Design, management and completion of the HypoCOMPaSS RCT evaluating potential for restoration of hypoglycaemia awareness in type 1 diabetes using conventional vs novel technologies; and exploration of potential phenotypes predicting persistent impaired awareness despite study intervention

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Abstract

Aim: To explore the extent to which impaired awareness of hypoglycaemia (IAH) can be improved using currently available treatment regimens in individuals with long-standing type 1 diabetes mellitus (T1DM), and to characterise those individuals whose awareness of hypoglycaemia did not improve.

Methods: A multicentre, 2x2 factorial 24-week RCT (HypoCOMPaSS) comparing multiple daily injections (MDI) and continuous subcutaneous insulin infusion therapy (CSII) with or without real-time continuous glucose monitoring (RT) in a population with T1DM and IAH was designed. The study was undertaken in five UK centres using established and novel outcome measures to assess hypoglycaemia awareness, glycaemic control and treatment satisfaction.

A second analysis was undertaken characterising individuals within the HypoCOMPaSS population as responders and non-responders. Complication status, autonomic symptom profile and hyperglycaemia avoidance scores were assessed.

Results: Overall, hypoglycaemia awareness improved, and biochemical hypoglycaemia, severe hypoglycaemia rate and insulin doses reduced without deterioration in HbA1c. There were no significant differences in awareness comparing MDI with CSII; and RT with conventional glucose monitoring. Between-group analyses demonstrated comparable reductions in severe hypoglycaemia, biochemical hypoglycaemia, fear of hypoglycaemia and insulin doses with equivalent HbA1c. Treatment satisfaction was highest with CSII. In the second study there was a suggestion that longer diabetes duration and increased age may impair ability to respond to the interventions but this did not correlate with severity of autonomic symptoms.

Conclusions: Hypoglycaemia awareness can be improved and recurrent severe hypoglycaemia prevented in long-standing T1DM without relaxing HbA1c. Similar biomedical outcomes can be attained with conventional MDI and SMBG regimens compared with CSII / RT. All individuals may benefit from biomedical interventions to improve awareness of hypoglycaemia. This

research provides a basis for further studies investigating impact of new technologies on severe hypoglycaemia and underlines the importance of tailoring treatment to avoid biochemical hypoglycaemia without relaxing overall control.

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Declaration

This thesis is a presentation of my original research work. Wherever contribution of others is involved, every effort has been made to indicate this clearly. It has not been submitted for any other higher degree or qualification.

Professor James Shaw conceived the idea for the multicentre study and obtained funding from Diabetes UK. I led study design, conducted the Newcastle component of the study, initiated the study at the four other sites and coordinated and managed the day to day running of the study with guidance from my supervisors Professor James Shaw and Professor Sally Marshall.

I researched the study topics and analysed the data with assistance from Dr Thomas Chadwick, Institute of Health and Society, Newcastle University. Charlotte Gordon and Leanne Thompson, Clinical Research Facility, RVI, Newcastle provided nursing assistance for the participant visits. Cath Brennand and Julia Stickland provided clinical trial monitoring expertise. Ruth Wood provided data management expertise including data cleaning and sending data queries to the study sites. Professors Jane Speight and Julia Newton provided advice on range of questionnaires to be included. Professor Jane Speight and Jessie Pairman entered the multicentre questionnaire data onto the database.

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Peer reviewed publications

1. **Little S,** Leelarathna L, Barendse S, Walkinshaw E, Tan HK, Lubina Solomon A, de Zoysa N, Rogers H, Choudhary P, Amiel SA, Heller S, Evans M, Flanagan D, Speight J, Shaw JAM. Severe Hypoglycaemia in Type 1 Diabetes Mellitus: Underlying Drivers and Potential Strategies for Successful Prevention. *Diabetes Metab Res Rev. 2013 Nov 3* (epub ahead of print)

2. **Little S**, Chadwick T, Choudhary P, Brennand C, Stickland J, Barendse S, Olateju T, Leelarathna L, Walkinshaw E, Tan HK, Marshall SM, Thomas RM, Heller S, Evans M, Kerr D, Flanagan D, Speight J, Shaw JAM. Comparison of Optimised MDI versus Pumps with or without Sensors in Severe Hypoglycaemia (the Hypo COMPaSS trial). *BMC Endocr Disord. 2012 Dec 13;12:33*

3. **Little S,** Leelarathna L, Walkinshaw E, Tan HK, Chapple O, Lubina-Solomon A, Chadwick T, Barendse S, PhD, Stocken DD, Brennand C, Marshall SM, Wood R, Speight J, Kerr D, Flanagan D, Heller SR, Evans ML, Shaw JAM. Recovery of hypoglycaemia awareness in long-standing type 1 diabetes: a multicentre 2x2 factorial RCT comparing insulin pump with multiple daily injections, and continuous with conventional glucose self-monitoring (HypoCOMPaSS). *Diabetes Care. 2014 Aug;37(8):2114-22*

4. Leelarathna L, **Little SA**, Walkinshaw E, Tan HK, Lubina-Solomon A, Kumareswaran K, Lane AP, Chadwick T, Marshall SM, Speight J, Flanagan D, Heller SR, Shaw JA, Evans ML. Restoration of self-awareness of hypoglycemia in adults with long-standing type 1 diabetes: hyperinsulinemic-hypoglycemic clamp substudy results from the HypoCOMPaSS trial. *Diabetes Care. 2013 Dec; 36(12):4063-70.*

5. **Little S**, Shaw J, Home P. Hypoglycemia rates with basal insulin analogs. *Diabetes Technol Ther. 2011 Jun: 13 Suppl 1*

6. **Little SA**, Barendse SM, Evans ML, Kyne D, Speight J, Thomas RM, Shaw JAM. The 'my hypo compass' psycho-educational intervention: design of a novel curriculum to aid the prevention of severe hypoglycaemia (abstract). *Diabetic Medicine (2011) 28 (suppl. 1) 32-203 P491.*

Presentations to Learned Societies

1. **Little S,** Leelarathna L, Walkinshaw E, Tan HK, Chapple O, Lubina-Solomon A, Barendse S, Chadwick T, Brennand C, Stocken D, Wood R, Marshall SM, Begley J, Kerr D, Speight J, Flanagan D, Heller SR, Evans ML, Shaw JAM. A Definitive Multicenter RCT to Restore hypoglycemia Awareness and Prevent Recurrent Severe Hypoglycemia in Adults with Long-standing Type 1 Diabetes: Results from the Hypo COMPaSS Trial *(ADA Scientific Sessions, Presidents Oral Session, Abstract 387-OR)*

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Abbreviations and definitions

ADA	American Diabetes Association
ASP	Autonomic Symptom Profile
AFT	Autonomic Function Tests
BGAT	Blood Glucose Awareness Training
BP	Blood Pressure
CGM	Continuous Glucose Monitoring
CI	Chief Investigator
CKD	Chronic Kidney Disease
CRF	Case Report Form
eCRF	Electronic Case Report Form
CSII	Continuous Subcutaneous Insulin Infusion
DAN	Diabetic Autonomic Neuropathy
DAFNE	Dose Adjustment For Normal Eating
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DKA	Diabetic Ketoacidosis
GCP	Good Clinical Practice
HbA1c	Glycosylated Haemoglobin
HFS	Hypoglycaemia Fear Survey II
HypoA-Q	Hypoglycaemia Awareness Questionnaire
HLA	Human Leukocyte Antigen
IAH	Impaired Awareness of Hypoglycaemia
IRAS	Integrated Research Application System
IMP	Investigational Medicinal Product
MDI	Multiple Daily Injections
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Care Excellence
NCTU	Newcastle Clinical Trials Unit
NPH	Neutral Protamine Hagedorn

RCT	Randomised Control Trial
RT	Real Time continuous glucose monitoring
SAE	Serious Adverse Event
SMBG	Self Monitoring of Blood Glucose
T1DM	Type 1 Diabetes Mellitus
TMG	Trial Management Group
TSC	Trial Steering Committee
TSH	Thyroid Stimulating Hormone

Chapter 1

Introduction

1.1 Content and scope

The overall objective of this thesis was to explore the potential to improve the awareness of hypoglycaemia and prevent severe hypoglycaemia in individuals with type 1 diabetes, and identify characteristics of people whose awareness of hypoglycaemia did not improve. This chapter will provide a background to the studies including:

1. The underlying aetiology and drivers of hypoglycaemia

2. Potential strategies available to prevent hypoglycaemia

1.2 Introduction

Diabetes Mellitus is the collective name for a group of disorders characterised by a hyperglycaemic state. The heterogeneous group of disorders can be classified on the basis of the pathophysiology leading to the hyperglycaemia. Type 1 diabetes mellitus (T1DM) is characterised by insulin deficiency resulting from an autoimmune mediated destruction of the beta cells of the islets of Langerhans in the pancreas. Type 2 diabetes mellitus is characterised by impaired insulin secretion, reduced insulin sensitivity and increased insulin production.

T1DM is one of the most common childhood metabolic diseases and the incidence is increasing. From 1989 to 2003 the annual increase in incidence in children under 15 years of age across Europe was 3.9% with the highest rate of increase (5.4%) in the 0-4 years age group (Patterson *et al.*, 2009). It has been estimated that the incidence of T1DM across Europe in this youngest of age groups will double between 2005 and 2020 (Patterson *et al.*, 2009).

Furthermore an inverse relationship has been reported between the overall incidence rate and the rise in incidence rate across European centres. Thus the previously low childhood incidence in central and eastern European countries may now be catching up with countries with higher incidence. The increase in annual incidence of childhood T1DM is not limited to Europe. The World Health Organisation's Multinational Project for Childhood Diabetes (DIAMOND, 2006), with a population sample of 84 million in 87 different countries, reported that between 1990 and 1999 the global annual increase in incidence was 2.8%

though the rate was higher (3.4%) during the last 5 years of the study. Unlike the inverse relationship between annual incidence and rate of increased incidence between European centres, globally the most significant increases in rates were seen in the continents that already have high incidence such as Europe.

A study from 2006 using an epidemiological model suggested that in 2006 there were 2,168,000 people with diabetes in England with 165,756 (7.3%) of these cases being T1DM (Forouhi *et al.*, 2006). This suggests an overall prevalence of 340 per 100,000 (0.34%). It was estimated that in the North East of England there were 8447 cases of T1DM. In the 2010-2011 NHS National Diabetes Audit the number of registrations of type 1 diabetes was 1,164 (Table 1.1) with a prevalence of 0.44% (Table 1.2).

The factors responsible for the likely T-cell mediated immune destruction of the insulin producing beta cells which leads to the clinical presentation of T1DM are not fully understood. Genetic susceptibility to T1DM involves many genes though it is thought that polymorphisms of the Human Leukocyte Antigen (HLA) genotype are responsible for 40-50% of genetic risk (Pociot and McDermott, 2002). Numerous other risk factors have been suggested to be responsible including seasonal variation of birth (Padaiga *et al.*, 1999) (Levy-Marchal *et al.*, 1995), diet (Norris *et al.*, 2003), infectious agents (Hyoty and Taylor, 2002), vitamin D deficiency (Bener *et al.*, 2009) and geographical variation (DIAMOND, 2006).

In contrast to the hypothesis that there is an as yet unidentified trigger solely responsible for the increased incidence in T1DM, the 'spring harvest' hypothesis has been proposed (Gale, 2005). This suggests that environmental factors are changing the natural history of T1DM disease progression. Epidemiological evidence of earlier disease presentation, increased disease incidence in children of previously considered intermediate risk HLA haplotype and the prevalence of immune-mediated diabetes not requiring insulin treatment in older people and the predecessors of affected children is cited to back up the hypothesis of disease acceleration and altered disease penetrance.

The large registry studies both within Europe and worldwide over recent decades have investigated the incidence of T1DM in children only and therefore

longitudinal studies with longer term follow up are needed to determine whether or not the apparent increase in childhood incidence is associated with increased overall lifetime risk.

Table 1.1   Diabetes registrations by type for Newcastle Primary Care Trust 2010-2011

	Number of registrations
All diabetes	10,581
Type 1 diabetes	1,164
Type 2 diabetes	9,323

Table 1.2   Prevalence of diabetes in Newcastle Primary Care Trust 2010-2011

	Newcastle Primary Care Trust		England	
	Prevalence of diabetes (%)	Percentage point change since 2009-2010 (%)	Prevalence of diabetes (%)	Percentage point change since 2009-2010 (%)
All diabetes	3.97	+0.11	4.57	+0.21
Type 1 diabetes	0.44	-0.01	0.41	0.00
Type 2 diabetes	3.50	+0.12	4.07	+0.20

1.3 Aims of treatment in type 1 diabetes

The results of the landmark Diabetes Control and Complications Trial (DCCT) concluded that the improvement of mean glycaemic control to as near normal as possible with intensive insulin treatment can delay the onset and slow the progression of the microvascular complications associated with T1DM such as nephropathy, retinopathy and neuropathy (DCCT, 1993). The sustained long-term benefit in reduction in micro-vascular complications was confirmed in the Epidemiology of Diabetes Interventions and Complications study (EDIC), which was a 17 year follow-up observational study of people with T1DM from the DCCT (Nathan *et al.*, 2005). On the basis of this information national guidelines such as that produced by the National Institute for Health and Care Excellence (NICE) suggest a target HbA1c of <58mmol/mol (7.5%) for people with T1DM (NICE, 2004).

1.4 Type 1 diabetes and hypoglycaemia

Type 1 diabetes is fatal unless it is treated with insulin replacement. Insulin was first used as a therapy for humans with diabetes in 1922 by a team from Toronto University consisting of Dr. Fredrick Banting, Charles Best, Professor J. J. R. Macleod and Dr. James Collip. In a landmark paper from this pioneering group which describes the metabolic outcomes after administration of the extract to patients with diabetes, the authors conclude that 'blood sugar can be markedly reduced even to the normal values' (Banting *et al.*, 1922). Within the same year that this paper was published the problem of iatrogenic hypoglycaemia was recognised in the literature (Fletcher and Campbell, 1922).

For many people with T1DM hypoglycaemia remains one of the most feared complications alongside retinopathy and nephropathy (Pramming *et al.*, 1991). Indeed, manifest fear of hypoglycaemia (FoH) is a recognised and relatively common phenomenon, particularly among those with a recent history of severe hypoglycaemia (Gonder-Frederick *et al.*, 2011). In a review on hypoglycaemia Cryer writes: ''at the very least an episode of hypoglycaemia is a nuisance and a distraction. It can be embarrassing and cause social ostracism" (Cryer *et al.*, 2003). At its worst hypoglycaemia can be even more devastating by causing behavioural changes, seizures, coma and in rare but tragic instances even

sudden death (Tattersall and Gill, 1991). Between these two extremes, hypoglycaemia reduces emotional well being and impairs quality of life. It is almost inevitably associated with negative mood states (e.g. depressed mood, anxiety, irritability) but the relationship is idiosyncratic (Gonder-Frederick *et al.*, 1989). Narrative research has found that patients rarely discuss hypoglycaemia with others and that it can affect views of themselves and interpersonal relationships (Ritholz and Jacobson, 1998). Loss of spontaneity and independence are reported commonly by those with recurrent severe hypoglycaemia, as well as other restrictions (e.g. on ability to drive, work, fulfil family commitments) that impair quality of life (Speight *et al.*, 2010).

1.5 Definition of hypoglycaemia

One of the factors limiting meaningful interpretation of existing literature and evidence-based guidelines for optimal clinical management of hypoglycaemia has been the lack of universally agreed blood glucose levels by which hypoglycaemia is defined. A clinically useful and globally accepted definition used in the Diabetes Control and Complications Trial defines a hypoglycaemic episode as 'mild' if self treatment is possible and 'severe' if external help is required for treatment (DCCT, 1993). Importantly this definition does not take into account asymptomatic hypoglycaemia, which is important in the aetiology of severe hypoglycaemia.

The American Diabetes Association (ADA) Workgroup on hypoglycaemia's overarching definition is "all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm" (ADA, 2005). The Workgroup further classifies hypoglycaemia into five categories: severe hypoglycaemia, documented symptomatic hypoglycaemia, asymptomatic hypoglycaemia, probable symptomatic hypoglycaemia and relative hypoglycaemia (Table 1.3).

The biochemical cut-off (≤ 3.9 mmol/L) proposed by the ADA may artificially inflate the amount of hypoglycaemia reported by inclusion of episodes with no clinical significance (Swinnen *et al.*, 2009). This is because the provocation of symptoms and cognitive impairment that is associated with low blood glucose will rarely be produced at levels between 3.5 - 4.0 mmol/L. It has therefore been argued that a value of 3.5 mmol/L should be used to ensure that only truly

significant episodes are recorded in clinical trials (Frier, 2009). The main argument for this is that the evidence suggesting that antecedent plasma glucose concentrations of 3.9 mmol/l reduce glucose counter-regulatory responses to subsequent hypoglycaemia is from a cohort of non-diabetic subjects, and therefore may not be clinically relevant in people with diabetes. Primarily this is because the diminished glucagon response seen in non-diabetic people is unlikely to be relevant because people with insulin treated diabetes develop deficient glucagon secretion at an early stage in the T1DM disease process. The alternative view is that a value of ≤ 3.9 mmol/L should be used as a cue for action (if not necessarily carbohydrate administration), to give patients enough time to take steps to prevent severe hypoglycaemia. It would also allow for some margin of error in the accuracy of blood glucose meters at low plasma glucose values (Cryer, 2009).

Any numerical definition used by healthcare professionals does not however reflect the spectrum of disruption hypoglycaemia causes to people with diabetes, which may start with mild inconvenience in everyday living but extends to a life threatening emergency. Any biochemical cut-off may be deemed arbitrary. Therefore when investigating hypoglycaemic episodes in study populations, which have a high risk of severe hypoglycaemia, it may be most appropriate to record low values below a range of thresholds (including all ≤ 3.9mmol/L) to evaluate impact on clinical outcomes.

Table 1.3   ADA working group definitions of hypoglycaemia

Definition	Description
Severe hypoglycaemia	An event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopaenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by low plasma glucose concentration.
Documented symptomatic hypoglycaemia	An event during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose ≤3.9 mmol/l.
Asymptomatic hypoglycaemia	An event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration ≤3.9 mmol/l.
Probable symptomatic hypoglycaemia	An event during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤3.9 mmol/l).
Relative hypoglycaemia	An event during which the person with diabetes reports any of the typical symptoms of hypoglycaemia, and interprets those as indicative of hypoglycaemia, but with a measured plasma glucose concentration >3.9 mmol/l.

1.6   The frequency of hypoglycaemia

While the ADA Workgroup report provides an extremely valuable framework, misreporting remains a risk if data on symptomatic and severe hypoglycaemia episodes are not collected meticulously. As the majority of these episodes occur outside times of routine blood glucose monitoring (i.e. before meals and bed) care is needed to optimise study protocols, to prevent over-reporting of biochemical hypoglycaemia without concomitant reporting of symptoms; or under reporting of symptomatic hypoglycaemia / severe hypoglycaemia due to the absence of sufficiently robust diary data when glucose levels have not been checked or recorded.

The occurrence of severe hypoglycaemia has a skewed distribution with relatively few individuals experiencing the majority of events (Pedersen-Bjergaard *et al.*, 2004). This has led to the recommendation that both the percentage of individuals affected and event rates (e.g. episodes per 100 patient years) are reported (ADA, 2005). Recall of the frequency of severe hypoglycaemia is reported to be reliable up to one year (Pramming *et al.*, 1991) while the recall of mild or minor events may be inaccurate beyond one week. This limitation in recall also contributes to the difficulties in analysing hypoglycaemia data.

In a retrospective epidemiological survey of an unselected population with type 1 diabetes (defined as a diagnosis of diabetes before the age of 40 years old, requiring insulin from the outset) prevalence of severe hypoglycaemia was reported to be 37% over a one-year recall period with 130 events occurring per 100 patient years (Pedersen-Bjergaard *et al.*, 2004). In this study, 5% of the participants experienced 54% of all severe hypoglycaemic episodes, providing further evidence for the highly skewed distribution. The rate of mild hypoglycaemia (defined as episodes with symptoms of hypoglycaemia manageable by the individual) was reported as two events per week. In a similar study the severe hypoglycaemia rate was reported as 150 events per 100 patient years with 41% affected over a one-year period (ter Braak *et al.*, 2000).

Estimates of the frequency of severe hypoglycaemia when determined in prospective population-based studies are likely to be the most reliable. An

incidence of severe hypoglycaemia of 115 episodes per 100 patient years was reported in one such study from Tayside (Donnelly *et al.,* 2005). A similar severe hypoglycaemia rate of 110 events per 100 patient years with prevalence of 22% in a patient group with T1DM duration of less than five years was reported in a multicentre prospective observational study over 9 - 12 months in the UK (UK-hypoglycaemia-studygroup, 2007). However, the rate rose to 320 events per 100 patient years with a prevalence of 46% in those with long duration diabetes (more than 15 years), indicating that those with a longer duration of diabetes are at higher risk of severe hypoglycaemia.

In the DCCT trial (DCCT, 1997) severe hypoglycaemia rates ranged from 61.2 events per 100 patient years in the intensively treated group to 18.7 events per 100 patient years in the conventionally treated group (three fold increase in intensively treated group). However it should be noted that people with type 1 diabetes and a preceding history of severe hypoglycaemia were excluded from the DCCT, which therefore excluded many with impaired awareness of hypoglycaemia. As will be discussed in section 1.9 the majority of clinical trials investigating pharmacological interventions in the management of T1DM have excluded those with previous recurrent severe hypoglycaemia meaning that only limited interpretation of the data concerning SH frequency can be made.

From a health economic viewpoint there are substantial costs to the NHS in the need for the emergency medical treatment of severe hypoglycaemia. It has been suggested that around 10% of episodes of severe hypoglycaemia required emergency medical assistance (Donnelly *et al.*, 2005).

Mild hypoglycaemia has been reported to occur on average twice weekly (Pramming *et al.*, 1991; Pedersen-Bjergaard *et al.*, 2004).

A summary of the epidemiology of severe hypoglycaemia is shown in Table 1.4.

Table 1.4   Summary of severe hypoglycaemia epidemiology in type 1 diabetes mellitus

Study	Prevalence of severe hypoglycaemia (%)	Incidence of severe hypoglycaemia (episodes/patient/year)
Pramming S et al (Pramming et al., 1991)	36	1.4
DCCT Research group (DCCT, 1997)	35 (men) 31 (women)	0.19-0.62
Ter Braak E W et al (ter Braak et al., 2000)	40.5	1.5
Pedersen-Bjergaard U et al (2004) (Pedersen-Bjergaard et al., 2004)	36.7	1.3
UK Hypoglycaemia Study Group (UK-hypoglycaemia-studygroup, 2007)	22 (<5 year duration) 46 (> 15 yrs duration)	1.1 (<5 years duration) 3.2 (>15 years duration)

1.7   Hypoglycaemic symptoms

Hypoglycaemic symptoms can be classified under 3 headings (autonomic, neuroglycopenic and other) depending on the aetiology of the symptom (Deary *et al.*, 1993).

(1) Autonomic symptoms are due to secondary activation of the sympatho-adrenal nervous system). Some autonomic symptoms are adrenergic (catecholamine mediated) such as palpitations, tremor, anxiety; while others are cholinergic (acetylcholine mediated) such as sweating, hunger and paraesthesia (Cryer *et al.*, 2003).

(2) Neuroglycopenic symptoms include dizziness, confusion, tiredness, difficulty in speaking, drowsiness and headache. These are secondary to the direct effect of glucose deprivation on the brain, particularly cortical function. Cerebral glycopenia affects cognitive performance including processing information and decision making. In experimental studies the performance of working memory and simple motor tasks such a finger tapping are more resilient and may deteriorate at around 2.4 mmol/L (Holmes *et al.*, 1986), while the performance of undertaking tasks requiring reaction times and operation of driving simulators are affected at plasma glucose levels of around 2.8 - 3.0 mmol/L (Heller and Macdonald, 1996). This may be due to the regional variations in brain glucose metabolism that have been clearly documented (Cranston *et al.*, 1998).

(3) Other symptoms include hunger, blurred vision and tiredness. These are symptoms that are difficult to reliably attribute to the other physiological mechanisms.

1.8   Aetiology and drivers of severe hypoglycaemia

1.8.1   Classical drivers

Fundamentally, low glucose is caused by relative insulin excess. The therapeutic ratio for insulin is extremely small, with doses sufficient to achieve normoglycaemia being sufficient also to induce hypoglycaemia in the same individual (Little *et al.*, 2011). Therefore, there is a particularly high risk of hypoglycaemia when insulin doses are large or ill-timed. Hypoglycaemia can

also occur when exogenous delivery of glucose is decreased (e.g. missed meals); when glucose utilisation is increased (e.g. during physical activity); when endogenous glucose production is reduced (e.g. post alcohol); when sensitivity to insulin is increased (e.g., weight loss, increased fitness) and when insulin clearance is decreased (e.g. renal failure, hypothyroidism) (Cryer *et al.*, 2003). However in the Diabetes Control and Complications Trial (DCCT), such classical risk factors were not found to be responsible for most severe hypoglycaemic events (DCCT, 1991). Table 1.3 has been adapted from Cryer (Cryer, 2008)) and illustrates the causes and risk factors for hypoglycaemia.

Table 1.5   Causes and risk factors for hypoglycaemia (adapted from Cryer, 2008)

Causes of relative or absolute therapeutic insulin excess	Risk factors

Inadequate intake of exogenous carbohydrate
 	
   a) Missed meals
   b) Dieting
   c) Breast feeding
   d) Malabsorption (coeliac disease)
   e) Gastroparesis (autonomic neuropathy)
 	
Increased utilisation of carbohydrate
 	
   a) Unexpected physical exertion
   b) Breast feeding
   c) Social situation; before and after sport, new job, travel
 	
Increased sensitivity to insulin
 	
   a) In the middle of the night
   b) Improved fitness
   c) Weight loss
   d) Honeymoon period following treatment in newly diagnosed diabetes
 	
Reduced insulin clearance
 	
   a) Renal failure
   b) Hypothyroidism
 	
Change in insulin or insulin pharmacokinetics
 	
   a) New formulation
   b) Dose ill timed or of wrong type
   c) Effects of temperature (e.g. hot bath)
   d) Effects of injection site
 	
Other causes
 	
   a) Concomitant endocrine conditions (hypopituitarism, adrenal insufficiency, hypothyroidism)
   b) Factitious insulin administration
	Impaired awareness of hypoglycaemia
	
	History of severe hypoglycaemia
	
	Strict glycaemic control
	
	C-peptide negativity
	
	Sleep
	
	Recent antecedent hypoglycaemia
	
	Duration of diabetes
	
	Exercise
	
	Loss of glucagon secretion

1.8.2 Tight glycaemic control and treat to target studies

In the DCCT, there was a three fold increase in severe hypoglycaemia in the intensive treatment group compared to the conventional treatment group (61.2 events per 100 patient years vs 18.7 events per 100 patient years) (DCCT, 1997). This landmark study has reinforced the dogma that tight glucose control is the predominant risk factor for severe hypoglycaemia while revealing that the majority of events are not solely due to conventional risk factors but instead occur in those with impaired awareness of hypoglycaemia. In the DCCT, predictors of risk of severe hypoglycaemia in the intensive treatment group included previous severe hypoglycaemia history, longer duration of diabetes, higher baseline HbA1c and lower recent HbA1c (DCCT, 1991). The DCCT also confirmed that the presence of detectable endogenous insulin as measured by residual C-peptide secretion is associated with reduced risk of severe hypoglycaemia (DCCT, 1997). It has been postulated that this may be mediated by the C-peptide itself, through an as yet unidentified mode of action, or simply through hypoglycaemia-induced reduction in residual endogenous insulin secretion.

