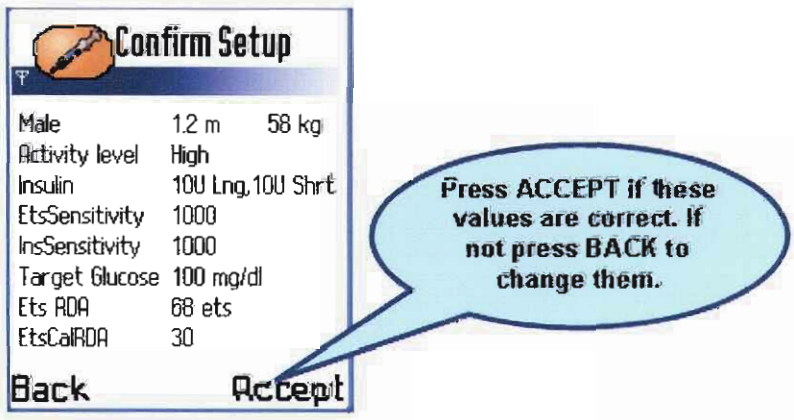
Step 6 – Enter your RDA values

These RDA's (Recommended Daily Allowances) gives an indication of how much energy you need during a day. These energy values are calculated to maintain your weight at a certain daily activity level. It also takes your age, weight, gender and height into account.



Step 7 – Confirm values

Make sure that all these values are correct. If they are not correct press BACK until you see the information that needs correction, and change it. Then press NEXT until you see the confirmation screen again, check the information again and press ACCEPT if everything is correct.



REMEMBER DO NOT CHANGE THE SETUP VALUES BY YOURSELF !

10 - WHAT IS ETS? HOW CAN IT HELP ME?

ets is short for Equivalent Teaspoons Sugar. We can use ets to quantify the amount of sugar energy that will enter the blood during digestion.

For example: **Can of**  **cola = 8 ½ ets**

(340ml)

This means that there is approximately 8 ½ teaspoons of sugar in a can of cola. This also means that one can of cola will have roughly the same effect on your blood glucose level as 8½ teaspoons of table sugar. Here are some more examples:

Slice of brown bread  2 ½ -ets	Slice of white bread  3 ½ -ets	Medium apple  2 ½ -ets
Big Mac burger  9 ½ -ets	Supersize fries  16 ¾ -ets	Glass Orange juice  4 -ets

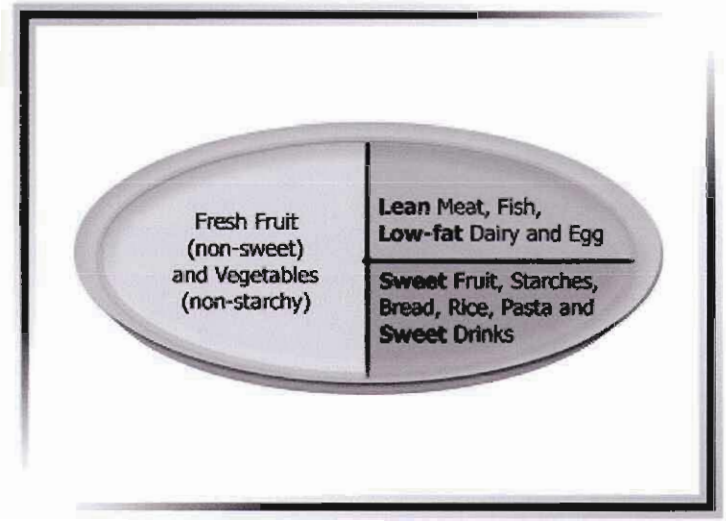
Note the difference between white and brown bread! Some foods may appear to be the same – but they are not. In general foods with more fiber contains less -ets than their fibreless equivalents! Highly refined carbohydrates (white bread, cake, candy etc.) therefore contain more -ets and will cause higher blood glucose surges!

Although -ets and carbohydrates are similar, they are not exactly the same. Both are measured in a different way. In general more carbohydrates means more -ets, but this is not always the case. Look at the following examples:

		
381g Apple = 50g Carbs = 5.8	111g Hi Fiber Bran = 50g Carbs = 6.6	63g Special K = 50g Carbs = 13.7

All three quantities have the same amount of carbohydrates (50g) but a different amount of . Can you see why counting carbohydrates can be problematic? Remember the higher the , the higher the rise in blood glucose!

Tip: It is important to balance your meals otherwise you may become hungry between meals and may not get all the fiber and micronutrients you need. We propose the easy-to-use ½ - ¼ - ¼ rule. By using the weight of the food, try to balance your meal as follows:



Remember to choose low-fat foods!

There is a relationship between your intake, the increase in your blood glucose level and therefore also the bolus insulin you need for a meal. allows us to calculate this increase in blood glucose level more accurately than when using carbohydrates. This means that if we eat less , less insulin will be needed.
If you want to choose low -foods there are a few general guidelines:

- Rough unrefined food (e.g. rye bread with full grains & seeds) are usually lower in -ets than their refined equivalents (white bread).
- Colourful vegetables are usually not that high in -ets. Starchy vegetables like potatoes are very rich in -ets and will cause high surges in your blood glucose. Try to avoid french fries.
- Fruit juice is often high in -ets. Many fruit can be squeezed into a single bottle. The fibre you get from eating a whole fruit is also beneficial for you thus rather eat whole fruit than drinking fruit juice.

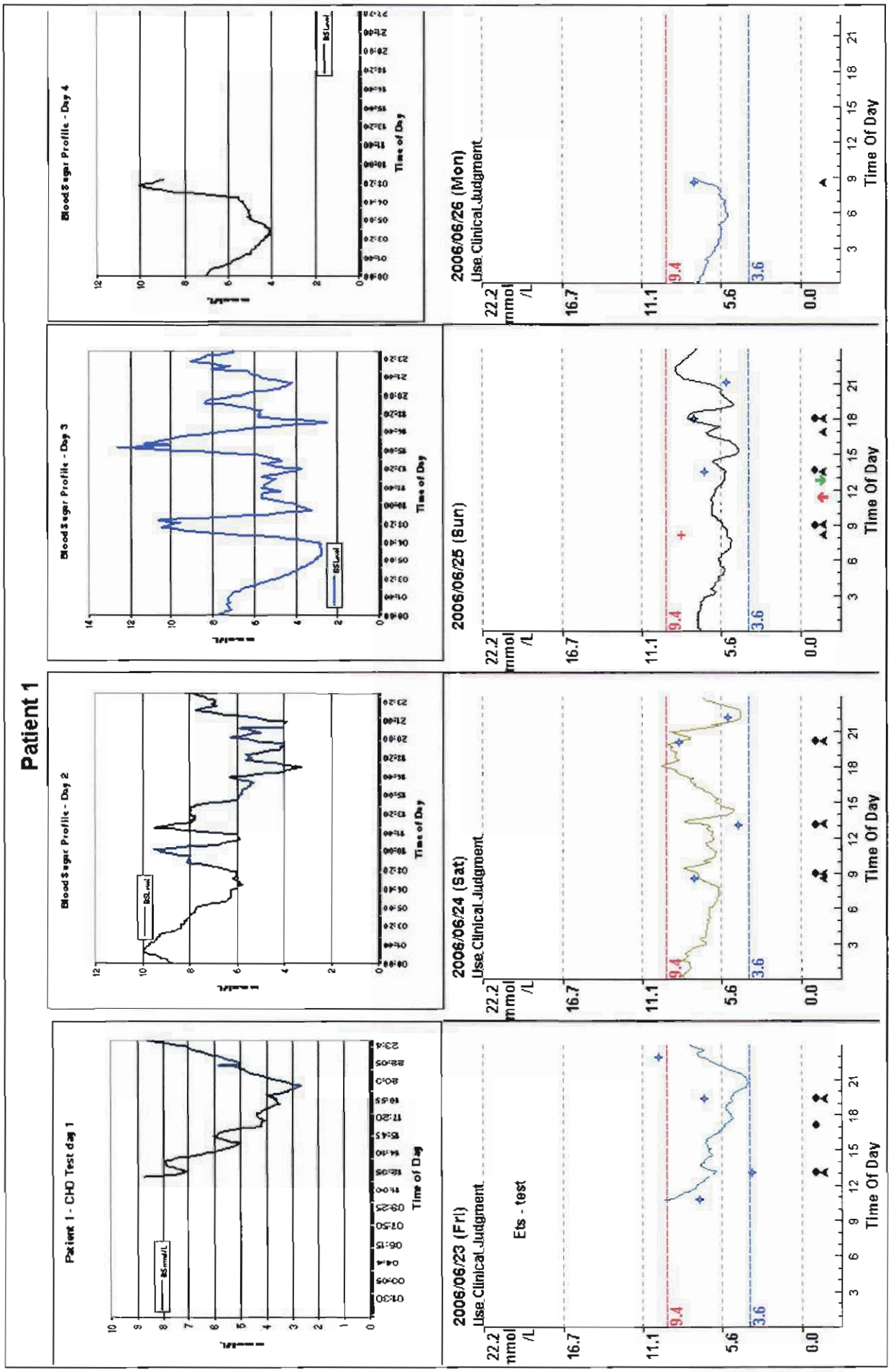
To summarise: By eating less -ets , less glucose is released into the blood meaning that less insulin is needed. Counting -ets helps us to calculate better insulin bolusses.

APPENDIX D - CLINICAL TRIAL DATA

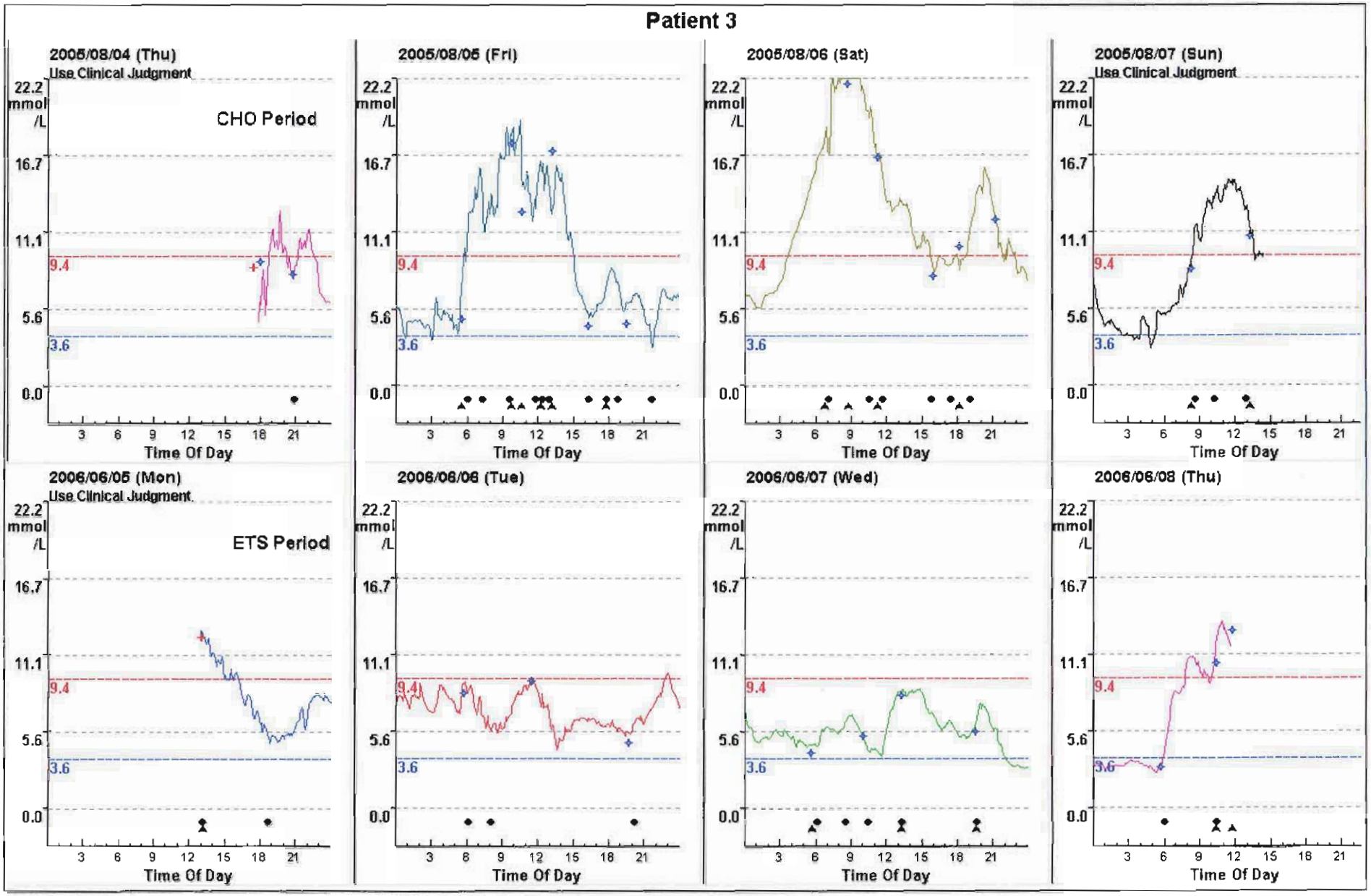
Appendix A - Contents

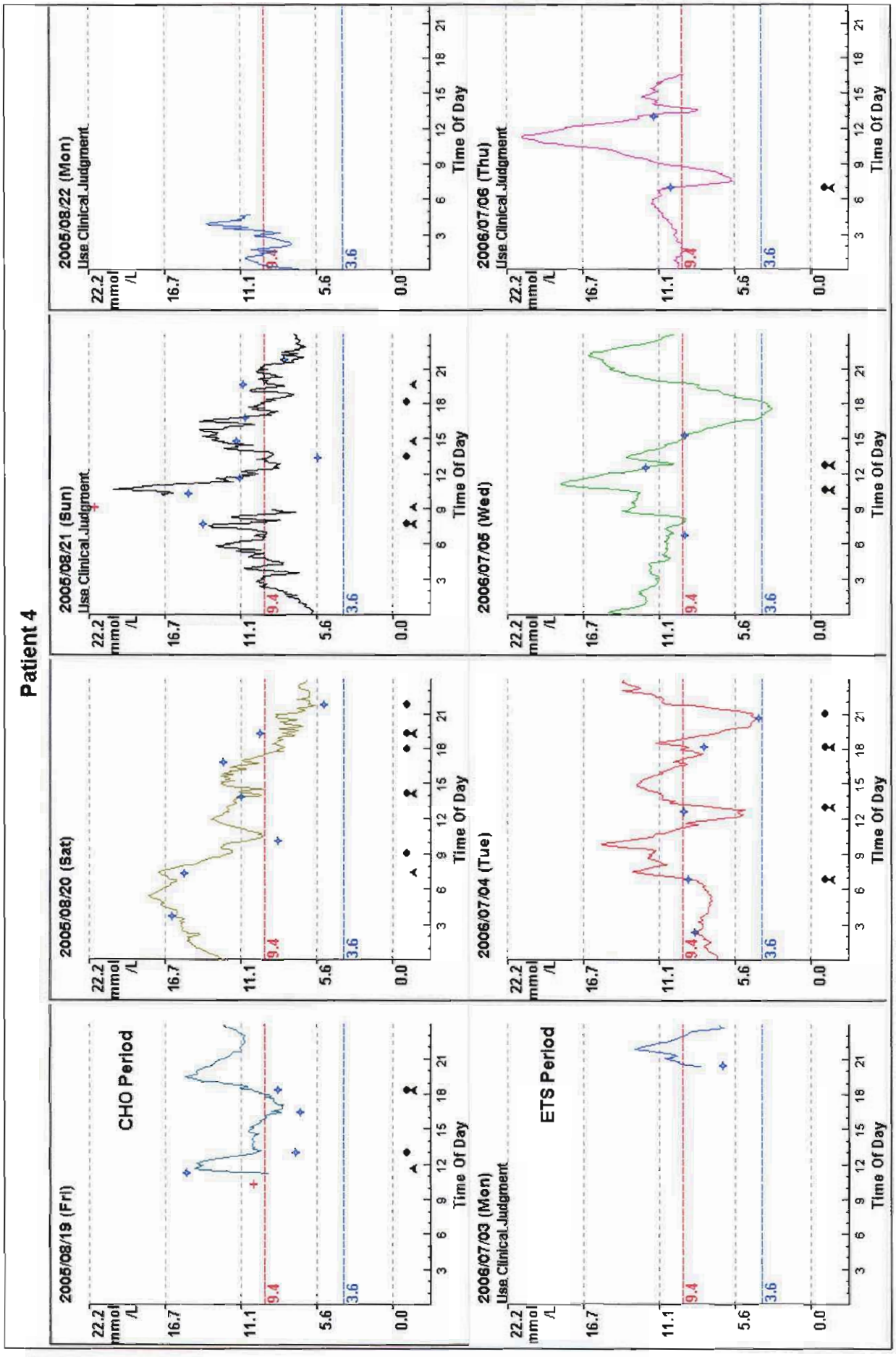
DIABETIC SUBJECTS CGMS PROFILES

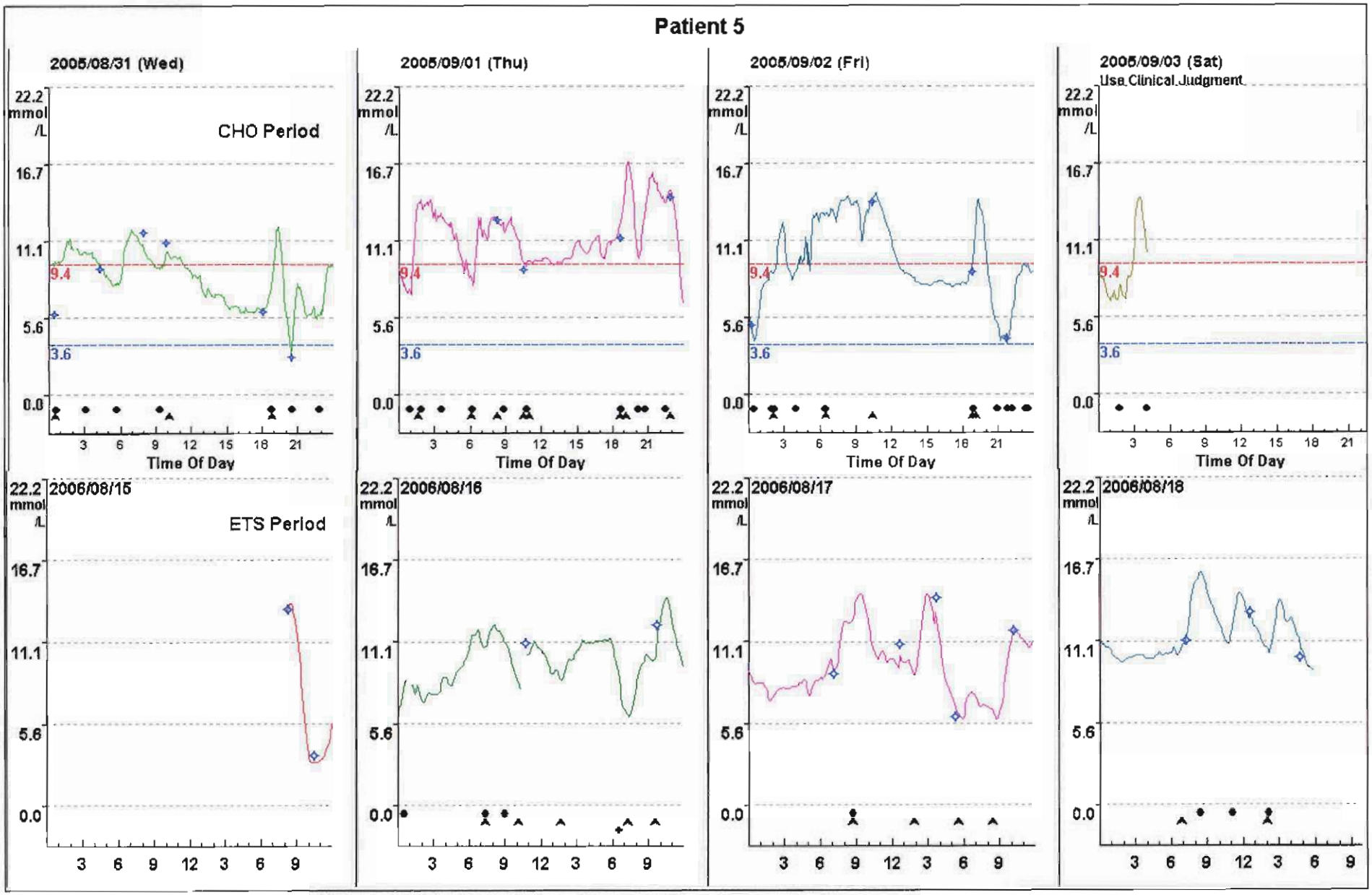
NON-DIABETIC SUBJECTS CGMS PROFILES

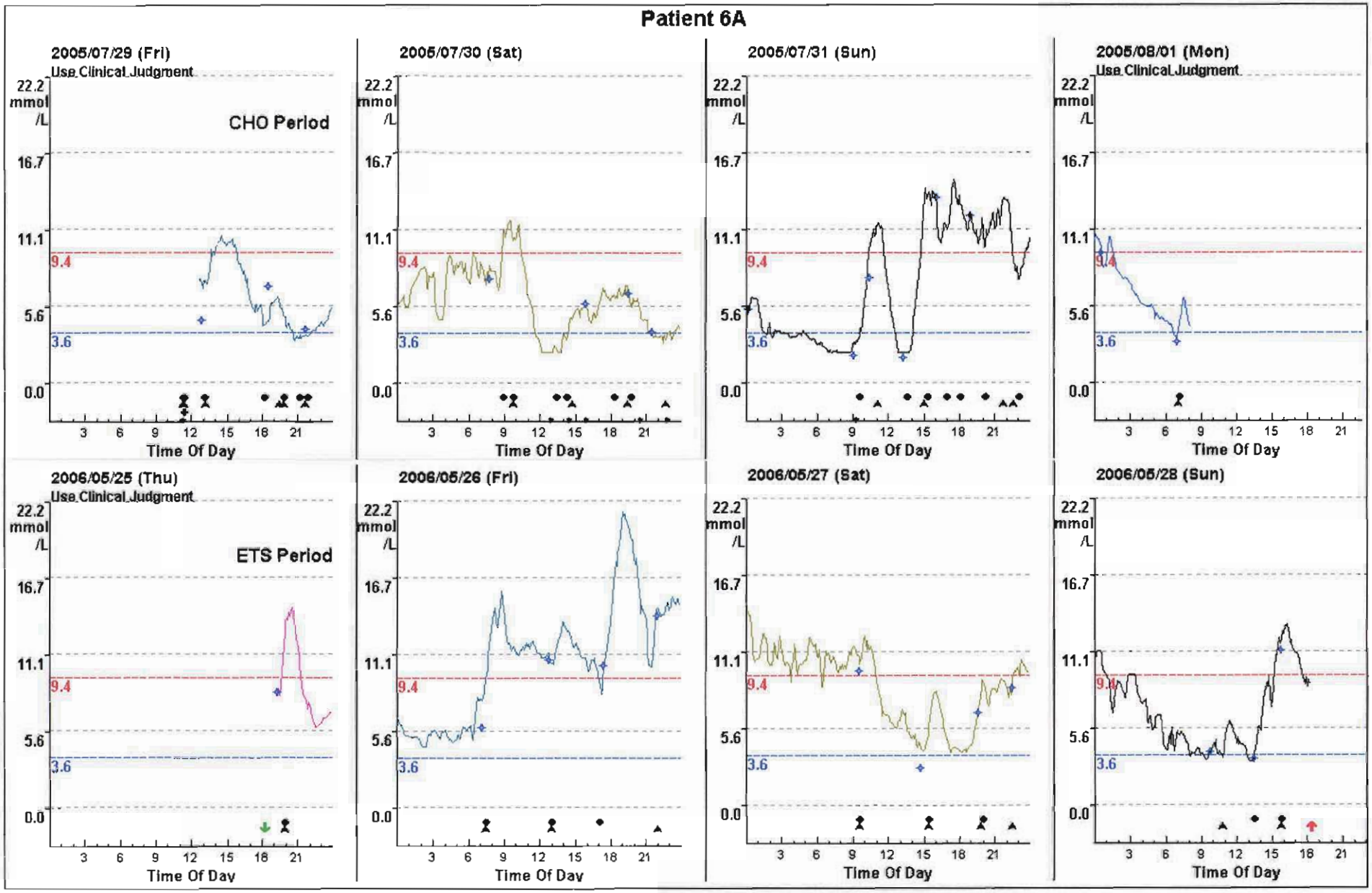

Patient 1
Patient 1 - CHO Test day 1
BS mmol/L
Time of Day
Blood Sugar Profile - Day 2