1.8.3 Biochemical hypoglycaemia and impaired counter regulation

Biochemical hypoglycaemia at a level associated with cognitive impairment is avoided in people without diabetes through a series of counter regulatory responses which result in increased endogenous production and reduced peripheral utilisation of glucose. This has been confirmed in seminal studies involving stepped hyperinsulinaemic hypoglycaemic clamps, which report glycaemic thresholds for counter-regulatory hormone secretion, symptoms of hypoglycaemia and cerebral dysfunction (Schwartz *et al.*, 1987; Mitrakou *et al.*, 1991; Fanelli *et al.*, 1994a). There is a distinct hierarchy of responses. As insulin secretion ceases, the counter-regulatory hormone glucagon is secreted, promoting hepatic gluconeogenesis and glycogenolysis, followed by activation of the autonomic nervous system and epinephrine release. Autonomic symptoms precede neuroglycopenic symptoms and progressive deterioration in cerebral function.

Glucagon secretion occurs first at a blood glucose level of approximately 3.8 mmol/l. Epinephrine secretion from the adrenal medulla follows, also increasing hepatic gluconeogenesis and glycogenolysis. Associated activation of the sympathetic nervous system stimulates hepatic gluconeogenesis by direct neuronal stimulation, which also contributes to autonomic symptoms. A plasma glucose level for increased epinephrine secretion of between 3.6 - 3.8 mmol/l has been reported (Schwartz *et al.*, 1987; Mitrakou *et al.*, 1991; Fanelli *et al.*, 1994a). In a different study the glucose levels required to trigger epinephrine secretion varied between individuals without diabetes from 2.7 - 4.1 mmol/l with a mean of 3.5 mmol/L (Amiel *et al.*, 1987). The same study concluded that the rate of glucose decline does not affect the threshold. This hierarchy of response prevents glucose from falling below the threshold for cognitive impairment (approximately 3.0 mmol/l) thus averting neuroglycopenic symptoms, collapse or need for assistance in administering carbohydrate to reverse hypoglycaemia (Mitrakou *et al.*, 1991).

People with C-peptide negative type 1 diabetes are unable to inhibit insulin secretion in the face of biochemical hypoglycaemia, and almost all have impaired physiological counter-regulatory hormone responses within a few years of diagnosis (Bolli *et al.*, 1983). The exact mechanism of this is not fully understood. However, the intra-islet hypothesis posits that intra-islet hyperinsulinaemia, due to exogenous insulin therapy, during hypoglycaemia leads directly to defective alpha-cell regulation (Banarer *et al.*, 2002). Recent animal studies have also suggested that an inhibitory effect of exogenous insulin on alpha-cell glucagon secretion may be mediated by the brain at the level of the ventromedial hypothalamus (Paranjape *et al.*, 2010).

Given the absent insulin and diminished glucagon responses in people with type 1 diabetes, the sympathoadrenal response is critical in their defence against hypoglycaemia (Rizza *et al.*, 1979). Individuals with reduced epinephrine responses including those with longer disease duration are at higher risk of severe hypoglycaemia (Fanelli *et al.*, 1994b). Amiel and colleagues reported that in people with tightly controlled T1DM by the means then available, the plasma glucose level at which epinephrine response was triggered was reduced (blood glucose: 2.6 mmol/L) (Amiel *et al.*, 1988). Conversely, the plasma glucose level required for epinephrine release was

found to be raised when glycaemic control was sub-optimal, demonstrating that thresholds for epinephrine secretion are dynamic.

In 1988 Amiel and colleagues (Amiel *et al.*, 1988) reported that in people with strictly controlled T1DM, treated with an intensive insulin regimen the threshold for epinephrine secretion was higher (blood glucose = 2.6 mmol/L) and that the epinephrine concentration was reduced at all glucose levels. In the same study the glucose threshold for epinephrine release were found to be lower when glycaemic control was poor. This confirmed that the absolute thresholds for epinephrine secretion are dynamic.

1.8.4 *Biochemical hypoglycaemia and hypoglycaemia associated autonomic failure (HAAF)*

Hyperinsulinaemic clamp studies in volunteers without diabetes, published in the early 1990s, established that short duration antecedent biochemical hypoglycaemia reduced both the counter-regulatory hormone and symptom response to subsequent hypoglycaemia (Davis and Shamoon, 1991; Heller and Cryer, 1991; Widom and Simonson, 1992). The same finding was reported in participants with type 1 diabetes (Dagogo-Jack *et al.*, 1993). Cryer hypothesised that iatrogenic biochemical hypoglycaemia was responsible for reduction in the counter-regulatory response to hypoglycaemia thus creating a vicious cycle, eventually leading to "hypoglycaemia associated autonomic failure" (HAAF) (Cryer, 1992b).

HAAF in T1DM is a concept that describes two clinical syndromes, the mechanisms of which are largely unknown. The first syndrome is that of defective glucose counter-regulation, as defined by a further reduced epinephrine response in the setting of an absent glucagon response (Bolli *et al.*, 1983). The second is impaired awareness of hypoglycaemia caused by reduced autonomic symptom responses associated with a reduced sympathetic neural response to lower glucose concentrations. When the threshold for these responses falls to around or below the threshold for cognitive impairment, neuroglycopenic symptoms can precede or impair recognition of autonomic symptoms leading to a severe event (Sussman *et al.*, 1963).

Impaired awareness of hypoglycaemia has been associated with a 6-fold increased risk of severe hypoglycaemia over a twelve month period (Geddes *et al.*, 2008). It is thus important that awareness of hypoglycaemia is regularly and formally assessed in those with type 1 diabetes. This includes ascertainment of glucose level at which symptoms are first experienced, whether earliest symptoms are autonomic or neuroglycopenic and whether these can be recognised as a harbinger of hypoglycaemia before others recognise this or help in treatment is required. Recognition of hypoglycaemia associated autonomic failure as a dynamic syndrome whereby 'hypoglycaemia begets hypoglycaemia' (Cryer, 1993) underlines how one episode of severe hypoglycaemia is an important risk factor for a further event with risk of being unable to detect hypoglycaemia being increased following a single episode of sustained biochemical hypoglycaemia (Dagogo-Jack *et al.*, 1993).

It has been postulated that the sympathetic neural response with subsequent increase in norepinephrine and acetylcholine secretion, as opposed to the adrenomedullary response with epinephrine secretion, is responsible for the majority of autonomic symptoms (Cryer, 2005). This is supported by evidence of maintained autonomic symptoms in patients who have had bilateral adrenalectomies (DeRosa and Cryer, 2004).

1.8.5 Neuroimaging correlates

Neuroimaging has been used to identify differences in brain responses (changes in cerebral blood flow) to hypoglycaemia between those who are symptom aware and those with impaired awareness of hypoglycaemia. The normal response to hypoglycaemia results in activation of brain areas important in the mediation of autonomic responses (thalamus) (Arbelaez *et al.*, 2008), stress (anterior cingulate, insula), food seeking (insula) and altered internal homeostasis, with a deactivation in areas involved with memory (hippocampus), vision (visual cortex) and reward or pleasure (lateral orbito-frontal cortex) (Teh *et al.*, 2010). This would suggest that hypoglycaemia is perceived as stressful and unpleasant. However, in individuals with impaired awareness of hypoglycaemia, there is less activation in the stress areas, with a failure of deactivation of the orbito-frontal cortex, consistent with a lack of internal motivation to avoid hypoglycaemia (Bingham *et al.*, 2005; Dunn *et al.*, 2007)

1.8.6   *The role of diabetic autonomic neuropathy*

Classical diabetic autonomic neuropathy (DAN) was traditionally thought to be an important factor underlying impaired awareness of hypoglycaemia but the evidence to support this is conflicting. Reported data are difficult to interpret due to confounding factors including duration of diabetes, age and glycaemic control and the lack of consensus regarding the diagnostic criteria for DAN. The reported prevalence of autonomic neuropathy in people with type 1 diabetes ranges widely, between 0 and 90%, depending upon the study, the population under investigation and the number and type of diagnostic tests performed (Vinik *et al.*, 2003).

As Cryer and others have highlighted, although one of the key associations of unawareness is loss of sympathoadrenal response (Heller and Cryer, 1991; Cryer, 1992a), impaired awareness of hypoglycaemia can be induced by just a few hours of mild hypoglycaemia and these changes are reversible, at least in part. Short-term functional changes are not consistent with classical DAN caused by slowly accruing and long-standing damage to the autonomic nervous system. Thus the term, hypoglycaemia associated autonomic failure (HAAF) (Cryer, 1992a), coined by Cryer to describe impaired physiological protection against hypoglycaemia following antecedent episodes, is distinct from any effect of classical autonomic neuropathy (Ryder *et al.*, 1990).

Nevertheless, there are data to suggest that DAN is associated with a modest increase in risk of severe hypoglycaemia. In a large epidemiological study comprising 3,248 people with type 1 diabetes, those with at least one episode of severe hypoglycaemia (1046 (32%)) within the preceding year were more likely to have impaired cardiac autonomic function (126 (13%)) (determined by measuring heart rate and blood pressure response to standing) than those without (157 (7.7%) p=0.002) (Stephenson *et al.*, 1996). Even after controlling for confounding factors, there was an association between history of severe hypoglycaemia and autonomic neuropathy. There is also evidence that DAN is associated with an impaired epinephrine response to experimental hypoglycaemia (Polinsky *et al.*, 1980; Hilsted *et al.*, 1981; Bolli *et al.*, 1983; Horie *et al.*, 1984; Meyer *et al.*, 1998).

However, people with T1DM but without autonomic neuropathy also have an attenuated epinephrine response to hypoglycaemia compared to people without diabetes. Studies involving glucose clamps in participants with T1DM with and without DAN, have reported reduced epinephrine responses with autonomic responses occurring at lower glucose concentrations compared to people without diabetes (Dagogo-Jack et al., 1993). These findings confirm those of a previous study, which reported no evidence of DAN in a cohort of people with type 1 diabetes and impaired awareness of hypoglycaemia; and no evidence of impaired glucose counter-regulation or impaired awareness of hypoglycaemia in patients with DAN (Ryder et al., 1990). A larger observational study (Hepburn et al., 1990), however, concluded that 'the precise relationship between diabetic autonomic neuropathy and loss of hypoglycaemia awareness remains undefined' after finding a positive association between impaired awareness of hypoglycaemia and DAN in the study population but not in the sub-group of people with type 1 diabetes duration greater than 15 years.

1.8.7 Psychosocial factors

The biomedical factors for hypoglycaemia discussed above help to explain the aetiology of many episodes of severe hypoglycaemia. However key studies have also reported significant rates of severe hypoglycaemia in patient groups with intact awareness of hypoglycaemia (Gold et al., 1994; Clarke et al., 1995a) and also in patient groups without many of the key risk factors (DCCT, 1991). A biopsychobehavioural model of risk of severe hypoglycaemia integrating psychosocial and behavioural factors in addition to biological processes has been described (Gonder-Frederick et al., 1997) to further elucidate severe hypoglycaemia risk. This model emphasises the need for skills based education as an intervention to reduce severe hypoglycaemia risk. With education focussed on avoiding high risk behaviour, optimising treatment decisions, modifying behaviour and helping to improve detection of hypoglycaemia it is suggested that overall risk of severe hypoglycaemia can be reduced (Cox et al., 2001; Hermanns et al., 2010).

A recent large study with 764 participants concluded that the frequency of severe hypoglycaemia is the most important factor in the development of fear of hypoglycaemia (Anderbro et al., 2010) which is widely accepted as

compromising overall glycaemic control and impairing quality of life. However there is very little research on fear of *hyper*glycaemia, which may be a driver of hypoglycaemia in some people with T1DM. Fear of hyperglycaemia is a psychological construct characterised by excessive worry about high blood glucose in combination with acceptance (and non-avoidance) of hypoglycaemia - as a 'necessary evil' to evade development of long-term complications, such as blindness. It may lead to inappropriate blood glucose lowering behaviours, including deliberate overtreatment or overzealous use of insulin, reluctance to attend to early symptoms of hypoglycaemia, and inappropriate pursuit of low blood glucose despite recurrent hypoglycaemia. Interviews with people with recurrent severe events suggest that fear of hyperglycaemia may be a highly relevant determinant of severe hypoglycaemia (Barendse *et al.*, 2012). The 'Hyperglycaemia Avoidance Scale' (Singh and al, 2010), assessing phobic concerns and behaviours related to hyperglycaemia, has been developed in the United States and has been adapted for use in the United Kingdom (Barendse *et al.*, 2011). While the scale shows promise for improving understanding of phobic behaviours there are as yet no published data on its use.

Recent qualitative research with participants who have impaired awareness of hypoglycaemia, has identified further attitudes which may prevent people from being motivated to regain awareness (Rogers *et al.*, 2012). These included normalising lack of awareness, underestimating its consequences, wanting to avoid the 'sick role' by not attending to their hypoglycaemia and, as described above, overestimating the consequences of hyperglycaemia. Another qualitative study by Speight et al (submitted) has identified that despite experiencing early symptoms of hypoglycaemia, individuals often delay intervention (with carbohydrate) due to being distracted, inaccurate assessment of risk, embarrassment, worry about rebound hyperglycaemia or unavailability of a preferred glucose source. In addition, use of an inappropriate slow-acting glucose (e.g. biscuit or chocolate) compromised prevention of severe hypoglycaemia.

1.9 The prevention of severe hypoglycaemia

1.9.1 Avoidance of biochemical hypoglycaemia

As outlined above it is now accepted that antecedent biochemical hypoglycaemia is the major factor in the development of impaired awareness of hypoglycaemia and, thus, increased risk of severe hypoglycaemia. A landmark study published in the New England Journal of Medicine in 1993 (Mitrakou *et al.*, 1993) reported the observation that in patients with insulinomas, recovery of counter regulatory hormone response and symptoms to hypoglycaemia was seen following surgical resection of the adenoma, demonstrating that in this patient group the loss of awareness was reversible.

The first study (Fanelli *et al.*, 1993) testing this hypothesis in a population with T1DM demonstrated that in a study population of 8 with short duration diabetes (mean 5 years) and short duration unawareness (mean 1.2 years) hypoglycaemia unawareness was reversible. In this study stepped hyperinsulinaemic hypoglycaemic clamps were undertaken two weeks and three months after careful hypoglycaemia avoidance. None of the patients in the study had classical diabetic autonomic neuropathy. At three months the threshold for epinephrine secretion normalised to the level of the non-diabetic control group although the magnitude of the response remained less. Interestingly at three months the glucagon response also improved although the threshold remained less with a lower magnitude. During the three months there was a significant reduction in the number of episodes of hypoglycaemia and there were no episodes of severe hypoglycaemia. There was also a significant increase in HbA1c from 40mmol/mol (5.8%) to 52mmol/mol (6.9%) suggesting that the prevention of hypoglycaemia was achieved at the cost of deterioration in overall glycaemic control.

The finding that awareness of hypoglycaemia could be reversed was also seen in a study with participants with longer term diabetes (duration range = 11 - 32 years) who all had history of impaired awareness (Cranston *et al.*, 1994). Two groups of participants were studied with a total study population of 12. One group had tight glycaemic control (HbA1c < 53mmol/mol (7.0%)); the other had variable control (mean HbA1c at baseline of 66mmol/mol (8.2%)). After a three week period in which all self monitored home blood glucose readings were

recorded as >3.5 mmol/L, significant reductions in the threshold for the onset of both autonomic and neuroglycopenic symptoms were seen in both patient groups. Significantly lower thresholds for epinephrine, norepinephrine and growth hormone secretion were also seen in both groups although unlike Fanelli's study (Fanelli *et al.*, 1993) no difference in the threshold to glucagon secretion was seen. There was also no deterioration in overall glycaemic control as assessed by HbA1c.

The concept that absolute biochemical hypoglycaemia avoidance can restore awareness has been confirmed in further studies. In a study with population n=21, improved counter regulatory and symptom responses were seen after three months of intensified insulin therapy during which meticulous prevention of hypoglycaemia was attempted (Fanelli *et al.*, 1994b). While Dagogo-Jack and colleagues (Dagogo-Jack *et al.*, 1994) did report improved symptomatic responses to hypoglycaemia after three months of strict hypoglycaemic avoidance, no significant reductions in the threshold for epinephrine or glucagon release were observed. The authors concluded that there were differences between mechanisms underlying hypoglycaemia awareness and defective glucose counter-regulation. These authors demonstrated that the improvement in symptomatic responses seen after only a short period of strict avoidance may be sustained with ongoing beneficial effect on hypoglycaemia episode frequency (Dagogo-Jack *et al.*, 1999).

1.9.2 Education and behaviour modification

A programme termed Blood Glucose Awareness Training (BGAT), which is described as a psychoeducational intervention to aid avoidance of both hypo- and hyperglycaemia has been developed. Evaluations of this programme have reported significantly improved detection of low blood glucose in people with impaired awareness of hypoglycaemia from baseline to 6 months (Cox *et al.*, 1995) and significantly reduced number of severe hypoglycaemia events from baseline to 6 months (Cox *et al.*, 2001). There is evidence that the mechanism for the improvement in awareness may be by reducing the attenuated epinephrine response to hypoglycaemia seen in people with intensively treated T1DM (Kinsley *et al.*, 1999). As of 2008 this training programme was made

available over the internet (Cox *et al.*, 2008), demonstrating how if successful education can be made easily accessible to large numbers of patients.

An RCT with 111 participants comparing a modified version of BGAT for use in a German speaking population with a standard education programme has also reported significant reductions of severe hypoglycaemia and significant improvement in awareness of hypoglycaemia (Schachinger *et al.*, 2005) in favour of BGAT.

An education programme termed HyPOS has been described in the literature and in contrast to BGAT focuses only on hypoglycaemia. An RCT comparing HyPOS (Hermanns *et al.*, 2007) to standard T1DM education with 164 participants all of whom had either confirmed impaired awareness of hypoglycaemia or history of at least one episode of severe hypoglycaemia within the preceding year was designed not to detect change in severe hypoglycaemia rate, but instead to detect change in awareness to hypoglycaemia. The study found significant improvements in awareness of hypoglycaemia as measured by the validated Clarke questionnaire (Clarke *et al.,* 1995) and a modified visual analogue scale of the Gold score (Gold *et al.,* 1994). No difference was seen in either severe hypoglycaemia rates or overall glycaemic control. The authors comment that in both groups there were improvements in awareness suggesting education per se is effective in improving awareness.

There is some evidence to suggest that an educational intervention whose content stresses only insulin, food, and exercise would be unlikely by itself to be sufficient to reduce the frequency of severe hypoglycaemia. In a study (Clarke *et al.*, 1999) with 93 participants, the preceding management behaviours with regards insulin, food and exercise before low blood glucose were predictive of hypoglycaemia, but were not different between those who did and did not have a history of severe hypoglycaemia.

The DAFNE (Dose Adjustment For Normal Eating) T1DM education programme which was derived from a training programme developed in Dusseldorf (Muhlhauser *et al.*, 1983), provides a holistic approach to improving glycaemic control. There is growing evidence suggesting that it reduces severe hypoglycaemia and improves hypoglycaemia awareness. In an audit of

participants attending courses in one year, 43% of those with impaired awareness at course entry (40% of the total) had restored awareness at one year (Hopkins *et al.*, 2012). In the same study there was also a significant reduction in severe hypoglycaemia rate from 1.7 ± 8.5 to 0.6 ± 3.7 episodes/person/year (p <0.001), within one year of undertaking the programme. In a similar audit in Australia, 28% of 145 DAFNE-trained participants reported a decrease in severe hypoglycaemia frequency at one year (McIntyre *et al.*, 2010). In the hub-and-spoke DAFNE study with 63 participants, there was a significant reduction in frequency of emergency call-out for severe hypoglycaemia in the year after undertaking the programme, though absolute numbers of events were small (Rogers *et al.*, 2009).

1.9.3 Pharmacology: basal insulin analogues

Hypoglycaemia has been studied inadequately for both of the commonly used long acting insulin analogues. Most of the large randomised control trials comparing long acting insulin analogues with neutral protamine Hagedorn (NPH) insulin have been treat to target studies (particularly in terms of lowest achievable fasting glucose) powered to detect changes in overall glycaemic control as measured by HbA1c and not hypoglycaemia frequency. In addition many of the key comparative studies have excluded participants with history of recurrent severe hypoglycaemia; and as a consequence have study populations with a mean age usually between 35 and 45 years old and a mean diabetes duration usually less than 20 years. The definition of hypoglycaemia in these studies is varied with a range from <4.0 mmol/l to 2.0 mmol/l.

1.9.4 Glargine

Glargine is a long acting insulin analogue, which is less soluble at physiological pH than human insulin. Because of this glargine precipitates in the subcutaneous tissue and therefore the rate of absorption is delayed and duration of action extended (Pieber *et al.*, 2000). There is evidence that glargine reduces the risk of nocturnal hypoglycaemia compared to NPH insulin when taken either with prandial unmodified human insulin (Pieber *et al.*, 2000; Ratner *et al.*, 2000) or rapid acting insulin analogues (Porcellati et al., 2004; Rossetti et al., 2003; (Fulcher *et al.*, 2005). A study comparing the combined

analogue regimen of glargine and lispro with NPH insulin and unmodified insulin (Ashwell *et al.*, 2006) reports a significant reduction in the monthly rate of nocturnal hypoglycaemia (0.66 ± 0.02 vs 1.18 ±0.02 episodes/month, p<0.001) in favour of the combined analogue group. The reduction in nocturnal hypoglycaemia in this group was also accompanied by a significant reduction in HbA1c and fasting plasma glucose (FPG).

1.9.5 Detemir

Insulin detemir is the second most commonly used genetically engineered long acting basal insulin. This insulin has an extended duration of action due to molecular features leading to increased albumin binding (Kurtzhals *et al.*, 1996). There is evidence that insulin detemir is also associated with reduced nocturnal hypoglycaemia (Vague *et al.*, 2003; De Leeuw *et al.*, 2005; Kolendorf *et al.*, 2006; Bartley *et al.*, 2008).

One study comparing detemir with NPH insulin was designed and powered to detect differences in hypoglycaemia (Kolendorf *et al.*, 2006). Patients with a history of recurrent severe hypoglycaemia and impaired awareness of hypoglycaemia were excluded from participation. No significant reduction was seen in severe hypoglycaemia, as total numbers were low and statistical analysis could not be done, however the number of episodes of severe hypoglycaemia was numerically lower in the detemir group. There was however a significant reduction in rate of total and nocturnal hypoglycaemic events per patient per year in favour of detemir (53.3 vs 64.7, p=0.001 and 6.0 vs 12.0, p<0.0001 respectively).

1.9.6 Glargine vs Detemir

One study comparing insulin detemir and insulin glargine has suggested a significant reduction in severe hypoglycaemia in favour of detemir (Pieber *et al.*, 2007). This study which also excluded those with history of recurrent severe hypoglycaemia and impaired awareness of hypoglycaemia, reported low absolute numbers of severe hypoglycaemia. In addition the fasting plasma glucose was significantly lower in the glargine group suggesting there may have been higher nocturnal glucose levels in the detemir group. The other head to

head comparison of glargine and detemir in the literature reports no difference in any hypoglycaemic event frequency (Heller *et al.*, 2009).

1.9.7 Rapid acting insulin analogues

Rapid acting insulin analogues were developed in order to better simulate the non-diabetic postprandial insulin response. This entailed the development of insulin that was both rapidly available in the circulation but which also had a duration of action short enough to minimise the risk of late post prandial hypoglycaemia. The genetically engineered insulin analogue lispro, which is exactly the same as human insulin except for the transposition of proline and lysine at positions 28 and 29 in the C-terminus of the B chain, was the first insulin to demonstrate a more physiological prandial insulin profile as compared to unmodified human insulin. After lispro administration peak insulin concentrations are both earlier and greater as compared to human insulin and concentrations return to baseline earlier than with unmodified human insulin (Torlone *et al.*, 1994).

The data from the subsequent clinical trials comparing lispro with human insulin suggest that the more physiological mode of action described is associated with reduced risk of hypoglycaemia. While there is good evidence that lispro significantly reduces the risk of nocturnal hypoglycaemia as compared to human insulin (Ahmed and Home, 1998; Heller *et al.*, 1999; Gale, 2000) the evidence does not appear to be as strong for reduced risk of severe hypoglycaemia. Holleman and colleagues reported a significantly lower incidence of severe hypoglycaemia with lispro than human insulin without deterioration in HbA1c during a 6 month cross over trial with 199 participants (Holleman *et al.*, 1997). An experimental study with 10 participants investigated whether lispro reduced the development of attenuated counter regulatory hormone responses to hypoglycaemia during intensive therapy as compared to human insulin (Heller *et al.*, 2002). The study which reported no difference in overall hypoglycaemia rates between groups, also found no difference in epinephrine or other counter regulatory hormone response.

A second commonly used rapid acting insulin analogue is insulin aspart, which has also been shown to have a more physiological profile than unmodified human insulin (Heinemann *et al.*, 1996). This genetically modified insulin differs

from human insulin in that the amino acid proline is substituted with an aspartic acid residue in order to reduce hexameric binding and thus improve absorption.

Overall evidence for a reduction in severe hypoglycaemia with aspart appears lacking. A multicentre randomised double-blind crossover study with 90 participants did demonstrate significantly reduced severe hypoglycaemia with aspart as compared to human insulin in addition to significantly improved postprandial glycaemic control (Home *et al.*, 1998). However larger randomised control trials comparing aspart with prandial human insulin (with basal NPH insulin) suggest no significant reduction with severe hypoglycaemia in favour of the insulin analogue (Home et al., 2000) (Tamas *et al.*, 2001)). Both of these studies demonstrate significantly improved overall glycaemic control with apsart without risk of increased severe hypoglycaemia or overall hypoglycaemia. Home and colleagues demonstrated a significant reduction in both nocturnal and late post-prandial hypoglycaemia in favour of aspart (Home *et al.,* 1998).

1.9.8 *Continuous subcutaneous insulin infusion (CSII) therapy*

CSII, commonly known as insulin pump therapy, has been recommended by several professional organisations (American Diabetes, 2004; NICE, 2008b). The National Institute for Health and Care Excellence states that insulin pump therapy can be considered if attempts to achieve target haemoglobin HbA1c levels with multiple daily injections (MDIs) result in the person experiencing disabling hypoglycaemia. For the purpose of the guidance, disabling hypoglycaemia is defined as the repeated and unpredictable occurrence of hypoglycaemia that results in persistent anxiety about recurrence and is associated with a significant adverse effect on quality of life.' (NICE, 2008b).

The majority of systematic reviews have failed to confirm a significant reduction in severe hypoglycaemia with CSII in RCTs, possibly due to a number of confounding factors such as short trial duration, insufficient study power and enrolment of subjects with low baseline rate of hypoglycaemia. A recent Cochrane review found no relevant benefit of CSII over multiple daily injections (MDI) for reducing non-severe hypoglycaemic events (17 studies) but data indicated a possible benefit of CSII over MDI in terms of reducing severe hypoglycaemia (15 studies) (Misso *et al.*, 2010). However, due to the use of

different methods for reporting both non-severe and severe hypoglycaemia, no meta-analysis was performed.

The majority of existing trials have not used both short- and long-acting insulin analogues in the MDI comparator group. Two small RCTs that compared optimised analogue MDI (with basal insulin glargine) regimens and CSII in participants with T1DM with (Thomas *et al.*, 2007) and without (Bolli *et al.*, 2004) previous recurrent severe hypoglycaemia showed no significant differences in frequency of hypoglycaemia between the two interventions. A short 10-week multicenter randomised, crossover study (Hirsch *et al.*, 2005) suggested a lower occurrence of nocturnal minor hypoglycaemic episodes in participants treated with CSII than those treated with MDI therapy including insulin glargine. However this study also suggested a higher rate of daytime minor hypoglycaemic episodes with CSII.

A more focused review that only included studies of at least six months duration where the rate of severe hypoglycaemia during MDI was >10 episodes/100 patient years of treatment suggested that CSII is significantly better than MDI in reducing the risk of severe hypoglycaemia (Pickup and Sutton, 2008). This review included both RCTs and before/after studies; 10 studies were in children or adolescents and 12 studies were in adults. The pooled severe hypoglycaemia event rate during MDI was 62 events per 100 patient years (95% CI 22 to 175). In RCTs, the random effect meta-analysis for severe hypoglycaemia rates showed that severe hypoglycaemia was markedly reduced during CSII compared with MDI, with a rate ratio of 2.89 (1.45 to 5.76). In before/after studies, the rate ratio for severe hypoglycaemia on MDI versus CSII was 4.34 (2.87 to 6.56) and overall rate ratio when all studies were included was 4.19 (2.86 to 6.13). The reduction was greatest in those with the highest initial severe hypoglycaemia rates on MDI (p <0.001). It is worth noting again that all studies in this review used insulin isophane or lente based MDI regimens rather than modern long-acting insulin analogues and few controlled for or used modern methods of teaching patients flexible insulin use in structured education programmes. In view of the advances in delivering MDI, there is a need for further studies comparing such modern methods with CSII.

1.9.9 Continuous glucose monitoring (CGM)

Modern blood glucose meters have extended memory capacity and computer download facilities. However despite these advances there remains inadequate testing in some people with type 1 diabetes, poor interpretation of the results by patients, and on occasion health care professionals, and the need for significant patient motivation. Furthermore this method of blood glucose monitoring omits the surveillance of blood glucose while sleeping, variations of which may significantly contribute to hypoglycaemia unawareness, as well as being a time of high risk of severe hypoglycaemia.

In recent years, advances in technology have allowed the development of real-time continuous glucose monitoring (CGM) devices that can be programmed in response to falling glucose, or when hypoglycaemia occurs or is predicted. These devices measure glucose in interstitial fluid, which lags behind blood glucose by 5-15 minutes (Rebrin and Steil, 2000). The sensitivity and specificity of these alarms is between 70 and 80% (Hoi-Hansen *et al.*, 2005), often resulting in false alarms and/or missed true hypoglycaemia.

There are a wide range of in-vivo glucose electrochemical biosensors, with variations in needle design, hardware and membrane coatings. The first application of an in-vivo glucose monitoring device was in 1982 (Shichiri *et al.*, 1982). Most sensors used commercially are based on the glucose oxidase catalyzed oxidation of glucose by oxygen. The design of the perfect sensor has many challenges. It needs to reliably monitor all glucose variations throughout the day with high speed. Further problems include the risk of immune rejection of the sensor by the body, difficulties with stability of the enzyme and transducer, the need for calibration and of course the over-riding need for it to be convenient and easy to use for the patient.

The subcutaneous siting of continuous glucose sensors can induce intense local inflammatory reactions associated with bacteria and macrophage adhesion with subsequent distortion of the glucose concentration next to the sensor. There has been considerable effort to develop sensors that have interfaces, which can resist this 'bio fouling'. Approaches have included a controlled release of nitric oxide, which inhibits platelet aggregation and bacteria

using polymeric coating to protect the outer layer of the sensor and use of the anticoagulant heparin.

Another major issue is the need for calibration (i.e. the requirement to transform the signal into an estimated glucose concentration) and maintain the calibration over the lifetime of the sensor.

Medtronic Minimed launched the 'sof-sensor' in 2008 and reported this glucose sensor to be as accurate in days 4 to 6 as in days 1 to 3 (data unavailable). The sensor measures the subcutaneous glucose concentration every 5 minutes, and then by using a transmitter relays the sensor information to an insulin pump, which provides the patient-data interface and alarms as required.

A number of studies have been performed investigating the added benefit of CGM in improving glycaemic control. The Juvenile Diabetes Research Foundation funded JDRF-CGM trial randomised 322 participants including children and adults with pre-study HbA1c 53 - 86 mmol/mol (7.0 - 10.0%) (Tamborlane *et al.*, 2008). Over 85% of participants used CSII and severe hypoglycaemia incidence in the preceding six months was low at 7.5% of participants. Although there was a clinically significant improvement in HbA1c of 5 mmol/mol (0.5%) in the adult group, there was no difference in biochemical hypoglycaemia measured using CGM between the control and intervention groups, and there was no difference in severe hypoglycaemia between groups. In the same study, a further 129 adults and children with HbA1c <53 mmol/mol (7.0%) were also studied (JDRF-CGM-study-group, 2009). 11% of these had a history of severe hypoglycaemia within the preceding six months. At 26 weeks, those with CGM had maintained their HbA1c at a mean of 46 mmol/mol (6.4%), with no severe hypoglycaemic events, while there was a significant increase in HbA1c in the control group. The study was designed and powered to detect change in time spent with a blood glucose ≤3.9 mmol/L as measured by CGM and although at the end of the study there was a reduction in favour of the real time CGM group, the difference was not found to be significant. The study did report a significant reduction in time spent with a blood glucose ≤3.3 mmol/L and time per day spent between 4.0 mmol/L and 10 mmol/L in favour of the real time CGM group.

The authors of the above studies also investigated whether there were any factors that could be predictive of use of and benefit from real-time CGM use (Beck *et al.*, 2009). The benefit referred to is HbA1c improvement rather than severe hypoglycaemia avoidance. Overall they found that previous history of severe hypoglycaemia was not a factor for either CGM use or benefit. Interestingly the study also found that baseline psychosocial measures such as fear of hypoglycaemia and perceived diabetes associated burden were also not predictive of CGM use.

Other studies have compared real-time CGM integrated with CSII (commonly known as sensor augmented pump therapy: SAP) with analogue MDI regimens. The STAR-3 study randomised 485 participants with T1DM and sub-optimal control (HbA1c 57 - 80 mmol/mol, 7.4 - 9.5%) on MDI to continued MDI or SAP (Bergenstal *et al.*, 2010). Although this study demonstrated a sustained reduction in HbA1c with SAP in all age groups, there was no difference in severe hypoglycaemia rate - although it is worth noting that incidence in both groups was lower than in the DCCT. Importantly this study excluded those with more than two episodes of severe hypoglycaemia over the previous year.

A smaller RCT with 83 participants compared SAP therapy with MDI in participants with suboptimal glycaemic control (baseline HbA1c 66 mmol/mol, 8.2%) (Hermanides *et al.*, 2011). This study reports a mean difference in reduction in HbA1c of 1.1% in favour of the SAP group with no significant difference in severe hypoglycaemia frequency or in blinded sensor mean area under the curve for hypoglycaemia (<4 mmol/L).

Only one study has compared outcomes between CSII and SAP in those with suboptimal glycaemic control on MDI (Raccah *et al.*, 2009). Although this study did show significant reduction in HbA1c (SAP: -0.96 vs CSII: -0.55, p<0.001) without any increase in hypoglycaemia, there was no evidence of reduced hypoglycaemia with SAP therapy.

Although studies of CGM have shown that with this technology, HbA1c can be reduced effectively without increasing hypoglycaemia, benefit in terms of reduced clinically significant hypoglycaemia has been difficult to demonstrate. A six-month prospective study comparing the outcomes of real-time CGM in patients using MDI and CSII showed a similar reduction in time spent with blood

glucose <3.0 mmol/L in both groups from baseline to endpoint (Garg *et al.*, 2011). However severe hypoglycaemia incidence was not reported. In a multi-centre randomised study with 120 adults and children with T1DM and a pre-study HbA1c <7.5% (58 mmol/mol), real-time CGM was associated with significantly reduced time spent with a blood glucose <3.5 mmol/L (Battelino *et al.*, 2011).

It is unfortunate that the study design and patient selection criteria of many of the major studies with CGM have prevented them from answering the question of whether or not CGM can reduce or prevent severe hypoglycaemia. In one of the first RCTs of CGM, there was in fact an increased number of severe events in the intervention arm (11 events vs 4 events). Seven occurred in the same individual, all when not wearing the device (Hirsch *et al.*, 2008).

One of the reasons for lack of severe hypoglycaemia reduction in these studies may also be the fact that people sleep through over 70% of the alarms (Buckingham *et al.*, 2005). However, in a recently published paper in a group of children with impaired awareness of hypoglycaemia, SAP therapy was shown to improve epinephrine response to hypoglycaemia during a stepped hypoglycaemia clamp (Ly *et al.*, 2011).

From the inadequately powered studies published to date there is no RCT evidence demonstrating that real-time CGM can prevent severe hypoglycaemia. This conflicts with data from studies assessing what patients and, in the case of children, carers perceive to be the benefits of this technology. Hypoglycaemia prevention and elimination of fear of hypoglycaemia have been reported to be the most common perceived benefits ahead even of improved glycaemic control (Cemeroglu *et al.*, 2010). The trials do suggest that the ability to lower HbA1c without increasing hypoglycaemia is enhanced by sensor use but reduction in severe hypoglycaemia remains an elusive goal.

1.9.10 Beta-cell replacement

While there have been advances in the pharmacological properties of modern insulins and in the development of technologies such as real-time CGM, complete replacement of normal beta-cell function remains the goal of many people with type 1 diabetes, researchers and clinicians. Only with beta-cell

therapy can the unique physiological homeostatic mechanisms of second-to-second glucose control be restored, entirely avoiding risk of severe hypoglycaemia.

Transplantation of whole pancreas together with its blood supply from a deceased donor offers the potential of a 'cure' for diabetes in terms of restoring normoglycaemia without the need for supplemental exogenous insulin in tandem with absolute avoidance of severe hypoglycaemia (White *et al.*, 2009). In addition to the need for life-long immunosuppression to prevent allo- and auto-immune rejection, pancreas transplantation requires major surgery with one-year mortality of 3-5% (Gruessner, 2011). It is thus largely performed together with a kidney transplant given the extremely high mortality of those with type 1 diabetes on dialysis, though it clearly has an additional role as a solitary transplant in those with truly life-threatening recurrent severe hypoglycaemia.

Allogeneic islet cell transplantation offers beta-cell replacement through minimally invasive percutaneous transplantation into the hepatic portal vein under radiological guidance. Under NICE (National Institute for Health and Care Excellence) guidance, this is available in the UK within the National Health Service for those with type 1 diabetes complicated by recurrent severe hypoglycaemia despite optimised insulin therapy, in addition to those already on immunosuppression following kidney transplant with on-going sub-optimal glycaemic control (NICE, 2008a).

Arguably the most important factor in the improvement of clinical outcomes post islet transplantation over the past decade has been the implementation of the Edmonton Protocol (Shapiro *et al.*, 2000). This treatment regimen uses a glucocorticoid free immunosuppressive regimen, which initially comprised sirolimus (a potent non-calcineurin inhibitor immunosuppressant), low-dose tacrolimus (a calcineurin inhibitor), and daclizumab (a monoclonal antibody against the interleukin-2 receptor) with transplantation of an adequate islet cell mass for at least short-term attainment of insulin independence (usually requiring more than one graft). The first published study using this protocol reported on the clinical outcomes in seven individuals with a mean duration of diabetes of 35 years who all had recurrent severe hypoglycaemia (Shapiro *et*

al., 2000). After a mean follow up period of 11.9 months following transplantation all recipients remained insulin independent with reported complete absence of severe hypoglycaemia.

A subsequent international multicentre trial using the Edmonton protocol was published in 2006 reporting clinical outcomes following islet cell transplantation in 36 participants (Shapiro *et al.*, 2006). Mean duration of diabetes was 25 years and 35 of the 36 participants had history of recurrent severe hypoglycaemia. At one-year post final transplant 72% of participants had at least partial graft function and no episodes of severe hypoglycaemia were reported within this group. Evidence of severe hypoglycaemia prevention in recipients of islet after kidney transplantation has also been published. One-year follow-up of seven recipients from the Miami centre reported 86% graft function and 30% insulin independence with no episodes of severe hypoglycaemia, even in those who were not insulin independent (Cure *et al.*, 2008).

In addition to the evidence of severe hypoglycaemia prevention post islet transplantation, there is also evidence that hypoglycaemia awareness is significantly improved. A retrospective cohort study reported a significantly reduced proportion of patients with impaired awareness of hypoglycaemia post-transplantation (Leitao *et al.*, 2008). Strikingly, this reduction was sustained even when results were stratified based on islet function meaning that in the groups in which function was lost or partially lost, there were significant reductions in the proportion of patients with reduced awareness.

1.10 Rationale for the studies

Severe hypoglycaemia is widely acknowledged as the major limiting factor for achieving optimised glycaemic control in established C-peptide negative type 1 diabetes, affecting nearly half of those with disease duration of >15 years every year (UK-hypoglycaemia-studygroup, 2007). It is therefore imperative that there are more randomised control trials investigating the use of conventional interventions in reversing IAH in populations with type 1 diabetes, and history of IAH and severe hypoglycaemia. This includes studies involving insulin analogues, continuous subcutaneous insulin infusion therapy and real time continuous glucose monitoring. Many previous studies involving these interventions have actively excluded those individuals at highest risk of severe hypoglycaemia. There is also a need for more research into what characteristics of people with type 1 diabetes and IAH may indicate a resistance to conventional interventions in improving awareness in order that consideration can be made to initiating alternative management plans such as psychological interventions or early beta cell replacement.

1.11 Aims and objectives of the studies

1. To establish and write the protocol for an adequately powered multi-centre peer reviewed principal investigator initiated 24-week randomised control trial (HypoCOMPaSS) comparing optimised multiple daily injections and continuous subcutaneous insulin infusion with or without adjunctive real time continuous glucose monitoring in individuals with type 1 diabetes and impaired awareness of hypoglycaemia.

2. To coordinate the multicentre study and conduct the Newcastle component. The aim of this study is to test the hypothesis that by avoiding biochemical hypoglycaemia using routinely available clinical interventions, awareness of hypoglycaemia can be improved thus reducing risk of severe hypoglycaemia requiring third party assistance.

3. Using the HypoCOMPaSS study population to undertake a study characterising the profiles of the participants with type 1 diabetes and impaired awareness of hypoglycaemia and whether these predict response and non-response to the trial interventions. The aim of the study is to test the hypothesis that there is a sub-group of patients who are resistant to conventional interventions in attempting to reverse hypoglycaemia unawareness.

Chapter 2

Methods

2.1 Objectives of the multicentre study

2.1.1 Primary objective

To demonstrate that by optimising conventional management, including the use of real-time continuous glucose monitoring (RT), in individuals with type 1 diabetes complicated by IAH, rigorous prevention of biochemical hypoglycaemia will restore awareness and reduce risk of recurrent severe hypoglycaemia.

2.1.2 Secondary objectives:

1. To quantify and compare biochemical hypoglycaemia identified by self-monitored blood glucose (SMBG) and blinded CGM profiles during each intervention.

2. To quantify and compare overall glycaemic control and glucose lability in each group by analysis of HbA1c, SMBG and blinded CGM.

1. To quantify and compare total daily doses of insulin before and after the intervention period.

2. To compare health utility and treatment satisfaction during each intervention using validated measures.

3. To perform secondary analyses of those who continue to experience IAH regardless of study intervention, to determine factors associated with absence of response. It was hypothesised that these would include two sub-groups: one in whom an absolute focus on avoidance of high glucose (evidenced from patient-reported outcome (PRO) measures) leads to continued biochemical hypoglycaemia despite the study goals; and a second with severe autonomic neuropathy (evidenced from clinical history) who are unable to recover autonomic warning symptoms of hypoglycaemia despite effective reduction in biochemical hypoglycaemia.

2.2 Preparatory work

The title of the multicentre study was confirmed as 'Prevention of recurrent hypoglycaemia: a definitive RCT comparing optimised MDI and CSII with or without adjunctive real-time continuous glucose monitoring'.

After I drafted the study design consultation began with other investigators about specific key aspects of the study. My role within the overall programme of research is outlined in Figure 2.1

The short title for the study was 'HypoCOMPaSS', an acronym for: Comparison of Optimised Multiple daily injections and Pumps with or without Sensors in Severe hypoglycaemia. I designed a graphic for branding purposes (Figure 2.2), which was used on all official study documents including the protocol and case report forms (CRFs).

Key aspects of the study's design were identified as needing preparatory work before commencement.

2.2.1 The assessment of IAH

Hypoglycaemic hyperinsulinaemic clamp studies are considered the gold standard experimental method of assessing awareness of hypoglycaemia. However including this as mandatory in the study protocol would potentially mean that many people who were not willing to be clamped, or who had cardiovascular disease or other medical comorbidities would be excluded from participation. It was therefore agreed that established and validated patient reported measures of hypoglycaemia awareness would be used as primary endpoint of the study (while also undertaking hypoglycaemic hyperinsulinaemic clamps on eligible participants using separate informed consent procedures). However, it was noted that the existing patient reported measures including the Gold (Gold *et al.*, 1994) and Clarke (Clarke *et al.*, 1995a) scores lacked ability to detect severity of the IAH and lack some sensitivity of change (Geddes *et al.*, 2007b). It was therefore agreed that a new questionnaire would be designed and optimised to measure for the detailed characterisation of problematical hypoglycaemia, including frequency, severity, impact and awareness of hypoglycaemia.

Figure 2.1   My role in the HypoCOMPaSS multicentre study

Chief Investigator
Professor JAM Shaw,

Trial Management Group
Trial manager
Data manager
Statistician
Senior academic advisor and
second MD supervisor

Newcastle
Dr S Little, coordinating
research fellow,

Trial Steering Committee
Independent Chair
Funder representative (Diabetes UK)
Sponsor representative (Newcastle upon Tyne
Hospitals NHS Foundation Trust)
Patient representatives
Principal Investigators (P.I)

- Design the study and formulate/circulate protocol to all sites/R&D departments
- Design all case report forms for study visits
- Obtain regulatory approvals including ethics and MHRA
- Undertake site initiation visits
- Undertake all study visits for Newcastle participants
- Chair monthly teleconferences with investigators
- Daily email contact investigators
- Coordinate the ordering and supply of study consumables including pumps, sensors, meter strips
- Publish study protocol and outcomes papers

Cambridge
P. Investigator
Research fellow

Sheffield
P. Investigator
Research fellow

Plymouth
P. Investigator
Research fellow

Bournemouth
P. Investigator
Research fellow

Figure 2.2   The HypoCOMPaSS study graphic
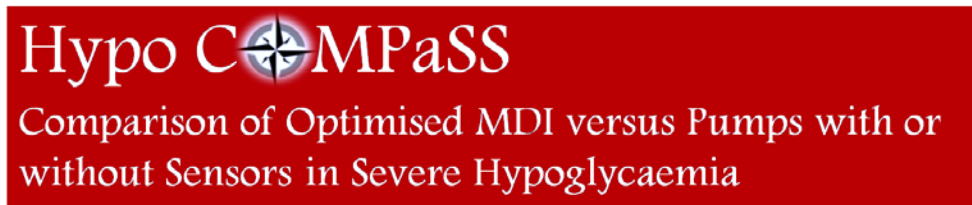
2.2.2 Insulin preparations

Given the lack of RCT evidence for the role of insulin analogues in the prevention of severe hypoglycaemia and the call from NICE for more studies (NICE, 2002), it was agreed that this study should use the long acting insulin analogue glargine and rapid acting insulin analogues.

2.2.3 Equality between intervention groups

A recognised major caution in interpreting previous studies in this field has been that some of the benefits of pump therapy may have risen from the increased attention of the investigator and the possibility that the CSII arm of the trials have included 'non-pump' elements such as carbohydrate counting and education that were not incorporated as vigorously in the MDI intervention groups (Pickup and Sutton, 2008). Therefore the design of the study was focussed around ensuring that the number and length of study visits, and the investigator, participant contact time and education outwith the subject of the insulin delivery advice was equal between intervention groups. Specific issues included:

1. The need to match the time spent providing education on the use of real-time continuous glucose monitoring in this intervention group, with the time spent providing education on SMBG in this intervention group.

2. The need to match the time spent providing education on the use of CSII with the time spent providing education on the use of an optimised MDI regimen.

3. The need to ensure that MDI participants were not disadvantaged by not having access to an easily accessible bolus calculator, which the CSII group would have. It was therefore agreed that all participants would be given an insulin pump (even those randomised to MDI) and all would be given self monitoring glucose meters, which wirelessly transmit data to the pump for bolus calculator use.

2.2.4 Standardised education between intervention groups and study sites

It was necessary for all investigators to give standardised advice on avoidance and treatment of hypoglycaemia. Based on the pilot study with influences from Blood Glucose Awareness Training (BGAT) (Cox *et al.*, 2001) a participant education programme would be required which was standardised as far as possible between sites.

2.2.5 Patient reported outcomes

We wanted to include patient reported outcomes to meet the following objectives:

1. To undertake a detailed baseline characterisation of hypoglycaemia to include psychological evaluation.

2. To compare health utility and well-being during each intervention using validated measures enabling comparison with other interventions.

3. To perform sub-group analyses of those who continue to experience severe hypoglycaemia and IAH despite successful avoidance of biochemical hypoglycaemia to evaluate associated risk factors.

Therefore considerable effort was taken to carefully select appropriate patient reported outcomes. This was undertaken by discussions with Dr Jane Speight, Chartered Health Psychologist and Director of AHP Research.

2.3 Protocol preparation

2.3.1 Early development stages of the new hypo-awareness questionnaire

Prior to undertaking this programme of research the established clinical methods for identifying IAH involved the use of self-report measures, the 'Gold score' (Gold *et al.*, 1994) and the 'Clarke questionnaire' (Clarke *et al.*, 1995b), separately or in combination (Geddes *et al.*, 2007a). The Gold score comprises a single question 'Do you know when your hypos are commencing?' with a 7-point response scale. Its advantages are its brevity and face validity (the extent to which it looks like it measures what is intended). However, it only enables identification of IAH and does not facilitate detailed characterisation.

Furthermore, its interpretation is problematic. While scores of '1' and '2' denote intact awareness and a score of ≥4 confirms IAH (Gold *et al.*, 1994), the clinical relevance and relative risks of scores from 3 through to 7 cannot be determined. It was evident that a single-item measure would be inadequate for characterising problematical hypoglycaemia and IAH, in our study populations. The Clarke questionnaire (Clarke *et al.*, 1995b) comprises eight questions characterising exposure to hypoglycaemia and glycaemic threshold for symptomatic responses. It is widely used and provides a detailed assessment but it has limitations: the severe hypoglycaemia definition is not that recommended by the ADA Hypoglycaemia Workgroup (ADA, 2005); there is a lack of consensus for the glycaemic thresholds used; the recall periods are inconsistent between questions and with the time periods used in most clinical trials; notably, events such as nocturnal hypoglycaemia are not captured. Thus, while both the Gold and the Clarke have good concordance in detecting IAH, they share a limited ability to characterise or evaluate severity of IAH and lack some sensitivity to change (Geddes *et al.*, 2007a).

Therefore prior to undertaking the studies described in this thesis there was an aim to design a novel, optimised measure for the detailed characterisation of problematical hypoglycaemia, including frequency, severity, impact and awareness of hypoglycaemia.

The limitations of existing IAH measures were discussed. The Clarke Questionnaire informed draft items, which were circulated for comment. An iterative approach was then used, involving several rounds of interviews with adults with type 1 diabetes, the results of which we discussed with other diabetologists and health psychologists. Between interview sets, which were undertaken by the health psychology team, questionnaire items were redrafted and circulated for comment. Further interviews took place until an optimised design was achieved and no further concerns were raised. In total, ten drafts of the HypoA-Q (hypoglycaemia awareness questionnaire) were needed.

Demographic and other clinical data were collected by self-report with HbA$_{1c}$ retrieved from medical records. National Research Ethics Committee approval was in place with site-specific approval at each centre. All participants were registered with one of two UK specialist diabetes centres (Newcastle and Manchester). Eligible participants were adults with type 1 diabetes who had experienced problematical hypoglycaemia, including previous severe hypoglycaemia and current IAH.

Each interview was conducted in distinct stages: exploratory; draft questionnaire completion; and questionnaire cognitive debriefing. Exploratory interviews took 54 ± 9 minutes. Following a brief break, participants completed the draft HypoA-Q unaided, and then took part in a cognitive debriefing ('think aloud') interview to determine the questionnaire's relevance, comprehensibility and ease-of-use (Willis, 2005).

Exploratory interviews were transcribed in full and subjected to a thematic analysis. Following each set of interviews, the health psychology team examined the detailed notes and completed questionnaires for relevant issues before discussing with me and Professor James Shaw, highlighting items needing improvement and agreeing suggestions for circulation to the wider specialist group. Further questionnaire revision was based on group consensus and checked with subsequent interviewees until questionnaire design was optimised.

The newly designed questionnaire was named the Hypoglycaemia Awareness Questionnaire (HypoA-Q). A subsequent psychometric validation study was then planned to take place in Edinburgh in collaboration with Professor Brian

Frier. A full manuscript regarding the development of this questionnaire has recently been submitted to *Diabetic Medicine* (August 2014). The HypoA-Q questionnaire is included as Appendix 1.

2.3.2 Development of a brief standardised education programme

Following experience in the pilot study (Thomas *et al.*, 2007) and informed by insights from the qualitative study (described above) a brief education programme (with formal curriculum and workbook, referred to as 'my hypo compass), was developed (Little *et al.*, 2012a). This was to ensure standardised education regarding hypoglycaemia avoidance was provided to all participants across the five study sites.

The curriculum was driven by findings from semi-structured interviews with people with T1DM and history of severe hypoglycaemia and learnings from the Blood Glucose Awareness Training (BGAT) programme (Cox *et al.*, 1995). Content was refined through an iterative design process, including: 1) repeated reviews by health psychologists, diabetes specialist clinicians and nurse educators, and 2) debriefing by patient experts.