BS_mol
Time of Day
Blood Sugar Profile - Day 3
BSLevel
Time of Day
Blood Sugar Profile - Day 4
BSLevel
Time of Day
2006/06/23 (Fri)
Use Clinical Judgment
Ets - test
22.2 mmol /L
16.7
11.1
9.4
5.6
3.6
0.0
Time Of Day
2006/06/24 (Sat)
Use Clinical Judgment
22.2 mmol /L
16.7
11.1
9.4
5.6
3.6
0.0
Time Of Day
2006/06/25 (Sun)
22.2 mmol /L
16.7
11.1
9.4
5.6
3.6
0.0
Time Of Day
2006/06/26 (Mon)
Use Clinical Judgment
22.2 mmol /L
16.7
11.1
9.4
5.6
3.6
0.0
Time Of Day

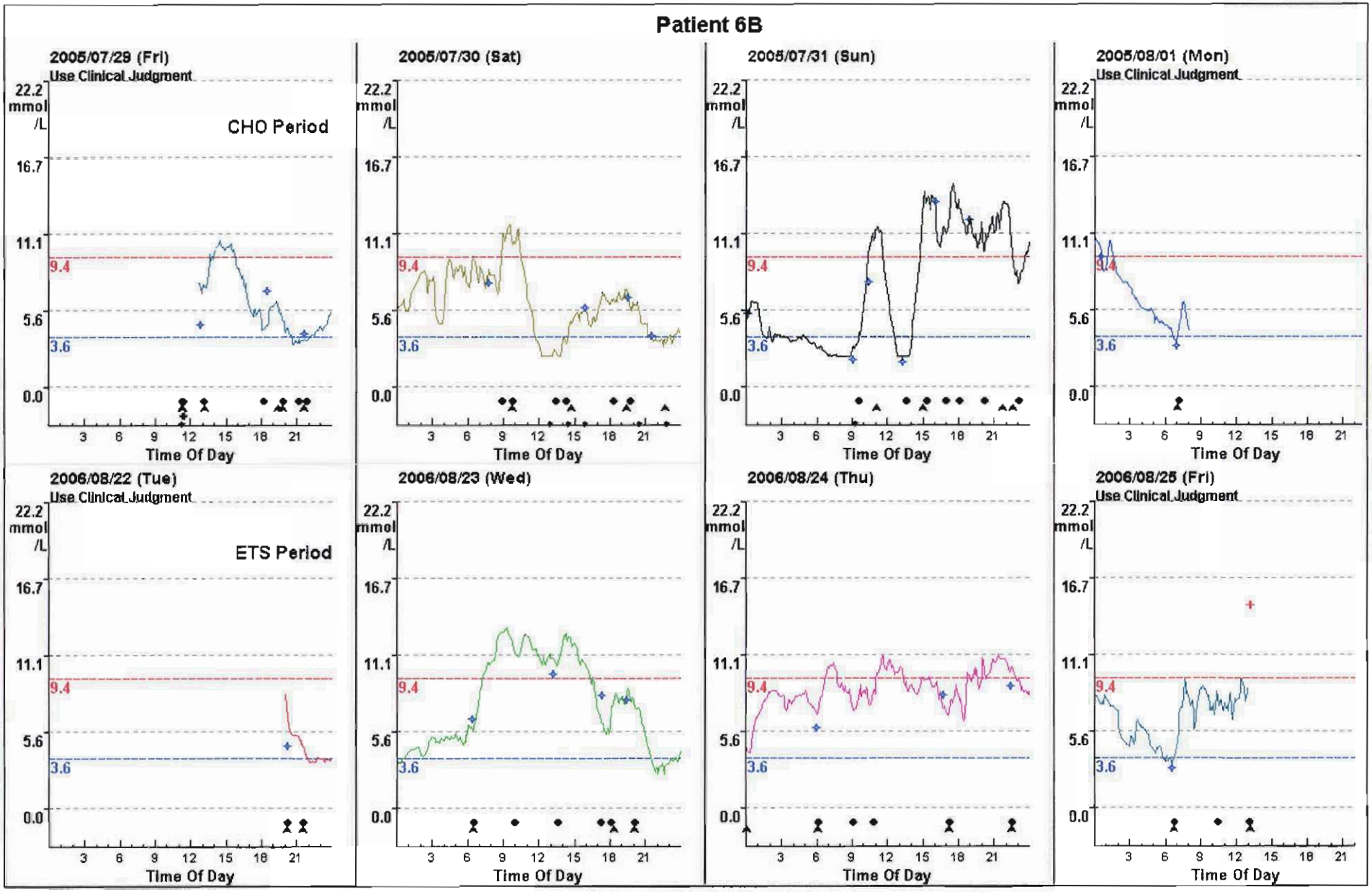
Patient 2
2005/08/30 (Tue)
CHO Period
2005/08/31 (Wed)
2005/09/01 (Thu)
2006/06/23 (Fri)
ETS Period
2006/06/24 (Sat)
2006/06/25 (Sun)
2006/06/26 (Mon)
Usa Clinical Judgment
22.2 mmol /L
16.7
11.1
9.4
5.6
3.6
0.0
3 6 9 12 15 18 21
Time Of Day