The aim of the education programme was to facilitate discussions and exercises targeted specifically at rigorous avoidance of biochemical hypoglycaemia while maintaining overall glycaemic control, based around four key elements forming the four points of the 'my hypo compass' (Figure 2.3) establishing the imperatives:

1. To never delay the treatment of hypoglycaemia and the optimal treatments for hypoglycaemia. (North)

2. To establish the individual's unique times of increased risk (East)

3. To recognise hypoglycaemia by the presence of subtle symptoms (South)

4. To be particularly careful (wary) about detecting and preventing nocturnal hypoglycaemia. (West)

Also included was advice on self-adjustment of insulin doses according to carbohydrate intake, SMBG and planned activity and recommendation for

oral carbohydrate administration for all glucose levels less than 4 mmol/l. The participant and facilitator handbooks for this education programme, which I led the design of, are included as Appendices 2 and 3 respectively.

Figure 2.3   'my hypo compass'

2.3.3 Trial management group

A Trial Management Group (TMG) was established with the following members:

1. Professor James Shaw (Chief Investigator)

2. Dr Stuart Little (co-ordinating researcher)

3. Dr Julia Stickland and Ms Cath Brennand (trial managers from Newcastle Clinical Trials Unit)

4. Dr Thomas Chadwick (statistician)

5. Professor Sally Marshall (Professor of Diabetes and advisor to the TMG, second MD supervisor)

6. Mrs Ruth Wood (data manager from Newcastle Clinical Trials Unit)

The study protocol was written with clinical trial management expertise input from the Clinical Trials Unit at Newcastle University. The protocol was signed by the Chief Investigator, Professor James Shaw; Principal Investigators at each study site; and the Sponsor's representative, Dr Lesley Hall on behalf of Newcastle upon Tyne Hospitals NHS Foundation Trust.

Permissions were obtained where necessary, for the use of established and validated patient reported outcome questionnaires proposed for use in the studies.

Patient Information Sheets and informed consent forms were designed and written with the assistance of the Clinical Trials Unit at Newcastle University.

Paper case report forms were designed for each study visit. These were then transcribed into Power Trial's Symphony web software system, which was used for data collection and management. This system provided electronic case report forms (eCRFs) that allowed remote data entry, source document verification, query resolution and audit trail of all entries, compliant with Good Clinical Practice (GCP) regulations. Data was then held on a secure server and automated failover and backup was provided. Only authorised users with appropriate access and permissions were able to enter, view and edit data.

The protocol for the study was prepared for publication in the journal *BMC Endocrine Disorders* (Little *et al.*, 2012b).

2.3.4 Study initiation visits

Initiation visits were undertaken to all participating study sites where the goals were: to orientate and train staff on the protocol and study related processes; to confirm readiness for study implementation; and to identify additional requirements that needed satisfied prior to site activation and participant recruitment. Full day visits to clinical research facilities at each of the five participating centres were undertaken in partnership with the trial manager from Newcastle Clinical Trials Unit.

2.4 Obtaining regulatory approvals

2.4.1 Ethical approval

I obtained ethical approval for the study after submission of the appropriate IRAS (integrated research application system) application forms and attendance at the local ethics committee meeting in Sunderland, UK.

2.4.2 Governance approvals and clinical trial registrations

Although using established medications under existing licenses the study needed the approval of the Medicines and Healthcare products Regulatory Agency (MHRA) which I obtained through IRAS application. Site-specific approvals were granted from all participating Acute NHS Trusts' Research and Development Departments. As this programme of research involved the collection of personal (though not identifiable) data outside of the acute trusts and onto University I.T. systems, Caldicott approvals were also obtained. The study was adopted by the National Institute of Health Research, a UK Government body that provides logistical support to clinical trials undertaken within the NHS. The study was issued with an International Standard Randomised Controlled Trial Number (ISRCTN) following registration on the clinical trials database (ISRCTN: 52164803). The study was also issued with a EudraCT number following registration on the European Union Drug Regulating Authorities Clinical Trials database (EudraCT: 2009-015396-27).

2.5   Ethical considerations

Potential participants were identified from existing clinics and research databases held at each centre. Only participants who fulfilled the inclusion and exclusion criteria of the study were invited to take part.

Potential participants were provided with written information, along with opportunity for questions and had a minimum of 24 hours to decide whether or not to take part. All the potential participants were fully informed of the intensive requirements of this study. These included the need for rigorous self blood glucose monitoring, the probabilities of being randomised to different treatment arms, including the use of real-time continuous glucose monitoring and continuous subcutaneous insulin infusion therapy; and the requirement for monthly blinded continuous glucose monitoring. The original signed consent form was retained in the investigator site file, with a copy kept in the clinical notes and a copy provided to the participant. The participants were specifically consented to their GP being informed of their participation in the study.

The right to refuse to participate without giving reasons was respected. Informed written consent was taken by a member of the research team at each site adhering to guidelines of Good Clinical Practice (Commission, 2001).

All the participants were provided with a 24-hour contact detail for the investigator at their site, to use were they have any problems related to the study.

No payments were provided to participants for taking part in this study. However, participants did receive expenses for travel costs incurred while attending study visits.

Study files were kept in a locked room in the Clinical Research Facility of each respective study site.   Participant confidentiality was maintained by ensuring that only participant initials and study number were mentioned in study documents.

The studies were performed in accordance with the principles of the Declaration of Helsinki (Association, 2008) and Good Clinical Practice (Commission, 2001)

2.6   Study population

2.6.1   Study centres

This was a multicentre programme of research and was conducted at the following hospitals, all of which are tertiary referral and established academic hypoglycaemia centres:

1.   Royal Victoria Infirmary, Newcastle upon Tyne

2.   Royal Bournemouth Hospital

3.   Derriford Hospital, Plymouth

4.   Addenbrooke's Hospital, Cambridge

5.   Northern General Hospital, Sheffield

2.6.2   Identification and recruitment

The target population was 100 participants with each of the five sites having a target of recruiting 20 participants. Participants identified as being potentially eligible were approached to give their written informed consent before undertaking a screening visit at which time inclusion criteria were checked. Potential participants were identified at all study sites except in Newcastle, where identification was undertaken at the Newcastle Diabetes Centre, Newcastle General Hospital (after approval as a participant identification centre).

2.6.3   Inclusion criteria

Participants recruited for this programme of research had to meet the following criteria for participation in the studies:

1.   Male or female aged 18-74 years inclusive at start of the trial.

2.   Diagnosis of diabetes mellitus according to ADA ('Diagnosis and classification of diabetes mellitus,' 2011) and WHO (WHO, 2006) criteria and consistent with a clinical diagnosis of type 1 diabetes mellitus.

3. Fasting serum C-peptide below the quality assured limit of detection for the assay and laboratory at each study site with simultaneous exclusion of biochemical hypoglycaemia (glucose <4.0 mmol/L) by laboratory glucose level analysis on a sample taken at the same time point.

4. History of severe hypoglycaemia in the preceding one year ((as defined by the American Diabetes Association (ADA, 2005)) (Table 1.3)) and / or impaired awareness of hypoglycaemia as confirmed by a score of ≥ 4 in the Gold score (Gold *et al.*, 1994).

2.6.4 Exclusion criteria

Potential participants presenting with any of the following were not considered for inclusion in the studies:

1. Any condition that in the investigator's judgement is likely to cause the participant to be unable to understand the information in the informed consent document or to provide informed consent.

2. Insufficient proficiency in English, below that to enable the participant to understand both verbal and written information during the study. This was due to the complexity of the education programme, the need for independent completion of the questionnaire measures, and the degree of communication required between participants and clinicians during the study.

3. Unwilling to undertake intensive insulin therapy, including randomisation to use of CSII, optimised MDI regimen or real-time CGM.

4. Unwilling to undertake glucose profiles using the subcutaneous continuous glucose monitoring (CGM) equipment.

5. Unwilling to undertake SMBG at least 4 times daily.

6. Unwilling to monitor and record signs and symptoms of hypoglycaemia.

7. A history of intolerance to insulin glargine.

2.7 Assessment of hypoglycaemia awareness

To ensure eligibility criteria were met all potential participants underwent assessment of hypoglycaemia awareness using the Gold (Gold *et al.*, 1994) and Clarke scores (Clarke *et al.*, 1995a) (described in 2.2.1). These measures were used at screening to ensure eligibility, baseline study visit and at study endpoint. The hypoA-Q was used in conjunction with the Gold and Clarke scores at baseline and endpoint.

2.8 Blinded / health care professional continuous glucose monitoring

All participants had a period of professional continuous glucose monitoring during the last week of the wash in period and for 1 week between study visits. The iPro professional continuous glucose monitoring system (CGMS) is a product from Medtronic Minimed. It involves continuous monitoring of interstitial glucose for a period of up to 7 days with the participant unaware of the result until such time the data are transferred to a data management system and analysed.

The first such device, ready for use in the clinical setting was the Minimed CGMS Physician-Use Glucose Monitoring System which was approved in America by the Food and Drug Administration in 1999 (Mastrototaro, 1999). In 2003, the CGMS Gold was introduced by Medtronic Minimed. This device captured data in a recorder that was attached to a sensor in the patient's subcutaneous tissue by a cable, which was then downloaded. The iPro device does not use a cable. Instead the recorder is attached directly to the sensor and secured to the patient's skin.

2.8.1 Professional CGM hardware and data download

The iPro CGMS device from Medtronic has three components:

1. The iPro recorder; a small rechargeable and waterproof device that stores the data;

2. The glucose sensor;

3. The iPro charger which can recharge the recorder in 20 minutes.

The glucose sensor used in the study (Sof sensor, Medtronic) consists of two semipermeable membranes that surround an impregnated glucose-oxidase enzyme containing material. When glucose and oxygen pass through the semipermeable membrane and react with the glucose oxidase enzyme in the presence of glucose, hydrogen peroxide is produced with two hydrogen ions, producing an electronic signal.

After each use of the iPro recorder data were then downloaded using Medtronic's Solutions software without unblinding either the participant or the investigator.

2.9 Self monitoring of blood glucose

In this programme of research all participants were asked to complete detailed paper self-monitored blood glucose diaries. Specifically participants were asked to complete daily 4 point profiles and weekly 8 point profiles, which included blood glucose concentrations before and two hours after the main meals of the day, before going to bed and at 4 am. The diaries also asked for clinical details of all glucose levels less than 4 mmol/L and symptomatic hypoglycaemic events.

All participants were given the Contour link ®, Bayer Healthcare meter and asked to use this meter only for the duration of the studies. Instructions on the use of the meter were provided at the screening visit. The study teams at each study site provided blood glucose testing strips for the meters. The blood glucose meters were calibrated at each 4-weekly follow up visit using Bayer's Contour ® control solutions.

2.10 Insulin preparations used in the study

2.10.1 Regulatory requirements

In accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and Directive 2001/20/EC the insulin preparations used in the study fell under the definition of 'investigational medicinal product' (IMP). Although the insulins used during this trial fell under the definition of IMPs they were used only under existing licence agreements.

A label was designed for all the study IMPs in accordance with regulatory guidelines and all local legal requirements. Each study centre maintained a drug disposition log in which they recorded information regarding the administration of study drug and return of unused vials.

2.10.2 Basal insulin used in MDI arm of study

All participants randomised to the Multiple Daily Insulin Injection (MDI) regimen used insulin glargine (Lantus ®) as basal insulin. This insulin is a recombinant human insulin analogue that is a long acting parenteral blood glucose-lowering agent. Glargine is a clear, colourless aqueous solution for subcutaneous injection. Insulin glargine was provided via the Solostar ® prefilled disposable device, which allows dose dialling in one-unit step increments between one unit and a maximum of 80 units. Participants were given boxes of 5 x 3mL Solostar® pens each containing glargine (100 units per millilitre).

2.10.3 Rapid acting insulins used in MDI arm of study

For the participants randomised to MDI, insulin aspart was the rapid acting insulin analogue of choice. However for those patients who had a history of a previous negative experience or adverse effect with insulin aspart the alternative of insulin lispro was offered.

Insulin aspart (*Novorapid ®*) is a recombinant human insulin analogue that is a rapid acting parenteral blood glucose-lowering agent. Aspart is a clear, colourless aqueous solution for subcutaneous injection. Each millilitre of aspart injection contains 100 Units of insulin aspart. Insulin aspart (Novorapid®) was provided via the *Novorapid Flexpen ®* which is a pre-filled disposable insulin delivery device. This device allows dose dialling in one-unit step increments between one unit and a maximum of 60 units. Participants were given boxes of 5 x 3mL Novorapid Flexpens® each containing aspart (100 units per millilitre).

For those participants who had a previous negative experience or adverse effect with insulin aspart the alternative of insulin lispro (Humalog ®) was offered. Insulin lispro is a recombinant human insulin analogue that is a rapid acting parenteral blood glucose-lowering agent. Lispro is a clear, colourless aqueous solution for subcutaneous injection. Lispro was provided in the

Humalog Kwikpen® which is a pre-filled disposable insulin delivery device for use of insulin lispro. This device allows dose dialling in one-unit step increments between one unit and a maximum of 60 units. Participants were given boxes of 5 x 3mL Humalog Kwikpens® each containing lispro (100 units per millilitre).

2.10.4 Insulin used in the CSII arm of the study

For participants randomised to CSII, insulin aspart (*Novorapid*®) was the insulin of choice. It was provided in 10 ml vials (100 Units/mL).

Insulin lispro (Humalog®) was used instead of insulin aspart in the CSII group for those participants who had previous negative experience / adverse effect with aspart. Insulin lispro for use in the CSII group was provided in 10ml vials (100 Units/mL).

2.11 Continuous subcutaneous insulin infusion device

The Paradigm Veo® insulin pump (Medtronic Minimed) was used in the study. Two different sizes of pumps (Paradigm 554 and 754) were available. The difference between the two insulin pumps is the size of reservoir each can hold. The 754 insulin pump can accommodate either a 3 ml reservoir or a 1.76 ml reservoir, which holds 176 units of insulin. The 554 insulin pump can accommodate just the 1.76 ml reservoir.

The Paradigm Veo® pump has a built in bolus calculator termed the bolus wizard®. This uses the inputted personal settings on insulin: carbohydrate ratio (ICR), insulin sensitivity factor (ISF), blood glucose readings, carbohydrate intake and active insulin duration to suggest a bolus amount.

Two different infusion sets were available to participants depending on body habitus and personal preference:

1. Quick-set infusion set; this is inserted at 90 degrees to the skin using a spring loaded insertion device.

2. Silhouette infusion set; this is inserted at 45 degrees to the skin usually by hand.

2.12 Real-time continuous glucose monitoring device

The first system integrating CSII with CGM was launched in 2006 by Medtronic Minimed and was called the Paradigm Real-time system. For this study an updated version was used: the Paradigm Veo System (Medtronic Minimed) using the Veo insulin pump and with an updated calibration algorithm for real-time continuous glucose monitoring.

When this study was initiated there were other real time continuous glucose monitoring systems available, though no others were integrated with an insulin pump. All available real time glucose monitoring systems approved for use at the time of study initiation are listed below.

1. GlucoDay (A Menarini Diagnostics, Italy)

2. Free style Navigator Continuous Glucose Monitor (Abbott, USA)

3. Seven System (Dexcom, USA)

4. Short term system STS (Dexcom, USA)

5. Guardian Real-Time System (Medtronic Minimed, USA)

6. Paradigm Veo System (Medtronic Minimed, USA)

All of these systems use the implantable needle type electrode described in 1.10.8 except the Glucoday system which uses microdialysis sampling. This systems use a hollow dialysis fibre, which is implanted in the subcutaneous tissue and perfused with isotonic fluid. The glucose which diffuses from the tissue into the fibre is then pumped towards the enzyme electrode.

2.12.1 Accuracy of the Paradigm Veo system (Medtronic Minimed)

The numerical accuracy of all continuous glucose monitoring systems including real-time CGM can be defined as the closeness between CGM readings and corresponding in-time reference blood glucose measurements. Several different measures have been used to assess this accuracy including the mean absolute difference (MAD), mean absolute relative difference (MARD), median absolute difference (MedAD), median absolute relative difference (MedARD) and ISO (International Standards Organisation) criteria. The ISO criteria refer

specifically to the percentage of CGM readings within 0.8 mmol/l from the blood glucose when <4.2 mmol/L or within 20% from reference when blood glucose is >4.2 mmol/L. Table 2.1 describes the clinical accuracy of three of the most widely available real-time CGM systems.

The numerical accuracy of different CGM devices has been investigated with regards hypoglycaemia detection (Kovatchev *et al.*, 2008). This has suggested that the Navigator as compared to the Guardian and Dexcom systems performs best (ISO: % readings within 0.8 mmol/l from reference when reference <4.2 mmol/l; guardian, 76.5%; Dexcom, 52.9%; Navigator, 79.4%).

The Paradigm Veo system (Medtronic Minimed) uses a new sensor calibration system as compared to the previous Paradigm Real time (PRT) system. In a retrospective analysis of the data from the STAR-1 study, in which sensor augmented pump therapy was compared to CSII and conventional monitoring, the Paradigm Veo calibration system has been compared to the PRT system (Keenan *et al.*, 2010). This study has shown that as compared to the PRT, when blood glucose is 2.2 - 4.4 mmol/L the number of CGM glucose measurements with the Veo calibration algorithm within 20% of the blood glucose reading is 81% as compared to 73% with PRT. The MARD for the Veo algorithm for blood glucose levels 2.2 - 4.4 mmol/L was 19.5 ± 23.8 as compared to 24.8 ± 27.6 with the PRT. The sensitivity for hypoglycaemic events as defined as a single blood glucose measurement <3.9mmol/L was 82.3% with the Veo and 54.9% with the PRT.

Figure 2.4   Example of CSII with integrated real-time continuous glucose monitoring (sensor augmented pump therapy (SAP))
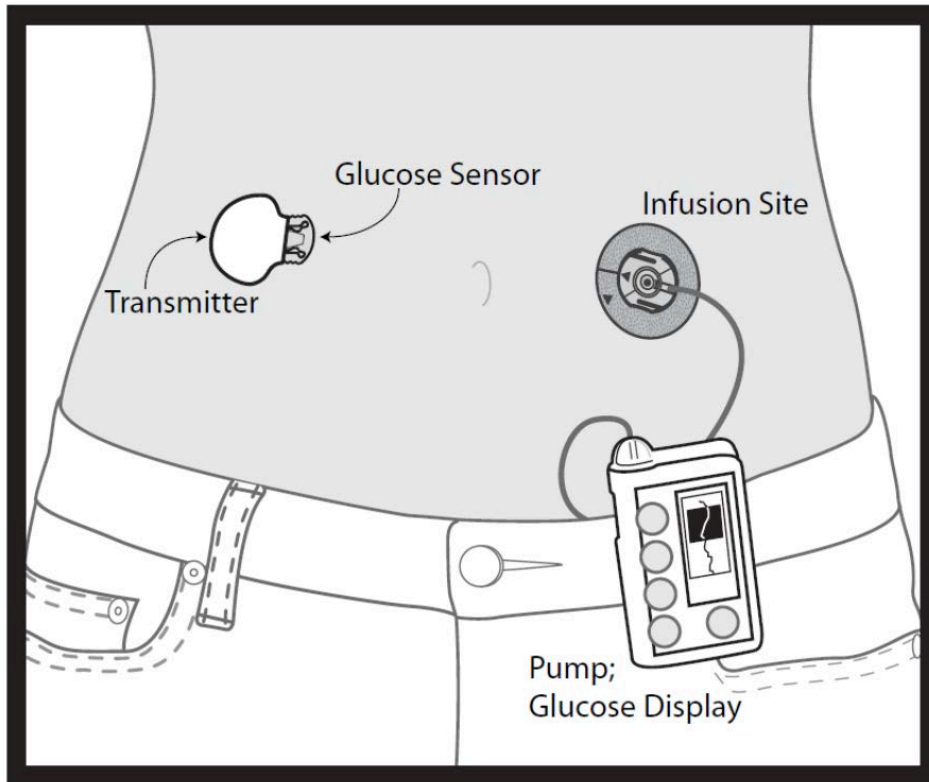
Table 2.1   Sensitivity of Paradigm Veo calibration compared to Paradigm Guardian calibration algorithm for detecting hypoglycaemic events as defined as a single blood glucose <3.9mmol/L (Kovatchev et al., 2008)

	Paradigm Guardian	Paradigm Veo
Number of blood glucose readings <3.9mmol/L	5841	
Sensitivity	54.9	82.3
Specificity	98.1	96.4
False positive rate	1.6	2.9

Table 2.2 Numerical point accuracy of three real time CGM devices (Keenan *et al.*, 2010)

	Guardian	Dexcom	Navigator
Point accuracy: euglycaemia (blood glucose = 3.9-10.0mmol/L)			
MAD*	0.91	1.24	0.89
MARD^	15.2	21.2	15.3
MedARD (mmol/L)**	13.3	18.4	11.8
ISO: % readings within 0.8mmol/L from reference when reference ≤4.2mmol/l	76.5	52.9	79.4

*MAD = mean absolute difference, ^MARD = mean absolute relative difference, **MedARD = median absolute relative difference

2.13 Patient reported outcomes

2.13.1 Diabetes treatment satisfaction questionnaire (DTSQ)

Brief and used previously to evaluate potential benefits of insulin glargine, the diabetes treatment satisfaction questionnaire (DTSQ) is a widely used and sensitive measure of satisfaction with diabetes treatment (Bradley, 1994). This questionnaire has been used in many trials with proven responsiveness to various treatment regimens (DAFNE Study Group, 2002; Ashwell *et al.*, 2008). The DTSQ (Appendix 12) is an eight item questionnaire with the Items of particular relevance to this programme of research being perceived frequency of hypoglycaemia as well as flexibility and convenience of the treatment. Each of the eight items is scored on a scale of 0-6.

Two versions of the questionnaire are available, the DTSQ status (DTSQs) and the DTSQ change (DTSQc).

2.13.2 Hypoglycaemia fear survey II

Fear of hypoglycaemia is an important issue for many people with recurrent severe hypoglycaemia and can be responsible for severely limiting quality of life. The hypoglycaemia fear survey II (Appendix 14) provides the only known measure of this phenomenon and was first developed alongside blood glucose awareness training (BGAT) in the United States (Cox *et al.*, 1987).

2.13.3 Hyperglycaemia avoidance scale

Fear of *hyperglycaemia* may be an important determinant of behaviours that lead to recurrent severe hypoglycaemia. The hyperglycaemia avoidance scale (HAS) was developed in the United States (Singh and al, 2010) and adapted for use in the United Kingdom for use in this study (Barendse *et al.*, 2011). This questionnaire has four subscales:

I.   Worry subscale: items 10, 13, 14, 15, 16, 18, 19, 20, 21, 23, 24.
II. Immediate action scale: items 1, 2, 4, 5.
III. Low blood glucose preference scale: items 3, 6, 11, 12, 17.
IV. Avoid extremes scale: items 7, 8, 9, 22.

2.14 Assessment of global autonomic dysfunction

The autonomic symptom profile is a patient reported outcome questionnaire from which the composite autonomic symptom scale (COMPASS) with item-weighting was established (with higher scores indicating more or worse symptoms). COMPASS explores a wide range of autonomic domains, providing an overall score and sub scores for eleven subscales: orthostatic intolerance, secretomotor dysfunction, male sexual dysfunction, bladder dysfunction, diarrhoea, constipation, pupillomotor symptoms, vasomotor symptoms, reflex syncope, upper GI symptoms and sleep dysfunction. This questionnaire has been validated against the composite autonomic scoring scale (CASS) in a population with peripheral neuropathy and neurogenic autonomic failure including people with diabetes (Suarez *et al.*, 1999). CASS is derived from the autonomic reflex screen which includes orthostatic blood pressure and heart rate responses to tilt; heart rate response to deep breathing; the Valsalva ratio; and beat-to-beat blood pressure measurements during the Valsalva manoeuvre, tilt, and deep breathing.

There are a total of 169 questions in this questionnaire, which has a complex scoring system. It yields one total score reflecting overall severity and eleven weighted subscale scores.

1. Orthostatic intolerance subscale: items 18, 20, 19, 25, 22, 37, 38, 39, 40.

2. Vasomotor symptoms subscale: items 54, 59, 60, 61,62, 55, 56, 57, 58, 63, 64.

3. Secretomotor symptoms subscale: items 66, 67, 68, 69, 70, 71, 72, 73, 74, 75.

4. Autonomic diarrhoea symptom subscale: items 87, 88, 89, 93.

5. Constipation symptom subscale: items 94, 95, 96, 97.

6. Male sexual dysfunction subscale: items 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 114, 115, 116, 122, 123.

7. Bladder dysfunction subscale: items 108, 109, 110.

8. Pupillomotor symptoms subscale: items 124, 125, 132, 126, 127, 134, 135.

9. Sleep disorder symptoms subscale: items: 136, 137, 138, 139, 140, 141, 142, 144.

10. Syncope symptoms subscale: items 42, 43, 44, 45, 46.

11. Upper GI symptoms subscale: items 80, 81, 82, 83, 84.

12. Under scoring items: 143, 167, 104, 105, 106, 107.

13. Over scoring items 166, 49, 51, 52, 102, 103.

2.15 Cardiac autonomic function assessment

At baseline and at study endpoint all participants also underwent cardiac autonomic function testing including:

1. Baroreceptor sensitivity

2. Spectral analysis of heart rate variability at rest

3. Spectral analysis of heart rate variability with paced breathing

4. Heart rate variability during deep breathing

5. Heart rate variability during the Valsalva manoeuvre

Fellow investigators in Sheffield prepared the standard operating procedure for this. Results of this are not presented within this thesis, as analysis of this data will be undertaken by my colleagues in Sheffield.

2.16 Stepped hypoglycaemic hyperinsulinaemic clamp studies

I established the standard operating procedure (SOP) for undertaking the hypoglycaemic hyperinsulinaemic clamp studies. These were undertaken as part of a sub-study with a requirement of separate informed written consent from eligible participants. The SOP included assessment of counter-regulatory hormone and symptom response to experimental hypoglycaemia and was included as part of the published study protocol. The SOP I prepared is included as Appendix 6. Results from the clamp studies are not presented

within this thesis as analysis of the data was undertaken by fellow investigators at Cambridge University.

2.17 Study visit schedule

A detailed account of the study visits is given in the published study protocol. A summary is provided below. Appendix 11 shows the timeline of study visits.

2.17.1 Screening visit (start of 4-week wash in period)

Participants attended for a screening visit to ensure that all study inclusion criteria were met and ensure that the nature and purpose of the research had been fully understood. At this visit it was ensured that the participant had had all their questions about the trial adequately answered. The following were performed at the screening visit:

1. The hypoglycaemia screening questionnaire comprising of the Clarke and Edinburgh hypoglycaemia scores and was completed or results reviewed if previously completed (Appendices 4 and 5 respectively).

2. Written informed consent was obtained if not done so previously.

3. Participants were issued with their unique trial number for the studies.

4. Venepuncture was undertaken during the screening visit and blood samples from each site were sent to their own respective laboratories for c-peptide, glucose and $HbA_{1c.}$

5. Patients were provided with a hand-held glucometer (Contour Link®) and educated in the use of prospective Self Monitoring Blood Glucose (SMBG) / hypoglycaemia diaries to measure daily 4 point profiles and weekly 8 point profiles in addition to clinical details of all glucose levels less than 4 mmol/L and symptomatic hypoglycaemic events during a 4-week wash in period.

2.17.2 Visit 2: CGM sensor placement

Participants attended for placement of subcutaneous sensor for 7-day blinded continuous glucose monitoring (CGM).

2.17.3 Visits 3: baseline (wash-in week 4, end of 28 day wash-in period)

The participant attended after 7 days blinded CGM and completion of the 4-week glucose / hypoglycaemia diary

A full clinical history and examination together with detailed history of severe hypoglycaemia number and consequences over the preceding twelve months was taken. Modified Clarke and Edinburgh questionnaire was repeated when completing study questionnaire pack of patient reported outcomes

The 4-week glucose / hypoglycaemia paper diary was transcribed into the eCRF.

The validated patient-reported outcome questionnaires (Gold and Clarke) in addition to the new instrument designed to be sensitive to change related to study interventions (HypoA-Q) were completed

Blood was taken for HbA1c, U&Es, liver function tests and lipid profile.

2.17.4 Visit 4: autonomic symptom profiling

Participants completed the autonomic symptom profile (ASP) questionnaire and underwent cardiac autonomic function tests.

2.17.5 Visit 5: autoimmune disease screening

Participants attended for a short synacthen test. This test was performed to screen for adrenocortical insufficiency. 2ml of blood was taken to measure basal cortisol (0 mins). This was followed by intravenous 250µg (in 1 ml) tetracosactide (synacthen). 2mls of blood was then taken at 30 mins and 60 mins for cortical analysis. At this visit a sample was also taken for serum TSH (Thyroid Stimulating Hormone) measurement to exclude thyroid disease and for anti-endomysial antibody analysis to exclude coeliac disease. New diagnoses of other autoimmune diseases did not preclude participation in the study. If indicated participants with newly diagnosed autoimmune disease were referred to an appropriate specialist for further investigation and management. All samples were analysed in local hospital laboratories.

2.17.6   Visit 6: education session

The results of the SMBG (self monitoring blood glucose) diary and baseline CGM profile were discussed with all participants forming the basis for the uniform structured re-education programme undertaken at each site (my hypo compass).

2.17.7 Randomisation

Participants were allocated by third party concealed randomisation by centre and baseline HbA1c (with stratification cut-off of 64 mmol/mol (8%) to 24 weeks CSII using insulin aspart (or insulin lispro if previous intolerance / negative experience with insulin aspart) or MDI using glargine and insulin aspart (or insulin lispro if previous intolerance / negative experience with insulin aspart). 50% of each of these two groups were randomised to the use of real-time continuous glucose monitoring. Therefore there were four intervention groups with 25 participants in each group as detailed below.

Intervention group 1:   CSII with RT
Intervention group 2:   CSII without RT
Intervention group 3:   MDI with RT
Intervention group 4:   MDI without RT

2.17.8   Visit 7: RCT commencement

All patients had an educational session solely on the technical aspects of the insulin administration equipment they were to use during the intervention period. The session for participants randomised to CSII was restricted to technical aspects of insulin pump management. The external pump, consumables and insulin were provided. The session for participants randomised to MDI was restricted to insulin device (pen) use and injection site care.

Each participant was provided with his or her appropriate titration regimen. (Appendices 8, 9 and 10).

The primary goal of titration throughout for all participants was the absolute avoidance of glucose levels <3 mmol/L as determined by CGM and SMBG.

This was achieved by setting '4 as the floor' with all glucose levels <4mmol/L treated by 15g glucose with repeat SMBG every 15 minutes until glucose >4mmol/L in addition to consideration of insulin dose reduction.

Where attainable without hypoglycaemia, SMBG before breakfast and 4am targets were 5 - 7 mmol/L with other pre-prandial targets 4.5 - 7 mmol/L and post-prandial targets 6 - 8 mmol/L (Appendix 7).

During the intervention period all participants were telephoned daily for the first week post randomisation for support in starting their new regimen, to review SMBG values and offer guidance in initial insulin dose adjustment. Thereafter participants were telephoned weekly for the remainder of the randomised control trial period. Participants had contact numbers for study personnel to contact between telephone calls/visits if further advice was needed.

On this day, study insulin was provided using study specific prescriptions with commencement of 24-week RCT of new intervention and 4-week glucose-monitoring / hypoglycaemia diary.   All participants were telephoned daily over the following 6 days for support in starting their new regimen, to review SMBG values and offer guidance in initial insulin dose adjustment.

2.17.9   Visit 8: review/blood glucose monitoring

At this visit, one week after RCT commencement, in addition to reviewing progress over the first week, using glucose data to achieve the primary goal of avoiding biochemical hypoglycaemia was discussed together with reinforcement of the other educational tenets of the study.

All participants randomised to real-time continuous glucose monitoring (RT) were given an educational session on the technical aspects of using the real-time monitors including trend analysis and the use of the hypoglycaemia and hyperglycaemia alarms. They were encouraged to wear the sensor continuously (re-siting every 7 days) but flexibly with a minimum of 7 days continuous monitoring in the last week of each month.   Participants not randomised to RT had an educational session on self-blood glucose monitoring.

At this visit arrangements for all participants to upload their anonymised data onto a central server (Carelink, Medtronic) was discussed to facilitate optimised

self-management (with the research team also having access to the data to support self management). Participants did not need to consent to this in order to participate in the study.

2.17.10 Telephone Contact

Participants were contacted by telephone weekly after visit 8 throughout the RCT to reinforce the primary goal of biochemical hypoglycaemia avoidance, provide clinical review / support, and ensure diary completion.

2.17.11 Study follow up

Participants attended for a study visit every four weeks during the RCT for collection of SMBG/hypoglycaemia diary and HbA1c. One week prior to each visit participants had a blinded CGM sensor fitted and these data were downloaded at the visit. Participants had their weight measured at each follow up visit and this, along with details of insulin dosage, was recorded on visit specific CRFs. Both investigator and participant remained blinded to the results of the blinded CGM data during the RCT period. Clinical review at each follow up visit reinforced the primary goal of biochemical hypoglycaemia avoidance. At each follow up visit information was collected on any episodes of hypoglycaemia experienced, duration of RT usage and RT alarm settings.

2.17.12 End of RCT visit

At week 24, participants attended for the primary RCT completion visit. This included blinded CGMS data download, collection of SMBG/hypoglycaemia diary, and HbA1c. Participants were also asked to complete the 'end of RCT' study-specific questionnaire booklets assessing hypoglycaemia experience and other PROs (Section 2.13).

On the same day, eligible participants were invited to attend for 'end of RCT' stepped hyperinsulinaemic hypoglycaemic clamp.

At the end of this intervention period, participants were asked to attend for repeat detailed cardiac autonomic function testing and to complete the autonomic symptom profile questionnaire.

2.18 Statistical analysis

The principal analysis examined the factorial structure of the treatment and monitoring regimen effects on the difference in IAH (Gold score) at 24 weeks using analysis of covariance (ANCOVA). Baseline IAH (Gold score) and stratification (centre and baseline HbA1c) variables were included among the covariates considered in addition to suitable summaries of questionnaire scores and glucose monitoring data collected at baseline prior to randomisation. The glucose monitoring data collected included time spent for the following separate ranges: <2.5 mmol/l, <3 mmol/l, <4 mmol/l, >7 mmol/l, >10 mmol/l, between 4 and 7 mmol/l and between 3 and 10 mmol/l. The inclusion of baseline HbA1c as a covariate enabled the examination of possible interactions between effects observed and these values.

Further analyses were undertaken concerning IAH to corroborate the Gold score; the Gold score was compared with scale and subscale scores derived from the Clarke questionnaire and the hypoglycaemia awareness questionnaire (HypoA-Q) at 24 weeks.

These measures were also subject to analysis as for the primary outcome. Additionally, a binary indicator of IAH response (defined as a Gold Score of <4 or ≥4) at 24 weeks) was analysed using logistic regression making use of the covariates used for the primary outcome analysis.

There was also an additional analysis of the (paired) change in IAH (Gold score) over the 24-week duration of the trial using the t-test without consideration of the intervention or monitoring groups in order to evaluate the effect of undergoing any intervention or monitoring over the 24-week period.

Outcomes were assessed at baseline and 24 weeks. Analysis methods were generally similar to that described for the primary analysis but alternative techniques such as McNemar's test and logistic regression were used as appropriate.

Further analyses were undertaken using HbA1c and the separate continuous glucose monitoring measures (time spent in the following separate ranges: <2.5 mmol/l, <3 mmol/l, <4 mmol/l, >7 mmol/l, >10 mmol/l, between 4 and 7 mmol/l and between 3 and 10 mmol/l) as outcome variables.

Similar analyses were undertaken on scores from all PRO measure scores.

A number of measures relating to severe hypoglycaemia (ADA criteria) were analysed: number of episodes of severe hypoglycaemia at 24 weeks, change in severe hypoglycaemia between baseline and 24 weeks (reported as difference in annualised rate pre and post-intervention), change in severe hypoglycaemia between baseline and 24 weeks (reported as the proportion of participants with reduction in number of severe hypoglycaemia events compared between the timepoints) and change in proportion without severe hypoglycaemia between baseline and 24 weeks.

Changes in weight, total daily dose of insulin, and in glucose lability were subject to analysis in a similar manner to the primary outcome.

Wherever possible participants who elected to withdraw from the study were followed up so that final outcome data were obtained, enabling their inclusion in an Intention to Treat (ITT) analyses. This formed the analysis groups for the analyses described above.

Analyses restricted to those participants who were allocated to use RT were undertaken, in order to allow use of the further covariate of low or high RT use (defined by consideration of a pre-defined cut-off value) throughout the 24-week period. Variables analysed in this manner included IAH (Gold score), episodes of severe hypoglycaemia, HbA1c and several of the glucose monitoring measures.

Significance levels were set at $\alpha = 0.05$ throughout.

Chapter 3

A multicentre 2x2 factorial randomised control trial comparing insulin pump with multiple daily injections, and continuous with conventional glucose self-monitoring

3.1 Introduction

Within months of the introduction of insulin therapy for type 1 diabetes (T1DM) in 1922, the potential for dangerous low glucose reactions was reported (Fletcher and Campbell, 1922). Over ninety years later, severe hypoglycaemia requiring the assistance of another person for recovery, remains the most feared complication of insulin therapy (Pramming *et al.*, 1991). Prevalence increases with diabetes duration, annually affecting nearly half of those with type 1 diabetes for more than 15 years (UK-hypoglycaemia-studygroup, 2007).

The landmark DCCT trial provided the incontrovertible evidence that intensive treatment of type 1 diabetes with either MDI or CSII reduces microvascular complications. The intensive therapy was, however, associated with increased risk of severe hypoglycaemia. Hypoglycaemia precludes the maintenance of euglycaemia and the subsequent associated vascular benefits. Furthermore, hypoglycaemia compromises physiological defences against further hypoglycaemia, further increasing the risk.

Single-centre studies in participants with T1DM and severe hypoglycaemia have shown that rigorous biochemical hypoglycaemia avoidance can restore awareness (Cranston *et al.*, 1994; Fanelli *et al.*, 1994b). A 24-week pilot study for this programme of research, comparing education alone with analogue MDI and CSII, demonstrated prevention of recurrent severe hypoglycaemia in >70% with all interventions, together with better overall glycaemic control in MDI and CSII groups than with education alone (Thomas *et al.*, 2007).

A meta-analysis comparing CSII with MDI has however countered the argument that intensive treatment with CSII is always associated with increased risk of severe hypoglycaemia (Pickup and Sutton, 2008). Pickup's study showed that with CSII, as compared to MDI, there was a mean 2.9 fold reduction in severe hypoglycaemia in the randomised control trials included. This was only based on studies using MDI regimens consisting of isophane and lente insulins. A Cochrane review comparing MDI and CSII therapy has concluded that there was no proven additional benefit with CSII (Misso *et al.*, 2010). Both of these reviews have highlighted the need for studies comparing CSII with MDI regimens based on short and long acting analogue insulins.

The use of real time continuous glucose monitoring in people with type 1 diabetes and IAH may be of benefit by alerting them to looming hypoglycaemia and provide them with an alternative awareness mechanism to replace the loss of the normal physiological mechanism. However, although with this technology a lower HbA1c has been seen, it has not been associated with a reduction in severe hypoglycaemia (Tamborlane *et al.*, 2008; Bergenstal *et al.*, 2010).

Large-scale intervention trials in T1DM generally focus on attainment of optimal HbA$_{1c}$ using a 'treat-to-target' approach (Little *et al.*, 2011). Despite the desire to show that new treatments carry less hypoglycaemia risk, trials have not been powered robustly to evaluate impact on significant hypoglycaemia, often excluding those with IAH or severe hypoglycaemia.

Informed by this, the aim of this study was to undertake the first ever multi-centre RCT in participants with established C-peptide negative T1DM complicated by IAH designed to determine robustly whether awareness can be restored and recurrent severe hypoglycaemia prevented through rigorous prevention of biochemical hypoglycaemia without worsening overall glycaemic control. CSII was compared with optimised analogue MDI; and adjuvant RT with conventional glucose self-monitoring.

3.2 Aims

The primary objective of this study was to investigate whether optimised MDI as compared to CSII with or without real-time CGM improves awareness of hypoglycaemia as measured by the validated Gold score in a high risk population.

The secondary objectives were:

1. To compare the rate of severe hypoglycaemia achieved by the interventions.

2. To compare the frequency of biochemical hypoglycaemia identified by blinded CGM during each intervention.

3. To compare the overall glycaemic control as assessed by HbA1c by each intervention.

4. To compare total daily insulin doses between each intervention.

5. To compare treatment satisfaction with each intervention.

6. To compare awareness of hypoglycaemia using a new novel measure (the HypoA-Q) before and after the intervention.

7. To compare the change in IAH (Gold score) and other markers of glycaemic control over the 24-week duration of the trial without consideration of the intervention or monitoring groups.

3.3 Study design

This was a 2 x 2 factorial, multi-centre, randomised control trial carried out at five UK tertiary referral centres, all routinely offering structured T1DM education with expertise in hypoglycaemia assessment / management and use of CSII / RT (Addenbrookes Hospital, Cambridge; Bournemouth Royal Hospital; Royal Victoria Infirmary, Newcastle upon Tyne; Derriford Hospital, Plymouth; Northern General Hospital, Sheffield). Eligible participants were aged 18-74 years with C-peptide negative T1DM and IAH confirmed by Gold score ≥4 (Gold *et al.*, 1994). After a four-week wash-in period during which a period of blinded CGM

was undertaken, a baseline study visit took place. At this visit a full clinical history and detailed history of severe hypoglycaemia was undertaken and self reported outcome measures were completed. Hypoglycaemia awareness was re-evaluated at baseline using validated Gold (Gold *et al.*, 1994) and Clarke (Clarke *et al.*, 1995a) questionnaires. To improve sensitivity to change over a short period, the hypoglycaemia awareness questionnaire (HypoA-Q) was utilised. Screening was undertaken for undiagnosed thyroid, Addison's and coeliac disease.

Prior to randomisation, all participants attended brief standardised education with formal curriculum and workbook, referred to as 'my hypo compass' (Little *et al.*, 2012a).

Following randomisation, number of study visits was the same for all participants, tailored for each group to technical aspects of their insulin administration and glucose monitoring intervention. All participants, whether randomised to aspart insulin delivery by CSII (Medtronic Paradigm Veo insulin pump) or MDI (aspart / glargine) were given an insulin pump enabling benefit from direct transmission of SMBG levels to bolus calculator. Those randomised to RT (REAL time continuous glucose monitor, Medtronic) were trained on sensor insertion, calibration and use of monitor including trend analysis and hypo- / hyper-glycaemia alarms.   Participants were able to individualise alarm settings but did not use the low-glucose-suspend feature. Continuous RT use was encouraged but not mandatory.

Participants were asked to record all episodes of severe hypoglycaemia prospectively and were recalled four weekly up to 24 weeks. They were given identical written guidance on insulin titration primarily targeted towards absolute avoidance of biochemical hypoglycaemia (Appendix 7). Glargine was administered before bed with addition of a second dose before breakfast in those with consistent glucose >7.0 mmol/L before evening meal or highly variable glucose levels between breakfast and evening meal. Each study visit was preceded by 7-day CGM profile, with participant and investigator blinded to data until study completion.   Between study visits, all participants were telephoned weekly to encourage use of insulin titration guidelines, with

maintained focus on hypoglycaemia avoidance. An outline of the study timetable can be seen in Appendix 11.

3.4 Randomisation

Using Newcastle University Clinical Trials Unit's web based system, participants were randomly allocated on an equal allocation basis, stratified by baseline HbA$_{1c}$ (<64 and ≥ 64 mmol/mol, 8.0%) and by centre, to one of four groups: MDI with SMBG; MDI with SMBG and RT; CSII with SMBG; CSII with SMBG and RT.

3.5 Statistical analysis

Informed by the pilot study, (Thomas *et al.*, 2007) recruitment of 100 participants was planned to give 80% power at a significance level of 0.05 to detect a difference of 1.1 between the 24-week Gold score of the 50 participants randomised to either of the groups allocated CSII and the 50 randomised to either of the groups allocated MDI. Results were analysed using SPSS version 21.0 for Windows (SPSS, IBM, New York, USA). A general linear model (ANCOVA) was used with baseline IAH (Gold score) and stratification variables (centre and baseline HbA1c) included among the covariates. A p-value <0.05 was considered to be significant for all analyses.

3.6 Results

110 individuals with IAH (defined as Gold score ≥4) were recruited. Figure 3.1 shows the trial profile. Prior to randomisation: 93 (97%) were using MDI regimens (pre-prandial insulin: aspart/ lispro 90 (94%), human soluble 3 (3%), porcine soluble 3 (3%); basal insulin: glargine 45 (50%); detemir 36 (40%), human isophane 6 (7%); porcine isophane 3 (3%)). Three (3%) were using insulin aspart / lispro as part of a CSII regimen.

Ninety-six participants were randomised, all with long-standing (mean duration 29 years) C-peptide negative (<50 pmol/l in all except two: 87; 103 pmol/l) T1DM. Baseline demographic and clinical characteristics were similar in all intervention groups and are seen in Table 3.1.

Baseline HbA1c was <64mmol/mol (8.0%) in just under half of the study population at 43%, with the mean HbA1c of the population being 66 ± 12 mmol/mol (8.2%). The majority of the study population was female (74%). The mean pre-study total daily dose of insulin was 0.64 units/kg.

In the overall study population the baseline annualised severe hypoglycaemia rate over the preceding six months was high at 8.9 episodes per patient-year. 77% of participants were affected over the preceding 6 months and 92% over the preceding 12 months (Table 3.4).

Figure 3.1   Trial profile
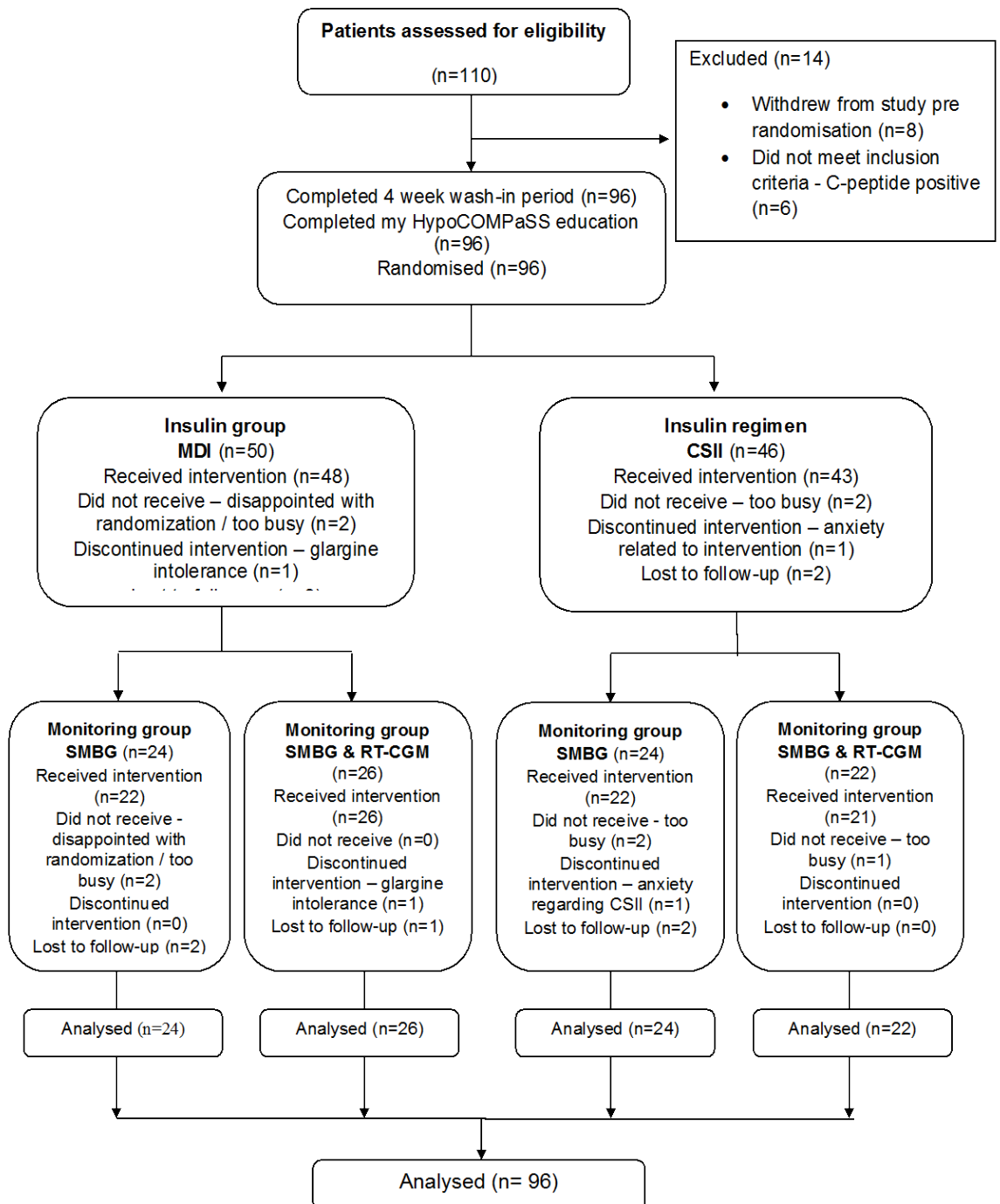
Table 3.1   Baseline characteristics of the study population

		Insulin comparison		Monitoring comparison	
	All	**MDI**	**CSII**	**SMBG**	**RT**
†Site -					
Bournemouth	16 (17%)	8 (16%)	8 (17%)	7 (15%)	9 (19%)
Cambridge	21 (22%)	11 (22%)	10 (22%)	11 (23%)	10 (21%)
Newcastle	22 (23%)	12 (24%)	10 (22%)	11 (23%)	11 (23%)
Plymouth	17 (18%)	10 (20%)	7 (15%)	9 (19%)	8 (17%)
Sheffield	20 (21%)	9 (18%)	11 (24%)	10 (21%)	10 (21%)
†Baseline HbA$_{1c}$					
<64 mmol/mol	41 (43%)	22 (44%)	19 (41%)	21 (44%)	20 (42%)
⩾64 mmol/mol	55 (57%)	28 (56%)	27 (59%)	27 (56%)	28 (58%)
*HbA$_{1c}$ (mmol/mol)	66±12	66±13	66±12	67±13	66±11
Age (years)	48.6 ±12.2	47.0 ±12.3	50.3 ±12.0	47.1 ±11.8	50.1 ±12.6
Male	35 (36%)	16 (32%)	19 (41%)	20 (42%)	15 (31%)
*Diabetes duration (years)	28.9 ±12.3	29.5 ±12.5	28.2 ±12.2	26.7 ±12.1	31.0 ±12.2
*Body weight (kg)	74.7 ±14.2	74.9 ±13.9	74.5± 14.6	74.5 ±14.6	75.0 ±13.9
*BMI (kg/m^2)	26.5 ±4.4	26.7 ±4.6	26.3 ±4.4	26.1 ±4.3	26.9 ±4.7
*Insulin dose (units/kg/24 hr)	0.64 ±0.23	0.63± 0.21	0.66 ±0.26	0.61 ±0.19	0.68 ±0.27

Data are number of patients (%) or mean±SD. †Stratification variable.
*Excludes participants with data missing for indicated variable (number missing: (HbA1c, one; duration of diabetes, one; body weight, one; BMI, one; insulin dose, two).

3.6.1 Results for the study cohort

In the overall study population, biochemical hypoglycaemia assessed by blinded CGM was significantly reduced according to all pre-specified criteria (table 3.2). The percentage of time spent ≤3.0mmol/L equates to a reduction by more than half from 53 minutes per 24 hours at baseline to 24 minutes at endpoint. This was achieved rapidly over the first four weeks and maintained throughout the study as illustrated in Figure 3.2.

This reduction in biochemical hypoglycaemia was accomplished in tandem with a sustained 8-unit reduction in mean total daily insulin dose with mean total daily dose falling from 0.64 to 0.53 units/kg (Figure 3.7). Other aspects of glycaemic control were assessed by HbA$_{1c}$, 8 point SMBG mean and CGM mean glucose (Table 3.3). There was improvement in glucose variability determined by CGM standard deviation (Tables 3.2). HbA$_{1c}$ remained within target (<64 mmol/mol (8.0%)) in those with a value below this cut-off at baseline; with a non-significant 3 mmol/mol (0.3%) improvement in HbA$_{1c}$ in those with baseline HbA$_{1c}$ ≥64 mmol/mol (Figure 3.3).

Across the study population awareness of hypoglycaemia improved, with significant reductions in Gold, Clarke and HypoA-Q IAH subscale scores (table 3.4). Gold score (primary study outcome measure) was significantly reduced at 24 weeks as compared to baseline (Figure 3.4). Clarke and HypoA-Q scores showed strong correlations (r=0.53 - 0.74) with Gold score at baseline and study endpoint. Annualised severe hypoglycaemia rate fell more than 10-fold, with 20% of participants experiencing severe events during the RCT in comparison to 77% over the preceding 6 months (Figure 3.5).

Fear of hypoglycaemia (Figure 3.8) and treatment satisfaction (Figure 3.9) improved significantly across the study population from baseline to endpoint (Table 3.5).