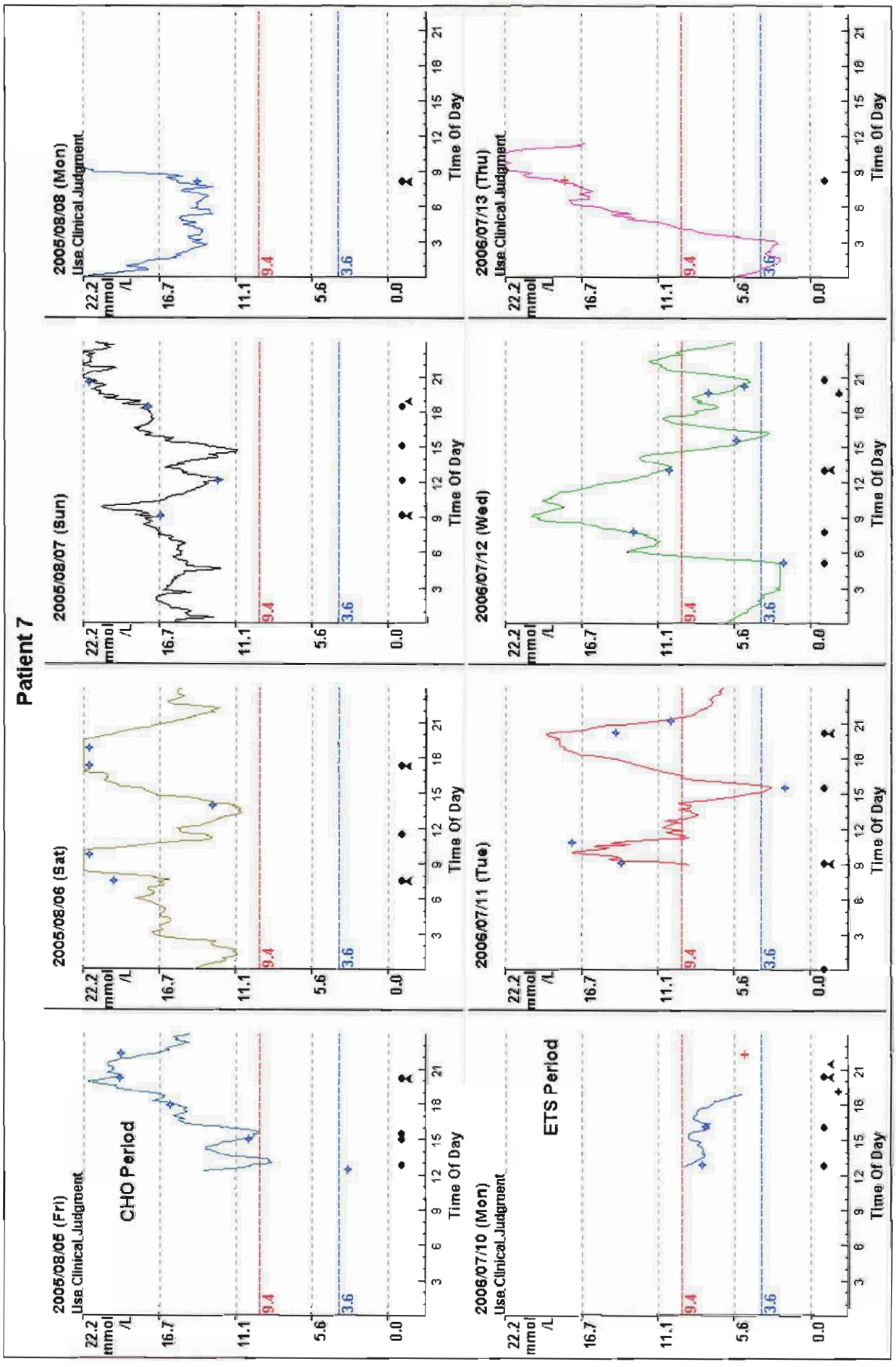

Patient 3
2005/08/04 (Thu)
Use Clinical Judgment
CHO Period
2005/08/05 (Fri)
2005/08/06 (Sat)
2005/08/07 (Sun)
Use Clinical Judgment
2006/06/05 (Mon)
Use Clinical Judgment
ETS Period
2006/06/06 (Tue)
2006/06/07 (Wed)
2006/06/08 (Thu)
22.2 mmol /L
16.7
11.1
9.4
5.6
3.6
0.0
3 6 9 12 15 18 21
Time Of Day

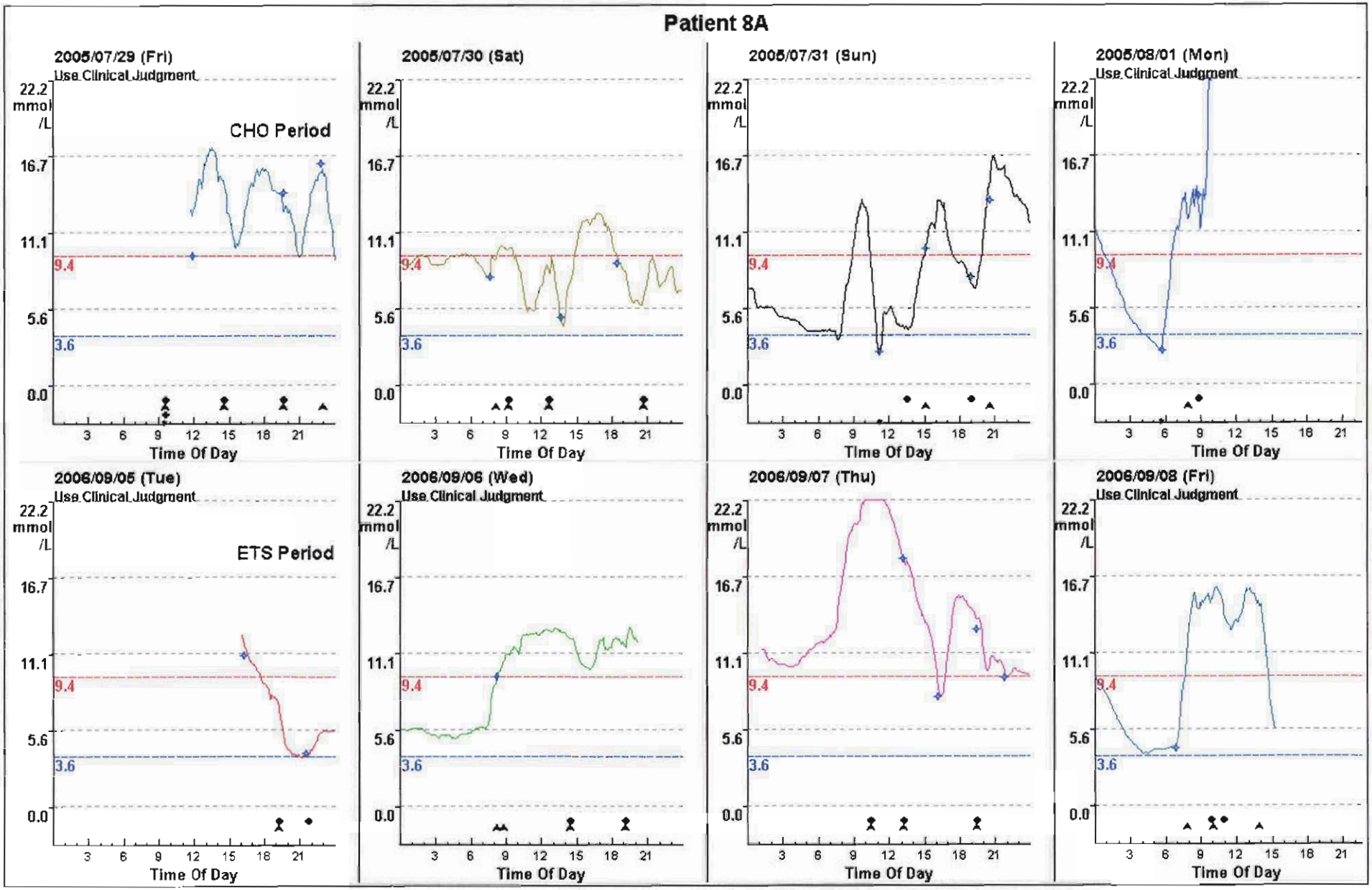

Patient 4
CHO Period
ETS Period
2006/08/19 (Fri)
2006/08/20 (Sat)
2006/08/21 (Sun)
2006/08/22 (Mon)
2006/07/03 (Mon)
2006/07/04 (Tue)
2006/07/05 (Wed)
2006/07/06 (Thu)
Use Clinical Judgment
22.2
mmol
/L
16.7
11.1
9.4
5.6
3.6
0.0
3
6
9
12
15
18
21
Time Of Day

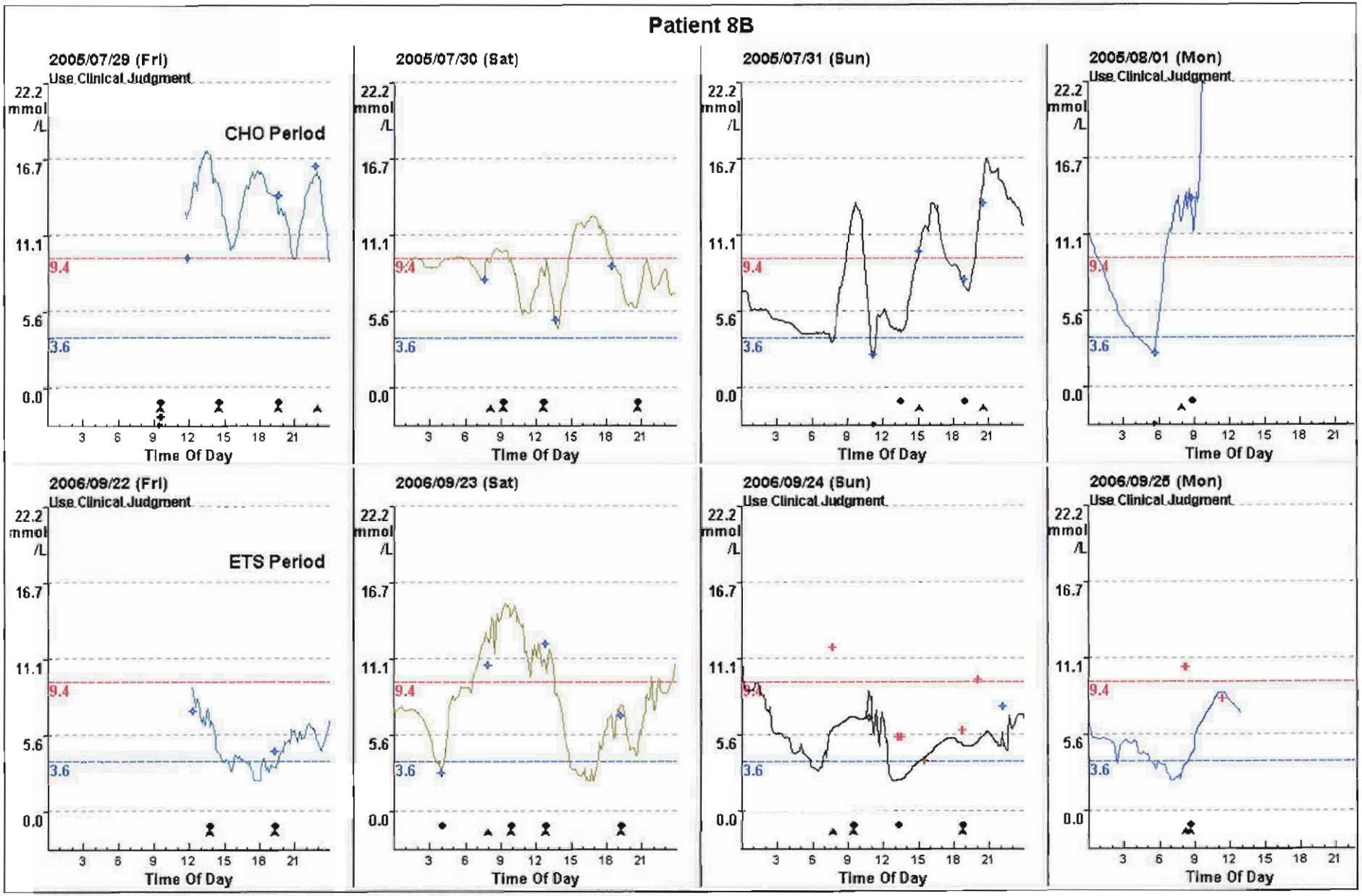

Patient 5
2005/08/31 (Wed)
CHO Period
2005/09/01 (Thu)
2005/09/02 (Fri)
2005/09/03 (Sat)
Use Clinical Judgment
2006/08/15
ETS Period
2006/08/16
2006/08/17
2006/08/18
22.2 mmol /L
16.7
11.1
9.4
5.6
3.6
0.0
3 6 9 12 15 18 21
Time Of Day
3 6 9 12 3 6 9