Table 3.2   Biochemical parameters of CGM in study population

	Trial Period							
	Baseline	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (endpoint)**	**P value***
CGM analysis	(n=84)	(n=84)	(n=80)	(n=76)	(n=85)	(n=80)	(n=83)	(n=82)
Biochemical hypoglycaemia (% time spent below threshold)								
≤2.5 mmol/l	2.1 ±3.2	1.1 ±2.2	1.0 ±1.7	1.1 ±2.8	1.1 ±1.8	1.1 ±1.9	0.77 ±2.2	0.01
≤3.0 mmol/l	3.7 ±4.4	2.1 ±3.7	2.0 ±2.7	1.8 ±3.7	2.1 ±3.1	2.3 ±3.6	1.7 ±3.9	<0.01
<4.0 mmol/l	8.5 ±7.1	5.4 ±6.3	5.6 ±5.1	5.5 ±5.9	5.7 ±5.8	7.0 ±7.8	5.7 ±7.1	0.01
Glucose mean (mmol/l)	9.4 ±2.0	9.3 ±1.7	9.1 ±1.3	9.3 ±1.7	9.2 ±1.8	9.1 ±1.7	9.4 ±1.9	0.81
Glucose SD (mmol/l)	3.9 ±1.0	3.4 ±0.9	3.4 ±0.8	3.4 ±0.9	3.3 ±0.8	3.4 ±0.9	3.4 ±0.8	<0.01
% time 4.0-6.9 mmol/l	25.9 ±13.2	25.9 ±14.0	27.1 ±11.4	25.9 ±11.8	26.2 ±13.6	28.4 ±13.9	25.3 ±13.9	0.37
% time 4.0-9.9 mmol/l	52.1 ±16.4	56.8 ±17.7	58.6 ±13.6	57.2 ±16.7	56.9 ±18.2	56.7 ±17.9	54.6 ±18.5	0.62
% time 3.1-9.9 mmol/l	57.1 ±17.9	60.2 ±18.4	62.2 ±14.6	60.8 ±18.0	60.4 ±19.7	61.4 ±19.5	58.8 ±19.8	0.84
% time ≥7.0 mmol/l	65.6 ±17.2	68.7 ±17.2	67.3 ±14.0	68.6 ±14.6	68.1 ±17.0	64.6 ±18.1	69.0 ±17.4	0.04
% time ≥10.0 mmol/l	39.4 ±19.0	37.8 ±18.9	35.8 ±15.4	37.3 ±18.2	37.4 ±20.3	36.3 ±20.1	39.6 ±20.2	0.56

Data are mean ± SD. * Paired t-test (complete pairs only) between week 24 endpoint and baseline.

Figure 3.2   Percentage time with glucose <3.0 mmol/L during monthly blinded continuous glucose monitoring in the overall study population. *Paired t-test (complete pairs only between week 24 endpoint and baseline (P=0.004)).
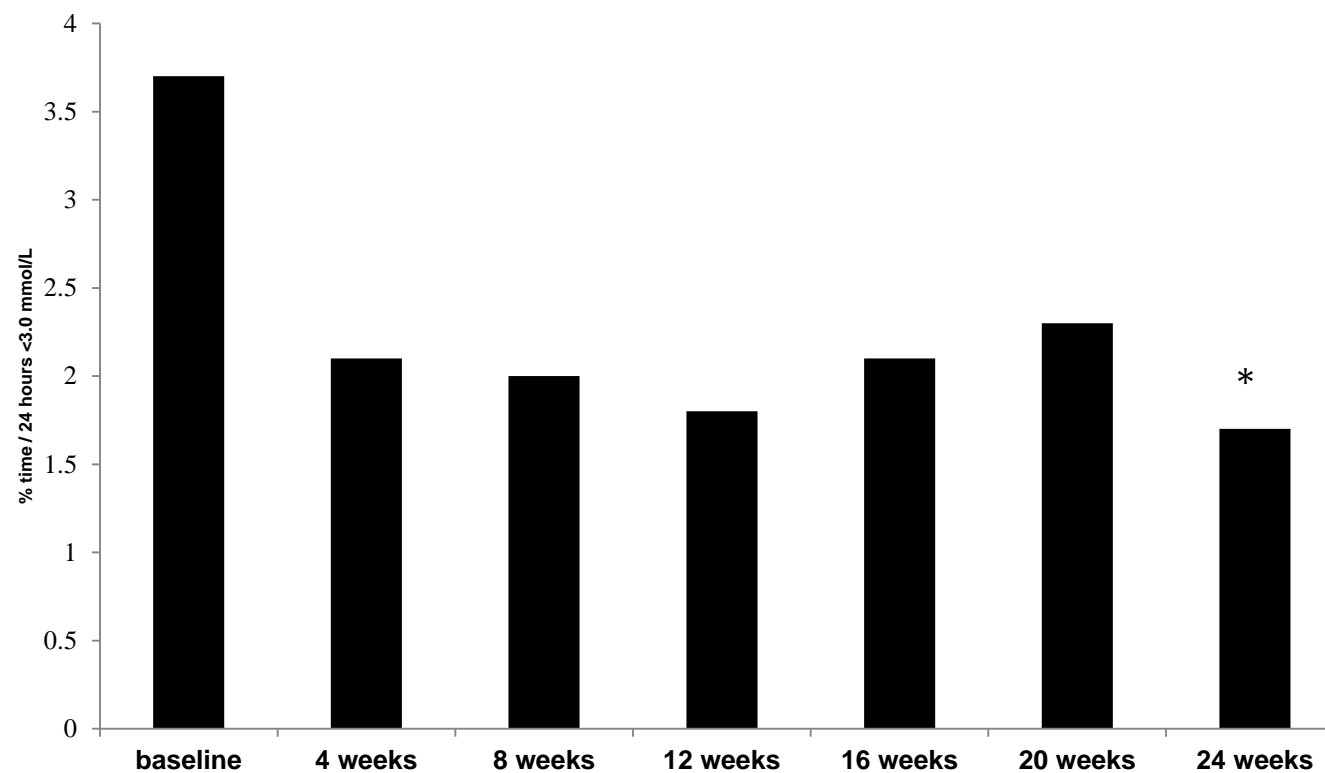
Table 3.3   Parameters of glycaemic control in overall study population over time

		Trial Period						
	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24 (endpoint)	P value*
8 point SMBG mean	9.5 ±2.8 (n=66)	9.4 ±1.8 (n=78)	9.5 ±2.2 (n=78)	9.3 ±2.2 (n=78)	9.1 ±1.7 (n=76)	9.3 ±2.1 (n=72)	8.8 ±1.9 (n=56)	0.16 (n=41)
HbA_{1c} (mmol/mol)	66±12 (n=95)	66±10 (n=90)	66±9 (n=87)	66±10 (n=86)	65±10 (n=85)	65±10 (n=89)	65±10 (n=89)	0.42 (n=89)
Weight (kg)	74.7± 14.2 (n=95)	74.8 ±13.8 (n=88)	75.4 ±13.7 (n=82)	74.3 ±13.4 (n=86)	74.3 ±13.6 (n=82)	74.0 ±14.8 (n=84)	75.3 ±13.6 (n=87)	0.75 (n=86)
Total daily insulin dose (units)	48.6 ±21.3 (n=95)	38.7 ±14.3 (n=90)	40.4 ±15.3 (n=87)	39.6 ±16.1 (n=90)	40.4 ±15.9 (n=89)	40.1 ±16.0 (n=97)	40.0 ±16.5 (n=90)	<0.001 (n=89)
Total daily insulin dose (units/kg)	0.64 ±0.23 (n=94)	0.51 ±0.14 (n=86)	0.52 ±0.15 (n=79)	0.52 ±0.16 (n=86)	0.53 ±0.17 (n=82)	0.56 ±0.34 (n=82)	0.53 ±0.17 (n=87)	<0.001 (n=85)

Data are mean ± SD. * Paired t-test (complete pairs only) between week 24 endpoint and baseline.

Figure 3.3   Mean HbA1c over time in the overall study population stratified by baseline value <64mmol/mol and ≥ 64mmol/mol (8.0%).
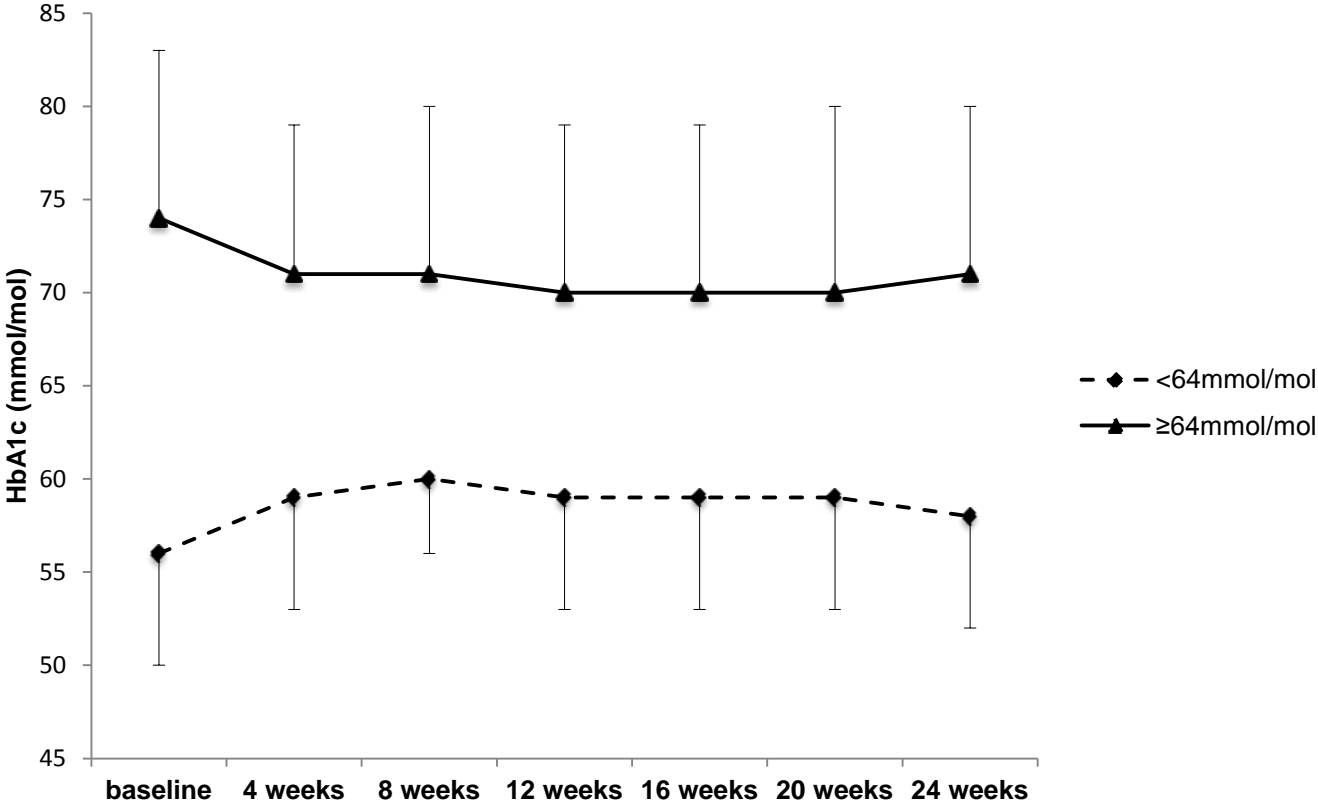
Table 3.4   Severe hypoglycaemia and hypoglycaemia awareness in overall study population at baseline and 24-week endpoint.

	Baseline	Week 24 (Endpoint)	*P value
Severe hypoglycaemia			
Annualised rate (patient-year)	8.9±13.4	0.8±1.9	<0.001
	4 [2-7] (n=96)	0 [0-0] (n=90)	(n=90)
Proportion affected (%)	77 (n=96)	20 (n=90)	<0.001 (n=90)
Impaired awareness of hypoglycaemia			
Gold score	5 [4-6] (2-7) 5.1±1.1 (n=96)	4 [3-5] (1-7) 4.1±1.6 (n=85)	<0.001 (n=85)
Clarke score	5 [4-6] (1-7) 4.1±1.6 (n=87)	3 [2-4] (0-7) 3.2±1.7 (n=80)	<0.001 (n=74)
HypoA-Q	14 [11-16] (5-20) 13.4±3.4 (n=92)	9.5 [6-12] (0-19) 9.1±4.2 (n=84)	<0.001 (n=80)

Data are median [interquartile range] (range) or mean ± SD. Number with available data denoted by n number in brackets. * Paired t-test (complete pairs only) between week 24 endpoint and baseline.

Table 3.5   Fear of hypoglycaemia and treatment satisfaction at baseline and 24-week study endpoint

	Baseline	Week 24 (Endpoint)	*P value
HFS II – Total	58 ±26 (n=94)	45 ±24 (n=87)	<0.001 (n=85)
HFS II - Behaviour	24 ±11 (n=94)	20 ±10 (n=87)	<0.001 (n=85)
HFS II - Worry	35 ±17 (n=96)	24 ±17 (n=87)	<0.001 (n=87)

Data are median [interquartile range] (range) or mean±SD. Number with available data denoted by n number in brackets. * Paired t-test (complete pairs only) between Week 24 endpoint and baseline.

Figure 3.4   Gold score (primary endopoint) in the overall study population. *Paired t-test (complete pairs only between week 24 endpoint and baseline (P<0.001)).
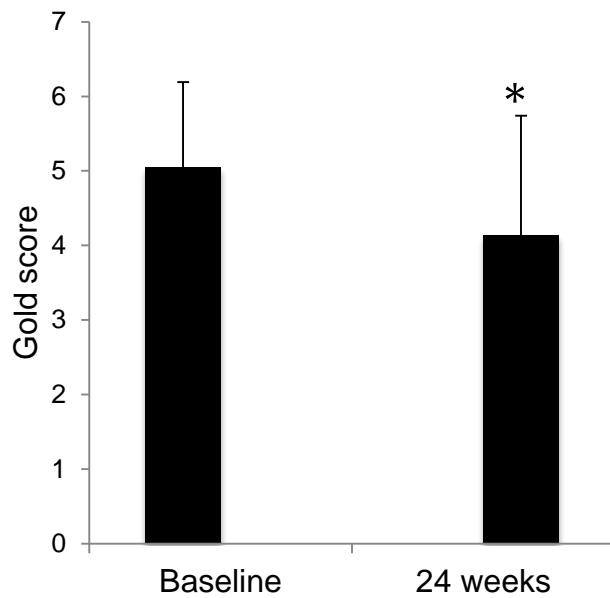
Figure 3.5   Severe hypoglycaemia events in the overall study population. *Paired t-test (complete pairs only between week 24 endpoint and baseline (P<0.001)).
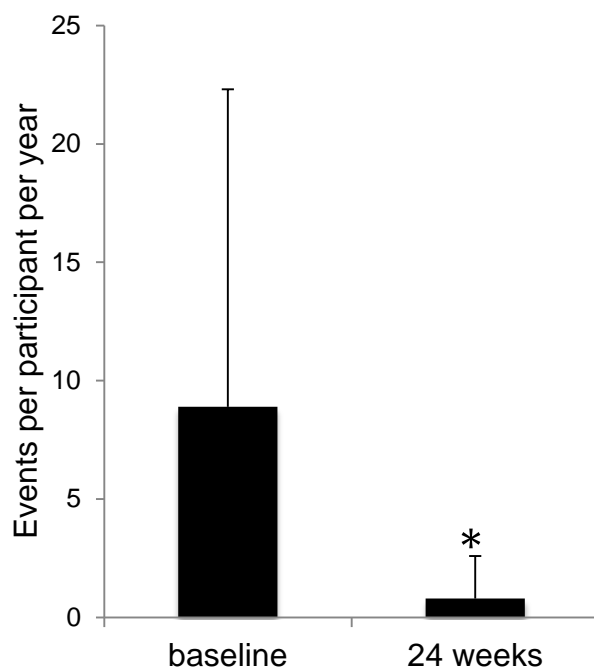
Figure 3.6   HbA1c in the overall study population between week 24 endpoint and baseline. Paired t-test (complete pairs only between week 24 endpoint and baseline (P=NS)).
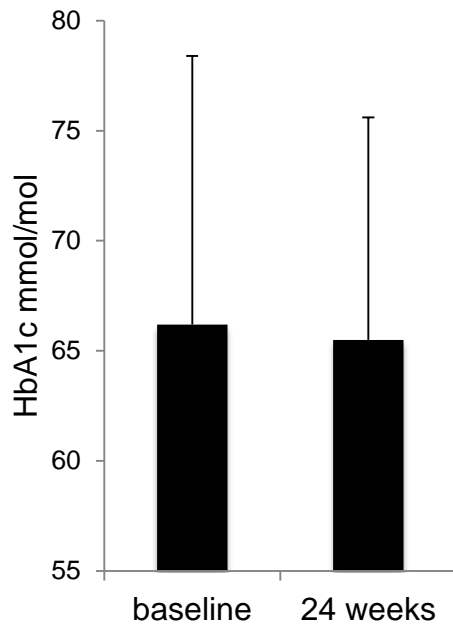
Figure 3.7   Mean total daily dose insulin in the overall study population. *Paired t-test (complete pairs only between week 24 endpoint and baseline (P<0.001)).
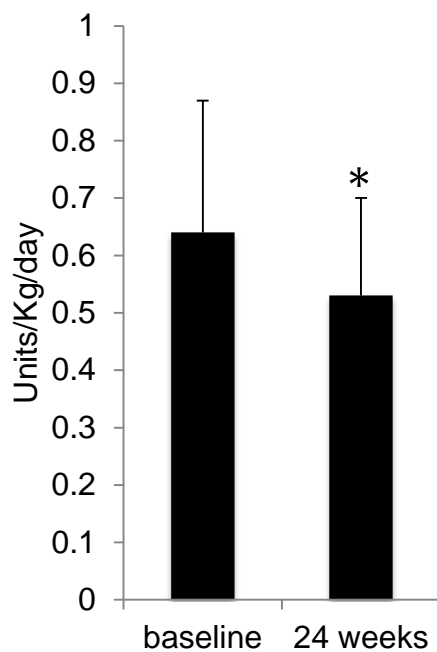
Figure 3.8   Fear of hypoglycaemia in the overall study population.
*Paired t-test (complete pairs only between week 24 endpoint and baseline (P<0.001)).
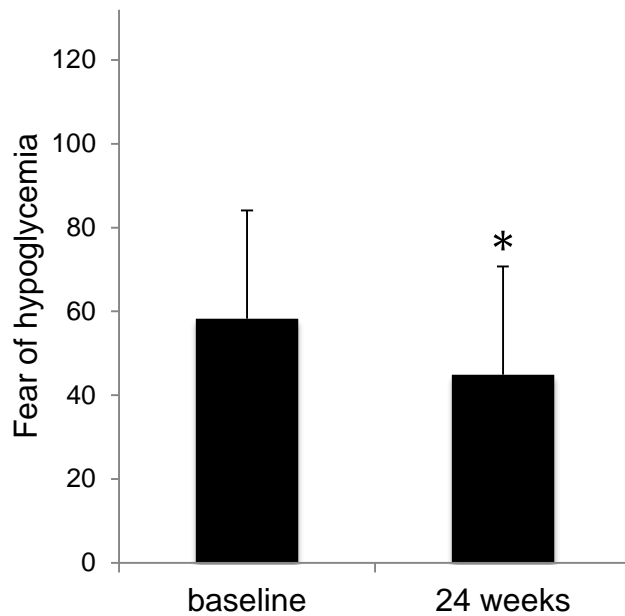
**Figure 3.9   Treatment satisfaction in the overall study population.**
*Paired t-test (complete pairs only between week 24 endpoint and baseline (P<0.001)).
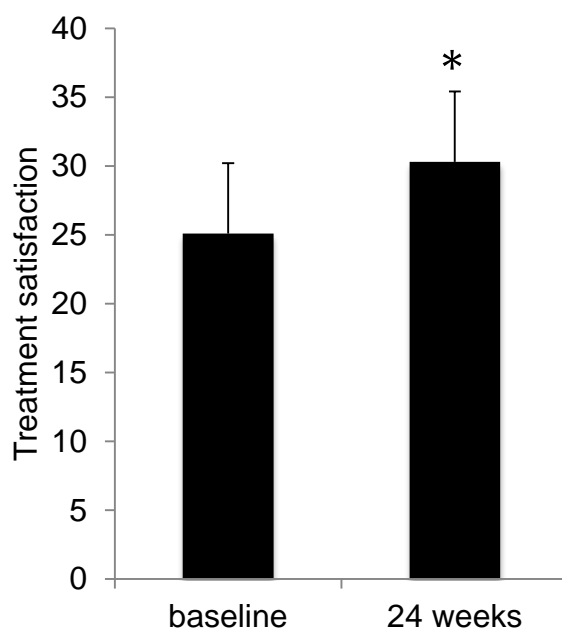
3.6.2 Comparisons of MDI vs CSII at 24-week study endpoint

This study has demonstrated that there was no difference in the improvement in hypoglycaemia awareness at 24 weeks between those randomised to optimised MDI and those randomised to CSII as assessed by the mean (±SD) Gold score ((MDI: 4.1 ± 1.6 vs CSII: 4.2 ± 1.7) (p=0.76)) (Figure 3.10). This was reflected in the accompanying measures of hypoglycaemia awareness used, the Clarke score (MDI 3.3 ± 1.8 vs CSII 3.0 ± 1.6 (p=0.31)) and the new measure the Hypoglycaemia Awareness Questionnaire (MDI 8.9 ± 4.3 vs CSII 9.4 ± 4.2 (p=0.60)).

Reductions in annualised rate of severe hypoglycaemia were also comparable in the MDI and CSII groups (MDI 1.0 ± 2.1 vs CSII 0.6 ± 1.7 (p=0.34)) and proportions of participants affected were also not statistically different (Figure 3.11 and Table 3.6).

Other metabolic secondary outcome measures were also equivalent in MDI and CSII groups with comparable percentage time spent in biochemical hypoglycaemia as assessed by CGM. Time spent (%) ≤3.0 mmol/L was 1.4 ± 2.5 in the MDI group as compared to 2.0 ± 4.9 in the CSII group (p=0.48). HbA1c was lower in the CSII group at 64 ± 9 mmol/mol as compared to 67 ± 11 mmol/mol in the MDI group though this was not significant (Figure 3.12).

There was an overall reduction in total daily dose of insulin seen in the study population however no difference was seen between MDI and CSII groups (Figure 3.13). Total daily dose comparisons at 24 weeks were (units/kg/24 hours) 0.51 ± 0.15 in the MDI group as compared to 0.55 ± 0.18 in the CSII group (p=0.31).

Fear of hypoglycaemia was reduced equally (Figure 3.14) as were perceived frequency of hypoglycaemia and hyperglycaemia (Table 3.9). Overall treatment satisfaction was, however, higher in those randomised to CSII (Figure 3.15). The mean endpoint DTSQ score for the MDI groups was 29 ± 6 in comparison to 32 ± 3 in the CSII group (p<0.001) (Table 4).

Table 3.6   Severe hypoglycaemia and hypoglycaemia awareness in MDI vs CSII at 24 week endpoint

	Insulin comparison		
	MDI	CSII	*P value
Severe hypoglycaemia			
Proportion affected (%)	23 (n=47)	16 (n=43)	0.399**
Annualised rate	1.0 ±2.1 0 [0-0] (n=47)	0.6 ±1.7 0 [0-0] (n=43)	0.34
Impaired awareness of hypoglycaemia			
Gold	4 [3-5] (2-7) 4.1±1.6 (n=45)	4 [3-5.5] (1-7) 4.2 ±1.7 (n=40)	0.756
Clarke	3 [2-5] (0-7) 3.3±1.8 (n=41)	3 [2-4] (0-6) 3.0±1.6 (n=39)	0.305
HypoA-Q	9 [5.5-12] (0-19) 8.9±4.3 (n=44)	10 [6-12.5] (0-18) 9.4±4.2 (n=40)	0.601

Data are median [interquartile range] (range) or mean ± SD. Number with available data denoted by n number in brackets. * 2 sample t-test between groups at week 24 except, ** Chi square test.

Table 3.7   Biochemical parameters of CGM analysis in MDI vs CSII at 24-week endpoint

	Insulin comparison		
	MDI (n=41)	CSII (n=42)	P value*
Biochemical hypoglycaemia on CGM (% time spent) mmol/l			
≤2.5 mmol/l	0.5 ±1.1	1.0 ±3.0	0.40
≤3.0 mmol/l	1.4 ±2.5	2.0 ±4.9	0.48
< 4.0 mmol/l	5.7 ±6.1	5.8 ±8.0	0.96
Glucose mean (mmol/l)	9.4 ±2.0	9.5 ±1.8	0.85
Glucose SD (mmol/l)	3.3 ±0.7	3.5 ±0.8	0.32
% time 4.0-6.9 mmol/l	25.5 ±14.3	25.1 ±13.7	0.89
% time 4.0-9.9 mmol/l	55.0 ±19.1	54.3 ±18.1	0.88
% time 3.1-9.9 mmol/l	59.4 ±20.9	58.3 ±18.8	0.80
% time ≥7.0 mmol/l	68.8 ±18.1	69.1 ±16.9	0.93
% time ≥10.0 mmol/l	39.4 ±21.5	39.9 ±19.1	0.91

Data are mean ± SD. * 2 sample t-test between groups at 24 weeks.

Table 3.8   Biochemical parameters of glycaemic control in MDI vs CSII at 24-week endpoint

	Insulin comparison		
	MDI	CSII	P value*
8 point SMBG mean	8.9 ±1.6 (n=28)	8.7 ±2.2 (n=28)	0.80
HbA$_{1c}$ (mmol/mol)	67 ± 11 (n=46)	64 ± 9 (n=43)	0.26
Total daily insulin dose (units/kg body weight)	0.51 ±0.15 (n=44)	0.55 ±0.18 (n=43)	0.31

Data are mean ± SD. * 2 sample t-test between groups at 24 weeks.

Table 3.9   Fear of hypoglycaemia and treatment satisfaction outcomes in MDI vs CSII comparisons at 24-week endpoint

	Insulin comparison		
	MDI	CSII	*P value
Fear of hypoglycaemia			
HFS II – Total	45±25 (n=46)	44±23 (n=41)	0.824
HFS II – Behaviour	21±10 (n=46)	20±10 (n=41)	0.613
HFS II – Worry	25 ±17 (n=46)	24 ±17 (n=41)	0.985
Treatment satisfaction			
DTSQ – Total satisfaction	29±6 (n=45)	32±3 (n=39)	<0.001
DTSQ2 Perceived frequency of hyperglycaemia	3±1.29	3±1.01	0.248
DTSQ3 Perceived frequency of hypoglycaemia	3±1.13	3±1.25	0.240

Data are median [interquartile range] (range) or mean±SD. Number with available data denoted by n number in brackets. Number completing DTSQ2 and DTSQ3 in each group are the same as those completing DTSQ – total satisfaction questions. * 2 sample t-test between groups at Week 24.

Figure 3.10   Gold score (primary endpoint) in MDI vs CSII. 2 sample t-test (comparison between groups at week 24 (P=NS)).

Figure 3.11   Severe hypoglycaemia events in MDI vs CSII. 2 sample t-test (comparison between groups at week 24 (P=NS)).

Figure 3.12   HbA1c in MDI vs CSII. 2 sample t-test (comparison between groups at week 24 (P=NS)).

Figure 3.13   Mean total daily dose insulin in MDI vs CSII. 2 sample t-test (comparison between groups at week 24 (P=NS)).

Figure 3.14 Fear of hypoglycaemia in MDI vs CSII. 2 sample t-test (comparison between groups at week 24 (P=NS)).

Figure 3.15 Treatment satisfaction in MDI vs CSII. *2 sample t-test (comparison between groups at week 24 (P<0.001)).
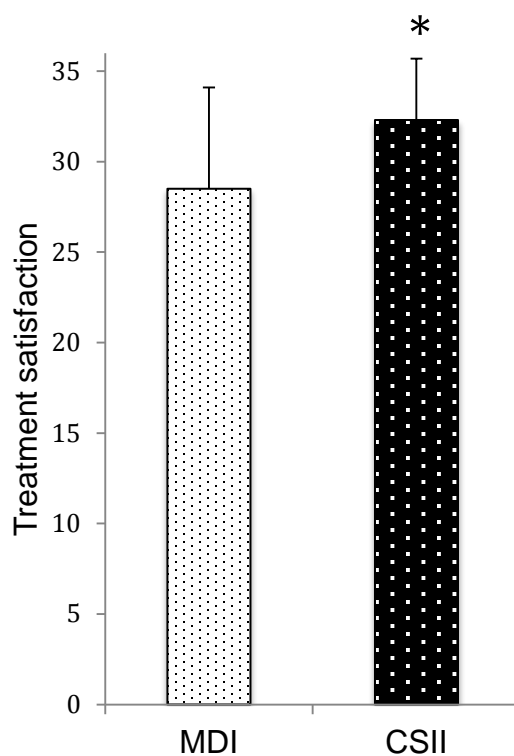
3.6.3 Comparisons of RT vs SMBG at 24-week study endpoint

In this 2x2 factorial study comparisons of the SMBG and RT groups similarly were equivalent with regards IAH scores and all other secondary outcomes.

Gold scores (mean ± SD) at study endpoint in the SMBG and RT groups were 4.3 ± 1.6 and 4.0 ± 1.7 respectively (p=0.42) (Figure 3.16). Clarke and HypoA-Q scores were also equivalent (Table 3.10).

Reductions in annualised rate of severe hypoglycaemia were equivalent in the SMBG and RT groups (SMBG 1.0 ± 2.1 vs RT 0.6 ± 1.7 (p=0.34)) and proportions of participants affected were also not statistically different (Figure 3.17 and Table 3.10).

Other metabolic secondary outcome measures were also equivalent in MDI and CSII groups with comparable percentage time spent in biochemical hypoglycaemia as assessed by CGM (Table 3.11). Time spent (% ± SD) ≤3.0mmol/L was 1.4 ± 2.5 in the MDI group as compared to 2.0 ± 4.9 in the CSII group (p=0.48). HbA1c was similar on both groups (Figure 3.18) as was total daily dose of insulin at study endpoint (Figure 3.19).

When patient reported outcomes were compared for SMBG and RT, fear of hypoglycaemia was reduced equally (Figure 3.20), as were perceived frequency of hypoglycaemia and hyperglycaemia (Table 3.13). Unlike the comparison of MDII and CSII, no difference was seen in overall treatment satisfactions between these interventions (Table 3.13 and Figure 3.21).

Table 3.10 Severe hypoglycaemia and hypoglycaemia awareness in SMBG vs RT at 24-week endpoint

	Monitoring comparison		
	SMBG	RT	*P value
Severe hypoglycaemia			
Annualised rate	0.9 ±2.1 0 [0-0] (n=44)	0.8 ±1.8 0 [0-0] (n=46)	0.95 0.92†
Proportion affected (%)	21 (n=44)	20 (n=46)	**0.92
Impaired awareness of hypoglycaemia			
*Gold	4 [3-5] (1-7) 4.3 ±1.6 (n=42)	4 [3-6] (1-7) 4.0 ±1.7 (n=43)	0.42
Clarke	3 [2-4] (0-6) 3.3 ±1.6 (n=39)	3 [2-4] (0-7) 3.1 ±1.8 (n=41)	0.83
HypoA-Q	10 [5-12] (0-16) 9.2 ±4.1 (n=40)	9 [6-12] (3-14) 9.0 ±4.4 (n=44)	0.83

Data are median [interquartile range] (range) or mean ± SD. Number with available data denoted by n number in brackets. † Mann Whitney U Test, * 2 sample t-test between groups at Week 24 except, ** Chi square test.

Table 3.11   Biochemical parameters of CGM analysis in SMBG vs RT at 24-week endpoint

	Monitoring comparison		
	SMBG (n=41)	RT (n=42)	P value*
Biochemical hypoglycaemia on CGM (%time spent) mmol/l			
≤2.5 mmol/l	0.7 ±1.4	0.8 ±2.9	0.71
≤3.0 mmol/l	1.3 ±2.1	2.1 ±5.1	0.36
< 4.0 mmol/l	5.2 ±4.2	6.3 ±9.1	0.47
Glucose mean (mmol/l)	9.5 ±1.7	9.4 ±2.1	0.73
Glucose SD (mmol/l)	3.4 ±0.7	3.4 ±0.8	0.81
% time 4.0-6.9 mmol/l	24.7 ±13.6	25.9 ±14.4	0.72
% time 4.0-9.9 mmol/l	54.0 ±17.8	55.3 ±19.3	0.75
% time 3.1-9.9 mmol/l	57.9 ±19.4	59.7 ±20.3	0.69
% time ≥7.0 mmol/l	70.1 ±16.1	67.9 ±18.7	0.56
% time ≥10.0 mmol/l	40.8 ±19.3	38.4 ±21.2	0.59

Data are mean ± SD. * 2 sample t-test between groups at 24 weeks.

Table 3.12   Biochemical parameters of glycaemic control in SMBG vs RT at 24-week endpoint

	Monitoring comparison		
	SMBG	RT	P value*
8 point SMBG mean	9.1 ±2.2 (n=27)	8.5 ±1.6 (n=29)	0.32
HbA_{1c} (mmol/mol)	65 ±9 (n=43)	66 ±11 (n=46)	0.80
Total daily insulin dose (units / kg body weight)	0.51 ±0.16 (n=44)	0.55 ±0.17 (n=43)	0.32

Data are mean ± SD. * 2 sample t-test between groups at 24 weeks.

Table 3.13　Fear of hypoglycaemia and treatment satisfaction outcomes in SMBG vs RT comparisons at 24-week endpoint

	Monitoring comparison		
	SMBG	RT	P value*
Fear of hypoglycaemia			
HFS II - Total	45±24 (n=42)	45±25 (n=45)	0.96
HFS II - Behaviour	21 ±9 (n=42)	20 ±11 (n=45)	0.94
HFS II - Worry	25 ±17 (n=42)	24 ±17 (n=45)	0.98
Treatment satisfaction			
DTSQ - Total satisfaction	30±5 (n=41)	30±5 (n=43)	0.79
DTSQ2 Perceived frequency of hyperglycaemia	3 ±1.17	3±1.18	0.70
DTSQ3 Perceived frequency of hypoglycaemia	3 ±1.09	3±1.27	0.75

Data are median [interquartile range] (range) or mean ± SD. Number with available data denoted by n number in brackets. Number completing DTSQ2 and DTSQ3 in each group are the same as those completing DTSQ – total satisfaction questions. * 2 sample t-test between groups at week 24.

Figure 3.16 Gold score (primary endpoint) in SMBG vs RT. 2 sample t-test (comparison between groups at week 24 (P=NS)).
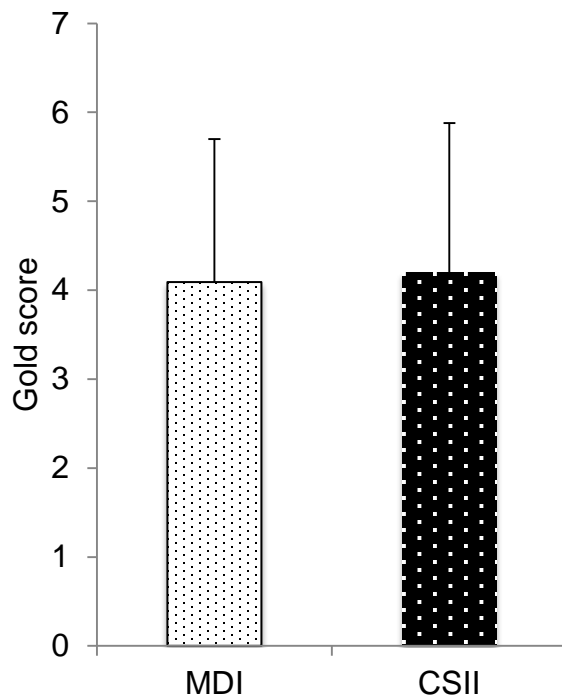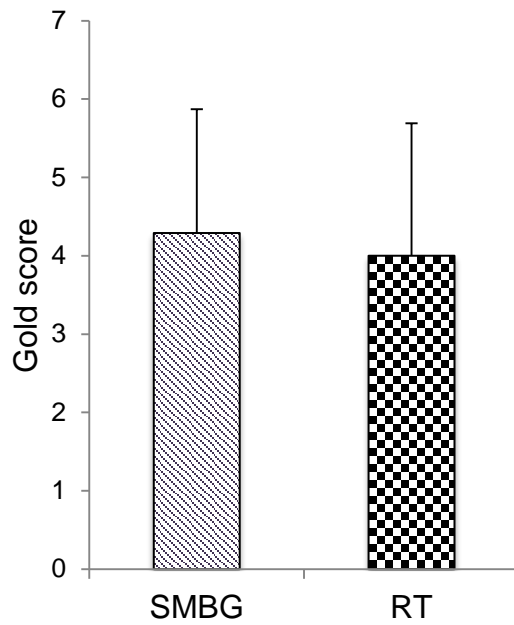

Figure 3.17 Severe hypoglycaemia events in SMBG vs RT. 2 sample t-test (comparison between groups at week 24 (P=NS)).
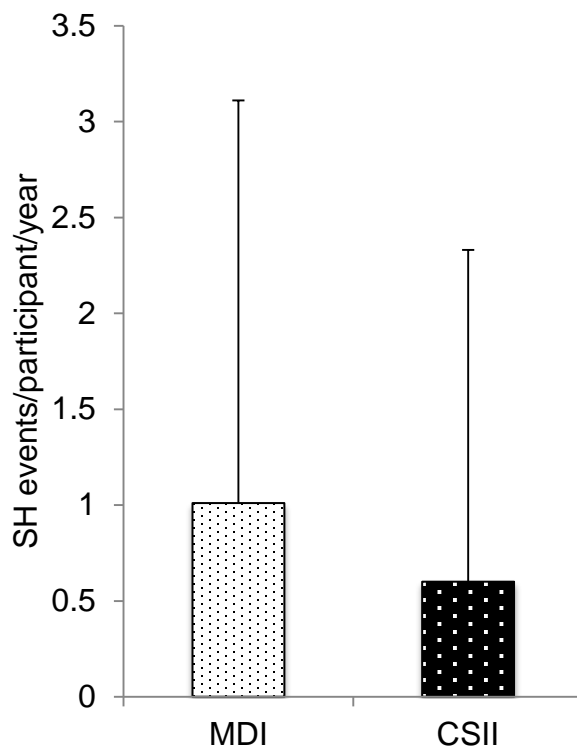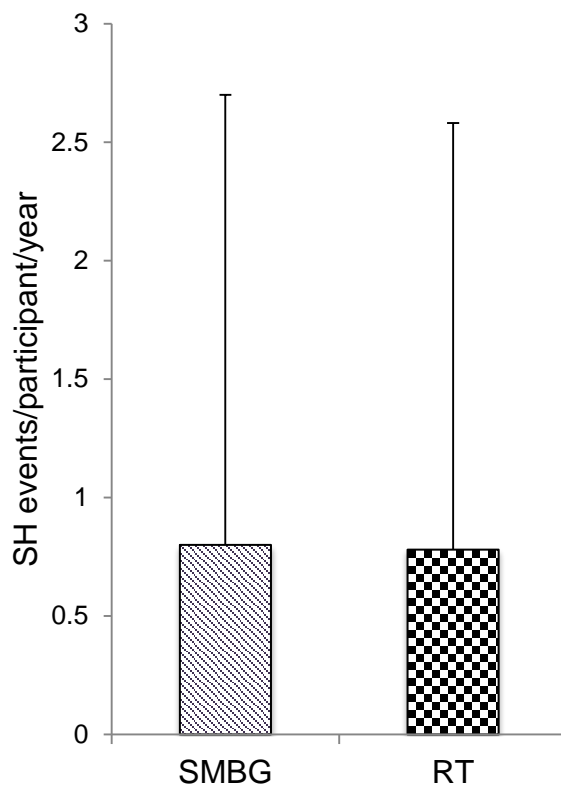
Figure 3.18 HbA1c in SMBG vs RT. 2 sample t-test (comparison between groups at week 24 (P=NS)).
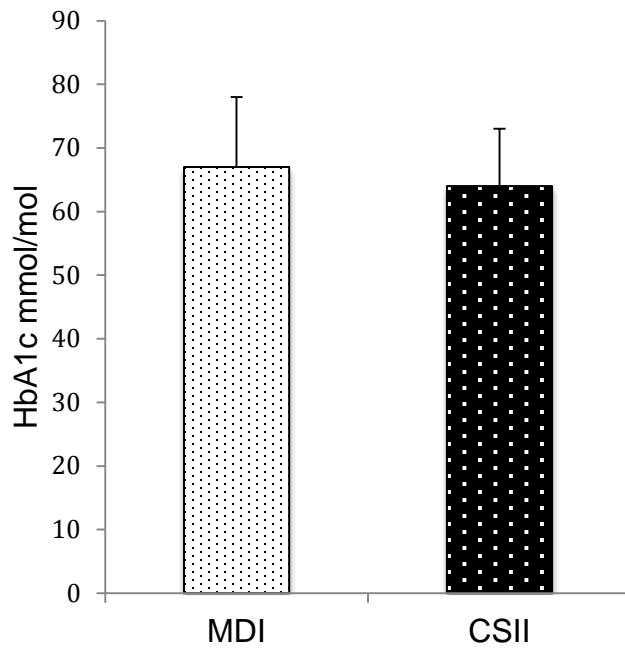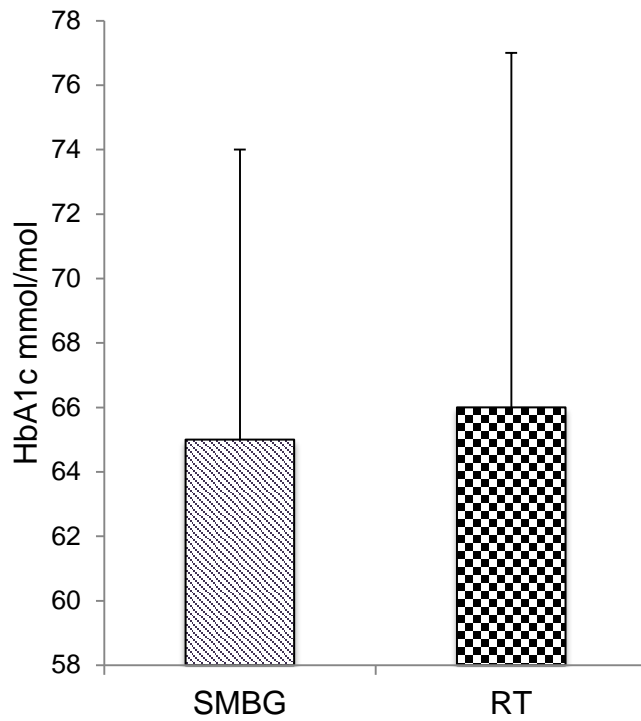

Figure 3.19 Mean total daily dose insulin in SMBG vs RT. 2 sample t-test (comparison between groups at week 24 (P=NS)).
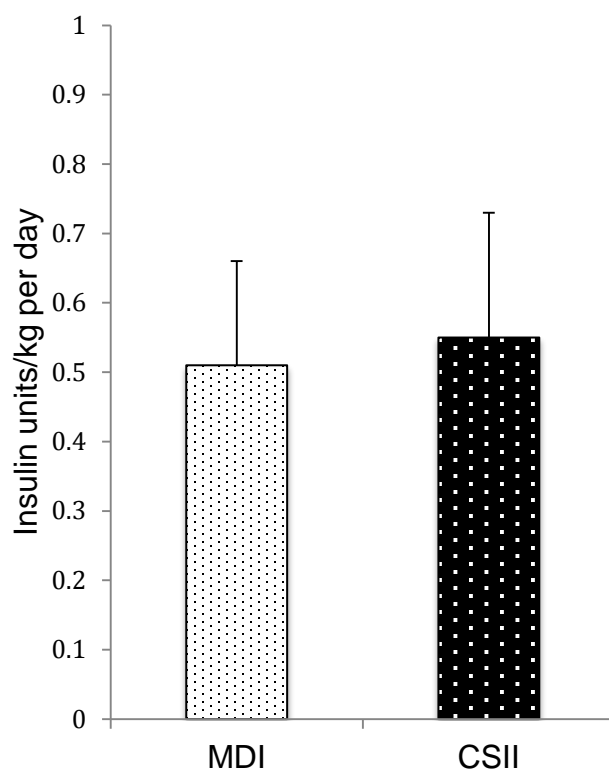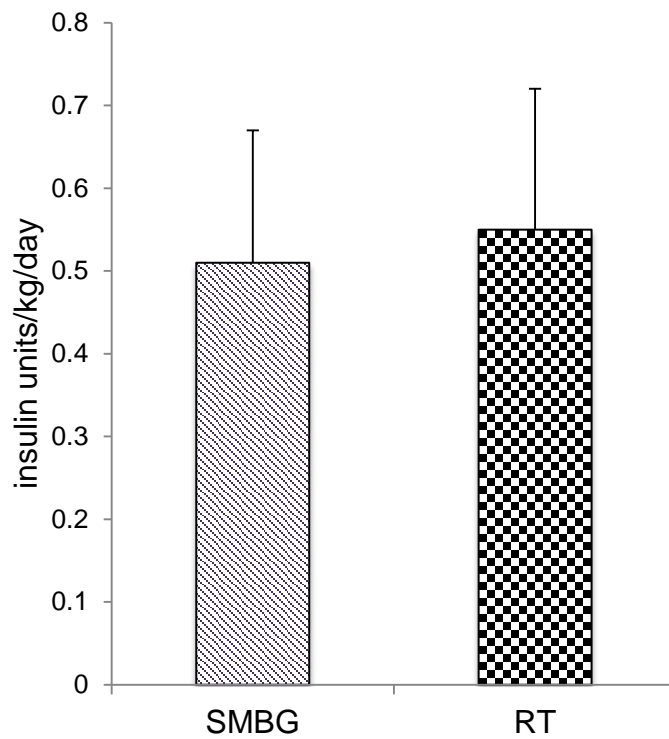
Figure 3.20 Fear of hypoglycaemia in SMBG vs RT. 2 sample t-test (comparison between groups at week 24 (P=NS)).
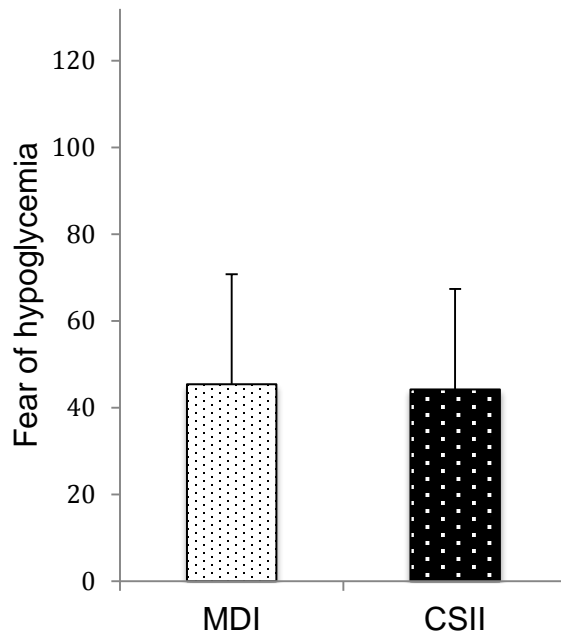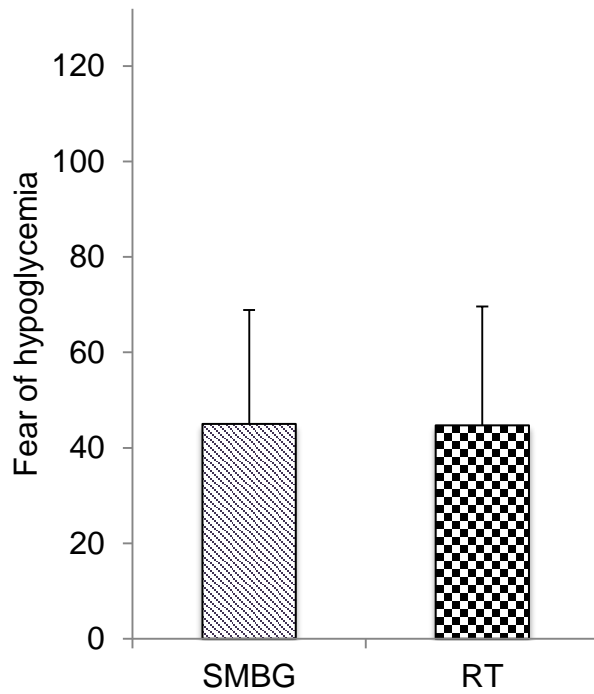

Figure 3.21 Treatment satisfaction in SMBG vs RT. 2 sample t-test (comparison between groups at week 24 (P=NS)).
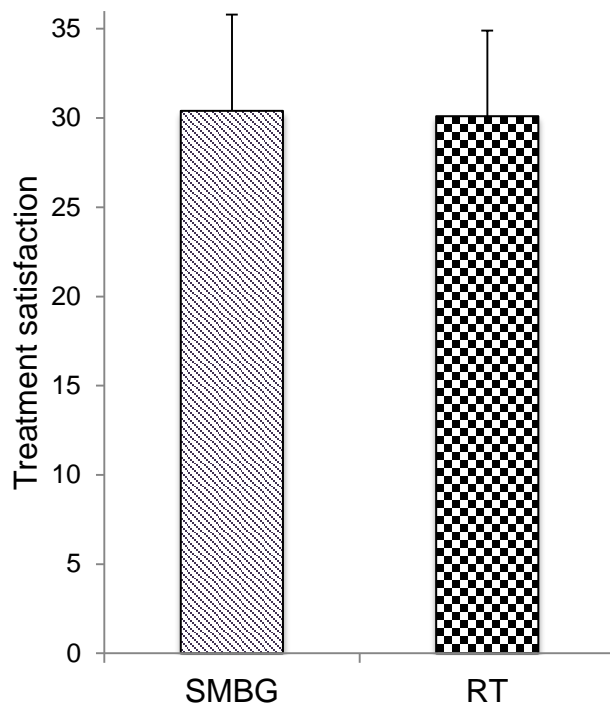
3.7 Compliance with RT

RT participants wore sensors for a median of 57% of time in study with sensor usage >80% in 17 individuals (Figure 3.21). Outcomes were not significantly different in those who used sensors for >50% of time, compared with less frequent users (Table 3.14). However higher users showed trends towards greater reduction in biochemical hypoglycaemia as defined as % time spent <4 mmol/L, ≤3 mmol/L and ≤2.5 mmol/L (Table 3.14). There was also a trend towards improved glycaemic control with the group using RT >50% of the time having an HbA1c (mean ±SD) of 64 ± 10 mmol/mol as compared to 68 ± 12 mmol/mol in the group using RT <50% of the time.

Figure 3.22   Histogram of percentage time the RT-continuous subcutaneous glucose monitor was worn during the study in those allocated to this intervention.   Frequency represents the number of individuals using RT for each percentage time range.
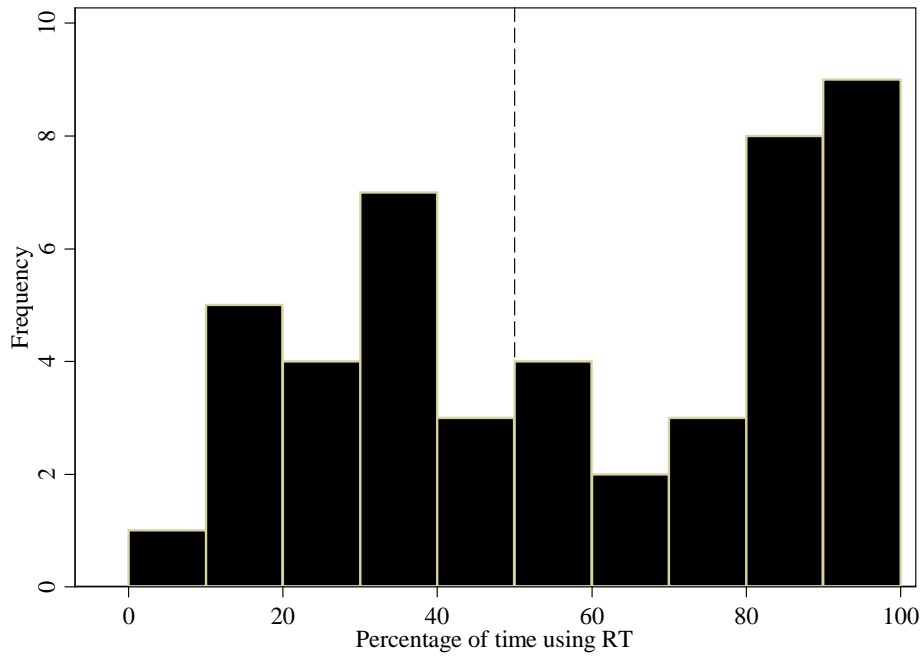
Table 3.14 Comparison of participants who used RT <50% of time with those who used it ≥50% of time at 24-week endpoint.

	Real time CGM use		
	<50%	≥50%	P* value
CGM analysis Biochemical hypoglycaemia on CGM (% time spent)	(n=17)	(n=25)	
≤2.5 mmol/l	1.4 ±4.4	0.4 ±1.0	0.28
≤3.0 mmol/l	3.7 ±7.6	1.1 ±1.7	0.10
<4.0 mmol/l	8.1 ±12.7	5.1 ±5.4	0.31
3.1-9.9 mmol/l	53.9 ±22.5	63.6 ±18.1	0.13
≥10.0 mmol/l	42.7 ±24.3	35.5 ±18.7	0.28
HbA$_{1c}$ (mmol/mol)	68 ±12 (n=20)	64 ±10 (n=25)	0.24
Impaired awareness of hypoglycaemia Gold	4.1 ±1.6 (n=17)	4.0 ±1.8 (n=26)	0.71
Clarke	3.3 ±1.9 (n=17)	2.9 ±1.8 (n=23)	0.47
HypoA-Q	9.2 ±4.3 (n=17)	8.8 ±4.6 (n=26)	0.74
Severe hypoglycaemia			
Annualised rate (patient-year)	0.5 ±1.7 (n=20)	1.0 ±1.9 (n=26)	0.43
Proportion affected (%)	10	30	**0.15

Data are mean ± SD. * 2 sample t-test between groups at 24 weeks. **Chi squared test.

3.8 ANCOVA analysis

ANCOVA adjusted for indicated covariates supported absence of influence of insulin treatment (Tables 3.15, 3.16, 3.17) or monitoring group (Tables 3.18, 3.19, 3.20) on primary and the majority of secondary outcome measures, either through analyses of change over the study period or explicit adjustment for baseline values. The analysis of the proportion of participants experiencing a reduction in severe hypoglycaemia was undertaken by logistic regression rather than ANCOVA.

Comparing the insulin regimens, the CSII group experienced a significantly larger increase in treatment satisfaction than MDI participants across all three fitted models (Tables 3.15, 3.16, 3.17).