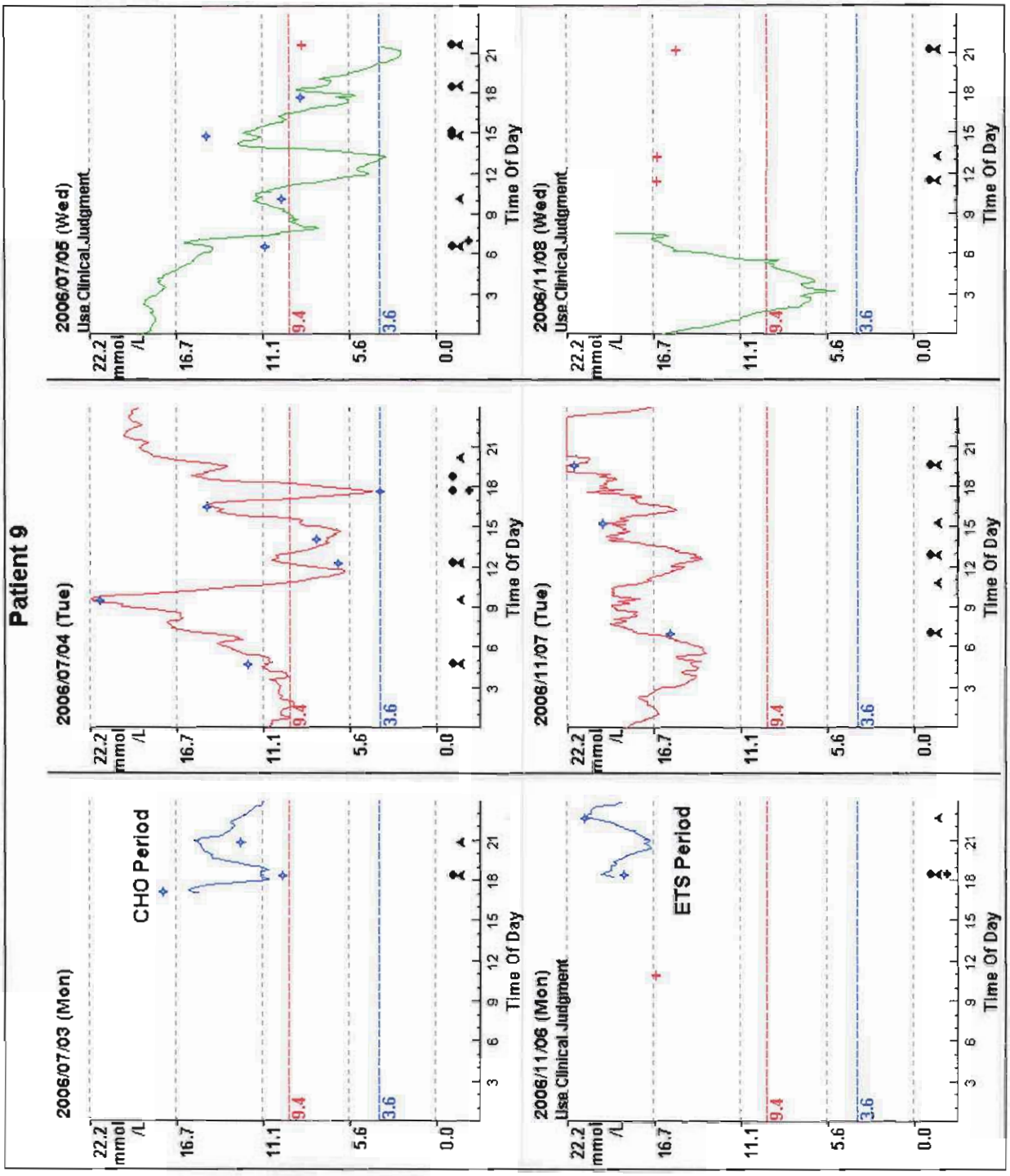

Patient 6A
2005/07/29 (Fri)
Use Clinical Judgment
CHO Period
2005/07/30 (Sat)
2005/07/31 (Sun)
2005/08/01 (Mon)
Use Clinical Judgment
2006/05/25 (Thu)
Use Clinical Judgment
ETS Period
2006/05/26 (Fri)
2006/05/27 (Sat)
2006/05/28 (Sun)
22.2 mmol /L
16.7
11.1
9.4
5.6
3.6
0.0
3 6 9 12 15 18 21
Time Of Day

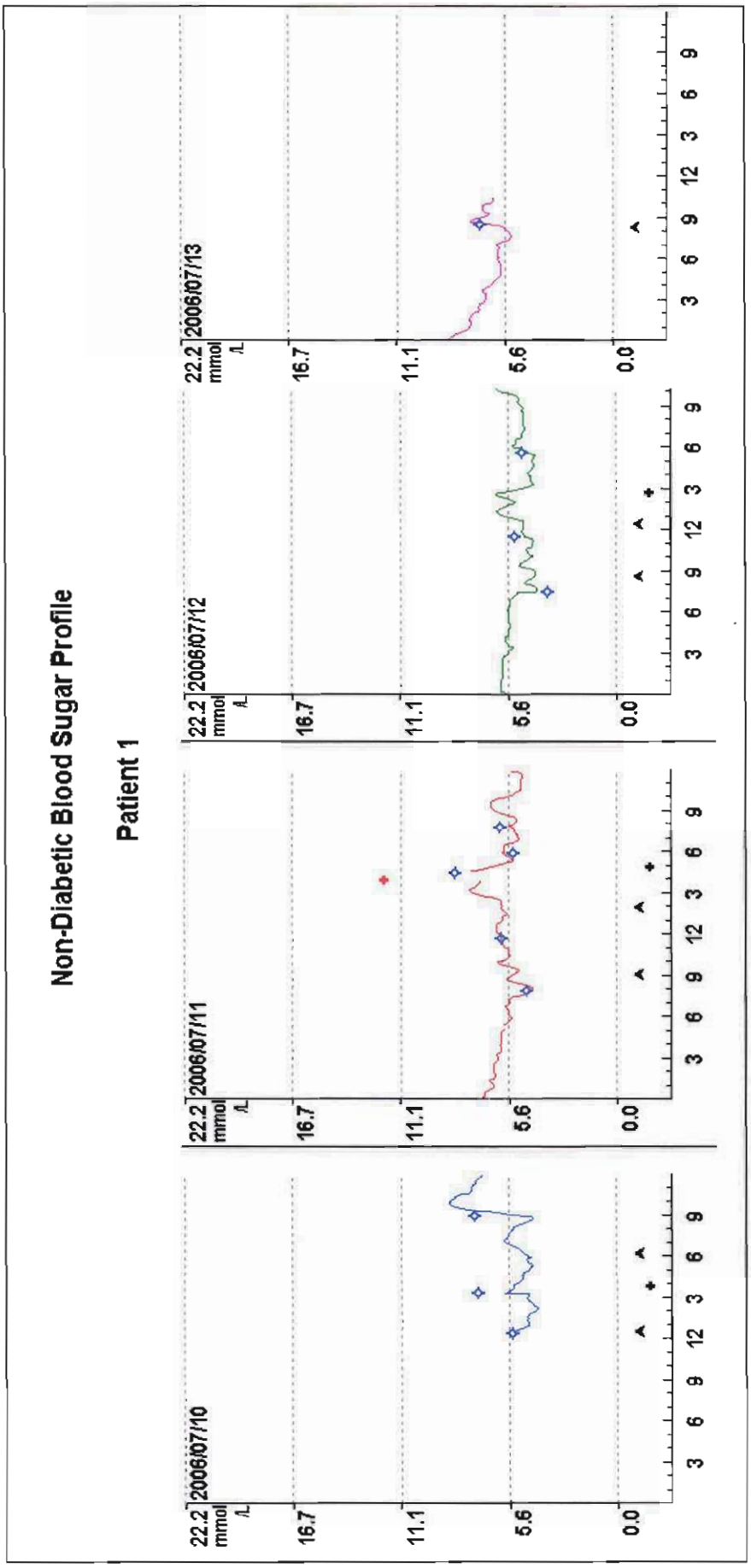

Patient 6B
2005/07/29 (Fri)
Use Clinical Judgment
CHO Period
2005/07/30 (Sat)
2005/07/31 (Sun)
2005/08/01 (Mon)
Use Clinical Judgment
2006/08/22 (Tue)
Use Clinical Judgment
ETS Period
2006/08/23 (Wed)
2006/08/24 (Thu)
2006/08/25 (Fri)
Use Clinical Judgment
22.2 mmol /L
16.7
11.1
9.4
5.6
3.6
0.0
3 6 9 12 15 18 21
Time Of Day


Patient 7
2005/08/05 (Fri)
Use Clinical Judgment
CHO Period
2005/08/06 (Sat)
2005/08/07 (Sun)
2005/08/08 (Mon)
Use Clinical Judgment
2006/07/10 (Mon)
Use Clinical Judgment
ETS Period
2006/07/11 (Tue)
2006/07/12 (Wed)
2006/07/13 (Thu)
Use Clinical Judgment
22.2 mmol /L
16.7
11.1
9.4
5.6
3.6
0.0
3 6 9 12 15 18 21
Time Of Day


Patient 8A
2005/07/29 (Fri)
Use Clinical Judgment
CHO Period
2005/07/30 (Sat)
2005/07/31 (Sun)
2005/08/01 (Mon)
Use Clinical Judgment
2006/09/05 (Tue)
Use Clinical Judgment
ETS Period
2006/09/06 (Wed)
Use Clinical Judgment
2006/09/07 (Thu)
2006/09/08 (Fri)
Use Clinical Judgment
22.2 mmol /L
16.7
11.1
9.4
5.6
3.6
0.0
3 6 9 12 15 18 21
Time Of Day


Patient 8B
2005/07/29 (Fri)
Use Clinical Judgment
CHO Period
2005/07/30 (Sat)
2005/07/31 (Sun)
2005/08/01 (Mon)
Use Clinical Judgment
2006/09/22 (Fri)
Use Clinical Judgment
ETS Period
2006/09/23 (Sat)
2006/09/24 (Sun)
Use Clinical Judgment
2006/09/25 (Mon)
Use Clinical Judgment
22.2 mmol /L
16.7
11.1
9.4
5.6
3.6
0.0
3 6 9 12 15 18 21
Time Of Day


Patient 9
2006/07/03 (Mon)
CHO Period
2006/07/04 (Tue)
2006/07/05 (Wed)
Use Clinical Judgment
2006/11/06 (Mon)
Use Clinical Judgment
ETS Period
2006/11/07 (Tue)
2006/11/08 (Wed)
Use Clinical Judgment
22.2 mmol /L
16.7
11.1
9.4
5.6
3.6
0.0
3 6 9 12 15 18 21
Time Of Day


Non-Diabetic Blood Sugar Profile
Patient 1
2006/07/10
2006/07/11
2006/07/12
2006/07/13
22.2
mmol
16.7
11.1
5.6
0.0
3 6 9 12 3 6 9

Non-Diabetic Blood Sugar Profiles
Patient 2
2006/10/11 (Wed)
Use Clinical Judgment
2006/10/12 (Thu)
2006/10/13 (Fri)
2006/10/14 (Sat)
Use Clinical Judgment
22.2
mmol
/L
16.7
11.1
9.4
5.6
3.6
0.0
3
6
9
12
15
18
21
Time Of Day

End Calculations

Group Method

Table 10 shows the processed results of the *Group Method* calculations for the diabetic test subjects:

Table 10: Summary of CGMS end results - Group Method

Monitor Period	Subject	Tightness Control (ABCM)		Hypoglycaemic events		Hyperglycaemic events		AUC (HbA1c)	
[hours]	Subject	*CHO*	*Ets*	*CHO*	*Ets*	*CHO*	*Ets*	*CHO*	*Ets*
45	1	3560	2599	1	0	2	0	16677	17443
46	2	6318	4821	3	3	2	1	18540	15782
68	3	15411	6068	2	1	6	2	41480	26740
42	4	5635	4705	0	0	6	6	28426	25332
59	5	5303	5726	0	0	7	8	42905	35521
44	6	5079	7668	5	0	5	5	16199	26641
44	7	5079	5399	5	2	5	3	16199	29491
59	8	11714	12728	3	3	6	4	40353	36246
60	9	8091	10973	3	0	6	4	39192	45538
60	10	8091	7315	3	4	6	1	39192	23483
37	11	8623	5008	0	0	6	4	30204	37146
	Average	**7537**	**6637**	**2.27**	**1.18**	**5.18**	**3.45**	**29942**	**29033**
	Ets factor	**1.14**		**1.92**		**1.50**		**1.03**	

Overall Ets Performance **1.44**
for the whole group

Individual Method

With the *Individual Method* the values in Table 10 is used to calculate the 24 hour scaled values in Table 11:

Table 11: 24 Hour scaled values of variable control factors.

24h factor	Subject	ABCM/day		Avg Hypo's per day		Avg Hyper's per day		AUC per day	
	Subject	*CHO*	*Ets*	*CHO*	*Ets*	*CHO*	*Ets*	*CHO*	*Ets*
1.875	1	1899	1386	0.53	0.00	1.07	0.00	8894	9303
1.917	2	3296	2515	1.57	1.57	1.04	0.52	9673	8234
2.833	3	5439	2142	0.71	0.35	2.12	0.71	14640	9437
1.750	4	3220	2689	0.00	0.00	3.43	3.43	16243	14475
2.458	5	2157	2329	0.00	0.00	2.85	3.25	17453	14449
1.833	6	2770	4183	2.73	0.00	2.73	2.73	8836	14531
1.833	7	2770	2945	2.73	1.09	2.73	1.64	8836	16086
2.458	8	4765	5178	1.22	1.22	2.44	1.63	16415	14744
2.500	9	3236	4389	1.20	0.00	2.40	1.60	15677	18215
2.500	10	3236	2926	1.20	1.60	2.40	0.40	15677	9393
1.542	11	5593	3248	0.00	0.00	3.89	2.59	19592	24095

From Table 11 we see the maximum value from the Avg Hypo's per day and Avg Hypers per day was found to be 3.89. This value **was** rounded of to the next positive integer and the **Max Hypo/Hyper Factor** was then calculated to be **4**.

Table 12 shows the calculated variable control values of the non-diabetic subjects:

Table 12: Non-Diabetic variable control values.

Subject	*ABCM*	*Hypos*	*Hypers*	*AUC*	*Avg ABCM/day*	*Avg Hypos/day*	*Avg Hypers/day*	*Avg AUC/day*
	mmol.min/L	#	#	mmol. min/L	mmol.min/L	#	#	mmol.min/L
1	2682.41	0	0	23801	919.68	0.0	0.0	8160.34
2	1923.26	0	0	22913	623.76	0.0	0.0	7431.48
			Average		**771.73**	**0.00**	**0.00**	**7795.92**

The values from Table 11 and Table 12 was then used to determine the Overall Control Performance of each patient in the group for both the CHO and ETS periods, and these values in shown in Table 13 on the next page:

Table 13: Overall Control Performance of the diabetic subjects with Individual Method

	Tightness Control		Hypoglycaemic Events		Hyperglycaemic Events		AUC (HbA1c)		Overall Control Performance		
	ABCM_cho	ABCM_ets	HYPO_cho	HYPO_ets	HYPERS_cho	HYPERS_ets	AUC_cho	AUC_ets	Control Perf_cho	Control Perf_ets	Improvement Control
Subject	%	%	%	%	%	%	%	%	%	%	%
1	40.64	55.68	86.67	100.00	73.33	100.00	87.65	83.80	73.41	84.87	11.46
2	23.41	30.68	60.87	60.87	73.91	86.96	80.59	94.68	58.39	65.69	7.30
3	14.19	36.03	82.35	91.18	47.06	82.35	53.25	82.61	52.74	73.92	21.18
4	23.97	28.70	100.00	100.00	14.29	14.29	47.99	53.86	55.13	57.78	2.65
5	35.78	33.13	100.00	100.00	28.81	18.64	44.67	53.95	59.43	59.57	0.13
6	27.86	18.45	31.82	100.00	31.82	31.82	88.23	53.65	44.93	57.80	12.87
7	27.86	26.20	31.82	72.73	31.82	59.09	88.23	48.46	44.93	52.99	8.05
8	16.20	14.91	69.49	69.49	38.98	59.32	47.49	52.87	46.09	50.17	4.07
9	23.85	17.58	70.00	100.00	40.00	60.00	49.73	42.80	48.89	59.10	10.20
10	23.85	26.37	70.00	60.00	40.00	90.00	49.73	83.00	48.89	61.84	12.95
11	13.80	23.76	100.00	100.00	2.70	35.14	39.79	32.36	48.80	54.30	5.50
Avg - Group	24.67	28.32	73.00	86.75	38.43	57.96	61.58	62.00	52.88	61.64	
Avg Improvement	ABCM	3.65%	HYPOS	13.75%	HYPERS	19.53%	AUC	0.42%		CONTROL	8.76%
ETS VS CHO											