Comparing adjuvant RT and conventional SMBG groups (tables 3.19, 3.19, 3.20), there was a significantly larger decrease in annualised severe hypoglycaemia rate (RT: 11.3 events per patient-year at baseline reduced to 0.8 events per patient-year at 24 weeks; SMBG: 6.4 vs 0.8 events). This was driven by baseline differences in severe hypoglycaemia rate between the monitoring groups. Interaction between insulin and monitoring regimen was considered for primary outcome analysis but found to be non-significant.

Similar analyses (Tables 3.21, 3.22, 3.23) were conducted for the subgroup allocated to RT use, dichotomised by use of RT (≥50% or <50% time). Higher RT use was associated with significantly larger decrease in time ≤3.0 mmol/L but without evidence of impact on IAH scores or severe hypoglycaemia.

3.9 Safety data

There were no hospital admissions related to severe hypoglycaemia or injection / cannula / sensor site infections throughout the RCT. There were three episodes of diabetic ketoacidosis requiring hospitalisation: two in participants randomised to CSII without RT and one in a participant randomised to MDI without RT. All resolved without adverse sequelae. Seven other serious adverse events (SAEs) were reported in the CSII group and 4 in the MDI group. These include episodes of acute-angle closure glaucoma, pneumonia, gastroenteritis, fractured radius and need for intravenous antibiotics for pre-existing neuropathic foot ulceration. None were deemed related to trial intervention.

After 4 weeks intervention, 50% of participants in the MDI arm were injecting glargine twice daily, increasing to 68% at 24 weeks.

Table 3.15   Analysis of covariance results comparing insulin regimen groups model 1: insulin regimen group only considered as covariate

Outcome	Model 1			
	n	beta	se(beta)	Wald*, p
24-week Gold score	85	0.11	0.36	0.10 (1,83 df), p=0.76
24-week Clark score	80	-0.39	0.38	1.07(1,78 df), p=0.30
24-week hypo AQ score	84	0.49	0.93	0.28 (1,82 df), p=0.60
Severe hypoglycaemia data				
Number of events at 24 weeks	90	-0.19	0.19	1.01 (1,88 df), p=0.32
24-week change in annualised rate	90	0.27	2.77	0.01 (1,88 df), p=0.92
Proportion with reduction	90	0.89 $	0.42	p=0.80 $$
24-week change in HbA$_{1c}$	89	-1.94	1.86	1.09(1,87 df), p=0.30
24-week change in weight	86	-0.14	0.82	0.03(1,84 df), p=0.87
24-week change mean insulin	85	-0.003	0.04	0.01(1,83 df), p=0.94
24-week change in HFS-II score	85	1.45	4.10	0.12 (1,83 df), p=0.73
24-week change in DTSQ score	84	4.79	1.36	12.36 (1,82 df), p<0.01
CGM data: 24-week change				
% time ≤3.0	82	1.83	1.21	2.29 (1,80 df), p=0.13
% time 3.1-9.9	82	2.52	4.63	0.30 (1,80 df),p=0.59
% time ≥10.0	82	-4.31	4.61	0.88 (1,80 df), p=0.35
Glucose (Sensor) SD	82	-0.03	0.24	0.02 (1,80 df), p=0.90
Glucose (Sensor) mean	82	-0.46	0.44	1.06 (1,80 df), p=0.31
8 point SMBG mean	41	-0.59	0.92	0.41 (1,39 df), p=0.53

Significant p-values show a significant difference between groups following adjustment for other model covariates. Beta values show the relative difference between the groups (the value being the fitted difference for membership of the CSII group relative to MDI). 24-week change values are calculated as the value at baseline subtracted from the value at week 24.
* P-value taken from F test (unless otherwise noted).
$ Odds ratio reported in place of beta (logistic regression used).
$$ p-value from logistic regression model

Table 3.16   Analysis of covariance results comparing insulin regimen groups model 2: in addition to insulin regimen group, adjusted for stratification factors at randomisation (site, HbA1c group)

Outcome	Model 2			
	n	beta	se(beta)	Wald*, p
24-week Gold score	85	0.18	0.35	0.28(1,78 df), p=0.60
24-week Clark score	80	-0.35	0.37	0.86(1,73 df), p=0.36
24-week hypo AQ score	84	0.67	0.91	0.54 (1,77 df), p=0.47
Severe hypoglycaemia data				
Number of events at 24 weeks	90	-0.19	0.19	0.99 (1,83 df), p=0.32
24-week change in annualised rate	90	0.37	2.73	0.02 (1,83 df), p=0.89
Proportion with reduction	75~	0.73 $	0.39	P=0.55 $$
24-week change in HbA$_{1c}$ ^^	89	-1.95	1.77	1.21(1,83 df), p=0.27
24-week change in weight	86	-0.20	0.82	0.06(1,79 df), p=0.81
24-week change mean insulin	85	-0.004	0.04	0.01(1,78 df), p=0.92
24-week change in HFS-II score	85	0.94	4.13	0.05 (1,78 df), p=0.82
24-week change in DTSQ score	84	4.63	1.31	12.42 (1,77 df), p<0.01
CGM data: 24-week change % time ≤3.0	82	1.86	1.24	2.26 (1,75 df), p=0.14
% time 3.1-9.9	82	4.12	4.39	0.88 (1,75 df), p=0.35
% time ≥10.0	82	-5.93	4.30	1.91 (1,75 df), p=0.17
Glucose (Sensor) SD	82	-0.05	0.24	0.05 (1,75 df), p=0.83
Glucose (Sensor) mean	82	-0.64	0.41	2.47 (1,75 df), p=0.12
8 point SMBG mean	41	-0.31	1.02	0.09 (1,34 df), p=0.76

Significant p-values show a significant difference between groups following adjustment for other model covariates. Beta values show the relative difference between the groups (the value being the fitted difference for membership of the CSII group relative to MDI). 24-week change values are calculated as the value at baseline subtracted from the value at week 24.

* P-value taken from F test (unless otherwise noted).

$ Odds ratio reported in place of beta (logistic regression used).

$$ p-value from logistic regression model. ~ 1 site (Bournemouth) predicts reduction perfectly: data from this site excluded from this analysis.

^^ Not adjusted for HbA$_{1c}$ stratification factor (as baseline value is considered within 24-week change)

Table 3.17   Analysis of covariance results comparing insulin regimen groups model 3: in addition to insulin regimen group, adjusted for site, baseline Gold score, age, presence or absence of treated autoimmune thyroid disease

Outcome	Model 3			
	n	beta	se(beta)	Wald*, p
24-week Gold score	85	0.12	0.27	0.20(1,76 df), p=0.66
24-week Clark score ^	74	-0.06	0.37	0.03(1,64 df), p=0.86
24-week hypo AQ score^	80	0.02	0.73	<0.01 (1,70 df), p=0.97
Severe hypoglycaemia data				
Number of events at 24 weeks ^	90	-0.16	0.17	0.90 (1,80 df), p=0.35
24-week change in annualised rate	90	0.15	2.61	<0.01 (1,81 df), p=0.95
Proportion with reduction ^	75~	0.68 $	0.37	P=0.48 $$
24-week change in HbA_{1c}	89	-2.33	1.77	1.73(1,80 df), p=0.19
24-week change in weight	86	-0.09	0.82	0.01(1,77 df), p=0.91
24-week change mean insulin	85	-0.003	0.04	<0.01(1,76 df), p=0.95
24-week change in HFS-II score	85	0.42	4.16	0.01 (1,76 df), p=0.92
24-week change in DTSQ score	84	5.05	1.31	14.94 (1,75 df), p<0.01
CGM data: 24-week change				
% time ≤3.0	82	2.05	1.24	2.73 (1,73 df), p=0.10
% time 3.1-9.9	82	4.05	4.43	0.84 (1,73 df), p=0.36
% time ≥10.0	82	-6.05	4.34	1.95 (1,73 df), p=0.17
Glucose (Sensor) SD	82	-0.08	0.24	0.11 (1,73 df), p=0.74
Glucose (Sensor) mean	82	-0.67	0.40	2.79 (1,73 df), p=0.10
8 point SMBG mean	41	-0.61	1.01	0.37 (1,32 df), p=0.55

Significant p-values show a significant difference between groups following adjustment for other model covariates. Beta values show the relative difference between the groups (the value being the fitted difference for membership of the CSII group relative to MDI). 24-week change values are calculated as the value at baseline subtracted from the value at week 24.
* P-value taken from F test (unless otherwise noted).
$ Odds ratio reported in place of beta (logistic regression used).
$$ p-value from logistic regression model. ^ Also adjusted for baseline value of outcome measure (baseline annualised rate in case of number of severe hypoglycaemia events)

Table 3.18   Analysis of covariance results comparing glucose monitoring groups model 1: monitoring regimen group only considered as covariate

Outcome	Model 1			
	n	beta	se(beta)	Wald*, p
24-week Gold score	85	-0.29	0.36	0.65, p=0.42
24-week Clark score	80	-0.21	0.38	0.30(1,78 df), p=0.59
24-week change in Hypo-AQ score	84	-0.20	0.93	0.05 (1,82 df), p=0.83
Severe hypoglycaemia data				
Number of events at 24 weeks	90	-0.04	0.19	0.04 (1,88 df), p=0.84
24-week change in annualised rate	90	-5.42	2.70	4.02 (1,88 df), p=0.048
Proportion with reduction	90	2.71 $	1.36	P=0.046 $$
24-week change in HbA$_{1c}$	89	1.52	1.87	0.66(1,87 df), p=0.42
24-week change in weight	86	-0.14	0.82	0.03(1,84 df), p=0.87
24-week change in mean insulin	85	-0.06	0.04	1.99(1,83 df), p=0.16
24-week change in HFS-II score	85	1.84	4.09	0.20 (1,83 df), p=0.65
24-week change in DTSQ score	84	0.07	1.46	<0.01 (1,82 df), p=0.96
CGM data: 24-week change				
% time ≤3.0	82	0.86	1.22	0.49 (1,80 df), p=0.49
% time 3.1-9.9	82	3.79	4.62	0.67 (1,80 df), p=0.41
% time ≥10.0	82	-4.44	4.61	0.93 (1,80 df), p=0.34
Glucose (Sensor) SD	82	-0.16	0.24	0.46 (1,80 df), p=0.50
Glucose (Sensor) mean	82	-0.31	0.46	0.49 (1,80 df), p=0.49
8 point SMBG mean	41	-0.01	0.94	<0.01 (1,39 df), p=0.99

Significant p-values show a significant difference between groups following adjustment for other model covariates. Beta values show the relative difference between the groups (the value being the fitted difference for membership of the RT group relative to the group without RT). 24-week change values are calculated as the value at baseline subtracted from the value at week 24.
* P-value taken from F test (unless otherwise noted)
$ Odds ratio reported in place of beta (logistic regression used)
$$ p-value from logistic regression model

Table 3.19   Analysis of covariance results comparing glucose monitoring groups model 2: in addition to monitoring regimen group, adjusted for stratification factors at randomisation (site, HbA1c group)

Outcome	Model 2			
	n	beta	se(beta)	Wald*, p
24-week Gold score	85	-0.25	0.34	0.53(1,78 df), p=0.47
24-week Clark score	80	-0.21	0.37	0.32(1,73 df), p=0.57
24-week change in Hypo-AQ score	84	-0.17	0.91	0.04 (1,77 df), p=0.85
Severe hypoglycaemia data				
Number of events at 24 weeks	90	-0.04	0.19	0.04 (1,83 df), p=0.84
24-week change in annualised rate	90	-5.06	2.66	3.61 (1,83 df), p=0.06
Proportion with reduction	75~	3.01 $	1.67	P=0.046 $$
24-week change in HbA$_{1c}$ ^^	89	1.57	1.78	0.78(1,83 df), p=0.38
24-week change in weight	86	-0.01	0.82	<0.01(1,79 df), p=0.99
24-week change in mean insulin	85	-0.05	0.04	1.71(1,78 df), p=0.20
24-week change in HFS-II score	85	2.13	4.10	0.27 (1,78 df), p=0.60
24-week change in DTSQ score	84	0.14	1.40	0.01 (1,77 df), p=0.92
CGM data: 24-week change				
% time ≤3.0	82	0.85	1.24	0.46 (1,75 df), p=0.50
% time 3.1-9.9	82	5.07	4.34	1.36 (1,75 df), p=0.25
% time ≥10.0	82	-5.70	4.27	1.78 (1,75 df), p=0.19
Glucose (Sensor) SD	82	-0.19	0.24	0.64 (1,75 df), p=0.43
Glucose (Sensor) mean	82	-0.45	0.41	1.25 (1,75 df), p=0.27
8 point SMBG mean	41	-0.32	1.00	0.10 (1,34 df), p=0.75

Significant p-values show a significant difference between groups following adjustment for other model covariates. Beta values show the relative difference between the groups (the value being the fitted difference for membership of the RT group relative to the group without RT). 24-week change values are calculated as the value at baseline subtracted from the value at week 24

* P-value taken from F test (unless otherwise noted)

$ Odds ratio reported in place of beta (logistic regression used)

$$ p-value from logistic regression model

^^Model not adjusted for HbA$_{1c}$ stratification factor (as baseline value is considered within 24 week change)

~ 1 site (Bournemouth) predicts reduction perfectly: data from this site excluded from this analysis

Table 3.20   Analysis of covariance results comparing glucose monitoring groups model 3: in addition to monitoring regimen group, adjusted for site, baseline Gold score, age, presence or absence of treated autoimmune thyroid disease

Outcome	Model 3			
	n	beta	se(beta)	Wald*, p
24-week Gold score	85	-0.09	0.27	0.10(1,76 df), p=0.76
24-week Clark score ^	74	-0.09	0.36	0.06(1,64 df), p=0.80
24-week change in Hypo-AQ score^	80	-0.18	0.73	0.06 (1,70 df), p=0.81
Severe hypoglycaemia data				
Number of events at 24 weeks ^	90	-0.24	0.18	1.82 (1,80 df), p=0.18
24-week change in annualised rate	90	-5.93	2.58	5.28 (1,81 df), p=0.02
Proportion with reduction ^	75~	5.13 $	3.33	P=0.01 $$
24-week change in HbA$_{1c}$	89	1.45	1.83	0.63(1,80 df), p=0.43
24-week change in weight	86	0.17	0.84	0.04(1,77 df), p=0.84
24-week change in mean insulin	85	-0.04	0.04	1.04(1,76 df), p=0.31
24-week change in HFS-II score	85	1.68	4.26	0.16 (1,76 df), p=0.69
24-week change in DTSQ score	84	0.32	1.47	0.05 (1,75 df), p=0.83
CGM data: 24-week change				
% time ≤3.0	82	1.24	1.29	0.93 (1,73 df), p=0.34
% time 3.1-9.9	82	7.44	4.50	2.73 (1,73 df), p=0.10
% time ≥10.0	82	-8.45	4.41	3.68 (1,73 df), p=0.06
Glucose (Sensor) SD	82	-0.37	0.25	2.20 (1,73 df), p=0.14
Glucose (Sensor) mean	82	-0.80	0.41	3.84 (1,73 df), p=0.053
8 point SMBG mean	41	-0.15	1.13	0.02 (1,32 df), p=0.90

Significant p-values show a significant difference between groups following adjustment for other model covariates. Beta values show the relative difference between the groups (the value being the fitted difference for membership of the RT group relative to the group without RT). 24-week change values are calculated as the value at baseline subtracted from the value at week 24.

* P-value taken from F test (unless otherwise noted)

$ Odds ratio reported in place of beta (logistic regression used)

$$ p-value from logistic regression model

^ Model also adjusted for baseline value of outcome measure (baseline annualised rate in case of number of severe hypoglycaemia events)

~ 1 site (Bournemouth) predicts reduction perfectly: data from this site excluded from this analysis

Table 3.21   Analysis of Covariance results comparing sub-groups defined by level of RT use (those randomised to RT only) model 1: RT use group only considered as covariate

Outcome	Model 1			
	n	beta	se(beta)	Wald*, p
24-week Gold Score	43	-0.19	0.53	0.13 (1,41 df), p=0.72
24-week Clarke Score	40	-0.42	0.59	0.52 (1,38 df), p=0.47
Severe hypoglycaemia data				
Number of events 24 weeks	46	0.19	0.25	0.60 (1,44 df), p=0.44
24-week change in HbA$_{1c}$	45	-3.38	2.57	1.73 (1,43 df), p=0.20
CGM data – 24-week change				
% time ≤3.0	42	-3.96	1.88	4.44 (1,40 df), p=0.04
% time 3.1-9.9	42	5.78	6.32	0.84 (1,40 df), p=0.37
% time ≥10.0	42	-2.13	6.41	0.11 (1,40 df), p=0.74

Significant p-values show a significant difference between groups following adjustment for other model covariates.
Beta values show the relative difference between the groups (the value being the fitted difference for membership of the RT>=50% group relative to the <50% group).
24-week change values are calculated as the value at baseline subtracted from the value at week 24.
* P-value taken from F test

Table 3.22   Analysis of Covariance results comparing sub-groups defined by level of RT use (those randomised to RT only) model 2: in addition to RT use group, adjusted for stratification factors at randomisation (site, HbA$_{1c}$ group)

Outcome	Model 2			
	n	beta	se(beta)	Wald*, p
24-week Gold Score	43	-0.06	0.54	0.01 (1,36 df), p=0.92
24-week Clarke Score	40	-0.18	0.58	0.09 (1,33 df), p=0.77
Severe hypoglycaemia data				
Number of events 24 weeks	46	0.29	0.26	1.24 (1,39 df), p=0.27
24-week change in HbA$_{1c}$ ^^	45	-1.26	2.47	0.26 (1,39 df), p=0.61
CGM data: 24-week change				
% time ≤3.0	42	-5.31	1.97	7.26 (1,35 df), p=0.01
% time 3.1-9.9	42	3.53	5.66	0.39 (1,35 df), p=0.54
% time ≥10.0	42	1.43	5.79	0.06 (1,35 df), p=0.81

Significant p-values show a significant difference between groups following adjustment for other model covariates.
Beta values show the relative difference between the groups (the value being the fitted difference for membership of the RT>=50% group relative to the <50% group).
24-week change values are calculated as the value at baseline subtracted from the value at week 24.
^^ Not adjusted for HbA$_{1c}$ stratification factor (as baseline value is considered within 24 week change).
* P-value taken from F test.

Table 3.23 Analysis of Covariance results comparing sub-groups defined by level of RT use (those randomised to RT only) model 3: in addition to RT use group, adjusted for site, baseline Gold score, age, presence or absence of treated autoimmune thyroid disease

Outcome	Model 3			
	n	beta	se(beta)	Wald*, p
24-week Gold Score	43	0.35	0.41	0.73 (1,34 df), p=0.40
24-week Clarke Score ^	37	0.22	0.65	0.11 (1,27 df), p=0.74
Severe hypoglycaemia data				
Number of events 24 weeks ^	46	0.13	0.26	0.26 (1,36 df), p=0.61
24-week change in HbA_{1c}	45	-1.68	2.69	0.39 (1,36 df), p=0.54
CGM data: 24-week change				
% time ≤3.0	42	-4.80	2.04	5.52 (1,33 df), p=0.02
% time 3.1-9.9	42	4.41	6.38	0.48 (1,33 df), p=0.49
% time ≥10.0	42	0.04	6.47	<0.01 (1,33 df), p=>0.99

Significant p-values show a significant difference between groups following adjustment for other model covariates.
Beta values show the relative difference between the groups (the value being the fitted difference for membership of the RT>=50% group relative to the <50% group).
24-week change values are calculated as the value at baseline subtracted from the value at week 24.
^ Also adjusted for baseline value of outcome measure (baseline annualised rate in case of number of severe hypoglycaemia events).
* P-value taken from F test

3.10 Discussion

These results show that currently available modern multiple daily insulin injection (MDI) regimens and conventional glucose monitoring (SMBG), when optimised, can improve awareness of hypoglycaemia as effectively as continuous subcutaneous insulin infusion therapy (CSII) and real-time continuous glucose monitoring (RT). This is important given the global lack of availability and cost of these technologies.

These equivalent biomedical outcomes were matched with equivalent reduction in fear of hypoglycaemia with conventional MDI and SMBG regimens compared with CSII / RT. However, treatment satisfaction was higher in CSII users, a finding that is consistent with previous randomised controlled trials (Bolli *et al.*, 2009). Treatment satisfaction in those randomised to RT was no greater than in those continuing on conventional SMBG, in keeping with other studies reporting both benefits and hassles with RT (Tansey *et al.*, 2011).

Statistically significant improvement in IAH from baseline but absence of difference in the primary outcome measure between groups at study end-point has been confirmed in this adequately powered study in those at highest risk. Although caution is required when considering the data regarding overall improved hypoglycaemia awareness in the study population given the lack of a control group, the reduced biochemical hypoglycaemia and reduced severe hypoglycaemia incidence would suggest this finding is real. Thus, these results show that hypoglycaemia awareness can be improved and recurrent severe hypoglycaemia prevented through strategies targeted at rigorous avoidance of biochemical hypoglycaemia without relaxation of overall glycaemic control in adults with long standing T1DM and IAH.

Due to hypothesised relative insensitivity of the Gold score to change, a second validated IAH score and a newly designed measure were also included. The latter showed good correlation with existing measures but with much greater magnitude of clinical improvement at endpoint.

Biochemical hypoglycaemia was rapidly reduced in all groups within the first four weeks with this reduction sustained throughout the trial. It is striking that insulin dose reduction (a familiar correlate with insulin pump initiation) was also

seen in those remaining on MDI. Also of interest is the fact that this dose reduction was not associated with worsening of glycaemic control.

All except one individual randomised to CSII who commenced the intervention remained on it throughout the trial reporting greater treatment satisfaction than those remaining on MDI. All those who commenced RT following randomisation also continued to use the intervention, although improvement in treatment satisfaction was no greater than in those continuing on conventional glucose monitoring. The very high baseline rate of severe hypoglycaemia in those randomised to RT led to an apparent greater incremental benefit compared to the conventional monitoring group but without a difference between groups at study end-point. Those using RT for more than 50% of time were most successful in avoiding biochemical hypoglycaemia and in achieving best overall glycaemic control in keeping with published studies in those without IAH (JDRF-CGM-study-group, 2009; Battelino *et al.*, 2011; Garg *et al.*, 2011). However the larger reductions in % time spent in biochemical hypoglycaemia were not associated with differences in improved awareness of hypoglycaemia scores.

In this study use of RT did not translate to greater improvement in IAH and reduction in severe hypoglycaemia in this very high-risk group. Uninterrupted use of RT was not achieved and this may be viewed as a limitation given the established correlation between more regular use and clinical benefit (JDRF-CGM-study-group, 2009).

Other potential limitations of this study are that although multiple questionnaires were used to document hypoglycaemia awareness at baseline including the widely used and validated measures, the subjective nature of such methods may be considered a weakness. There also may be the potential for contamination in that my learnings from the use of the technology interventions, particularly the use of RT may have impacted on my work with the SMBG group. It is possible that the technology was more useful but that its benefits were spread across the whole group. However the fact that the reduction in biochemical hypoglycaemia happened so quickly suggests strongly that the education, training and professional support was what made a difference.

Another potential criticism of the study may be that the technology was not used to full potential in terms of:

a) The use of RT downloads and their interpretation which was not mandatory for all participants;
b) The patterns of use of unique features of insulin pump therapy - e.g. data regarding changes in basal patterns, configurated versus other basal patterns and of temporary basal features have not been analysed.

However, as another example of the study design ensuring congruent support was provided to all participants across the insulin intervention groups, It is important to state that everyone had access to an insulin pump in order that all could use the on board bolus calculator.   Similarly with the monitoring groups, the same pre-prandial and 2 hour post-prandial targets were set with primary goal again being avoidance of glucose <4 mmol/l - whether adjuvant RT was available or not. The weekly 8 point SMBG profiles including 4 am checks were another important factor in ensuring equivalence for SMBG group.

In this study there was an absolute focus on ensuring congruent education, support, attention and therapeutic targets for all groups. There was a focus to ensure that those individuals randomised to CSII or RT were not provided with extra 'non technology' education such as carbohydrate counting support as compared to those randomised to those in the MDI and SMBG groups. This is a strength of this RCT as compared to other studies investigating the impact of CSII and RT.

While blinded CGM was used before each study follow up visit for all participants, investigators and participants were blinded to this until the end of the study and therefore would not have had an impact on insulin titration and hypoglycaemia avoidance. This is an important point to emphasise when considering the potential implications for this work in clinical practice where blinded CGM may not always be easily accessible.

The relative impact of 'my hypo compass' and the treatment algorithms driving insulin dose changes cannot be determined from this study though it is noted that the reduction in biochemical hypoglycaemia was immediate from the start of the study interventions.

The results from this study suggest that through the use of conventional self-management and novel technologies supported by education achievable in the specialist clinical setting, restoration of hypoglycaemia awareness and avoidance of recurrent severe hypoglycaemia can be achieved in the majority of individuals without relaxation of overall glycaemic control.

Chapter 4

Characterisation of individuals with type 1 diabetes complicated by impaired awareness of hypoglycaemia: responders vs non-responders to conventional interventions

4.1   Introduction

The DCCT trial revealed that the majority of severe hypoglycaemia events occur in those individuals with type 1 diabetes who have impaired awareness of hypoglycaemia (IAH) (DCCT, 1997). IAH is one of the two components of hypoglycaemia associated autonomic failure (HAAF) and is caused by reduced autonomic symptom responses associated particularly with a reduced sympathetic neural response to lower glucose concentrations (Cryer, 1992b).

Avoidance of biochemical hypoglycaemia has been shown in experimental studies to reverse impaired awareness by providing higher blood glucose levels for the onset of autonomic and neuroglycopenic symptoms (Fanelli *et al.*, 1993; Cranston *et al.*, 1994).

It should therefore follow that clinical interventions aimed specifically at avoiding biochemical hypoglycaemia should improve awareness in all people with type 1 diabetes and IAH. However, in clinical practice this does not appear to be the case: avoiding biochemical hypoglycaemia does not seem to be enough to help all people regain awareness.

Given our understanding of the key role that biochemical hypoglycaemia avoidance has in regaining awareness perhaps those who are unable to do so could be classified into two groups:

1. Those who despite the intervention do not avoid biochemical hypoglycaemia;
2. Those who do avoid biochemical hypoglycaemia but whose awareness does not respond due to an additional pathology.

What may be the underlying drivers in both these two groups? As discussed in chapter one while the concept of fear of hypoglycaemia is well recognised fear of *hyper*glycaemia is a psychological construct characterised by excessive worry about high blood glucose in combination with acceptance (and non-avoidance) of hypoglycaemia - as a 'necessary evil' to evade development of long-term complications, such as blindness (Singh and al, 2010). It could be hypothesised that people with this excessive worry over high glucose may

demonstrate acceptance of biochemical hypoglycaemia and continue to have impaired awareness with any treatment regimen.

With regards those who do successfully avoid biochemical hypoglycaemia but cannot regain awareness perhaps there is a role for the presence of diabetic autonomic neuropathy (DAN). While the data surrounding the role of DAN's role in severe hypoglycaemia is conflicting there are epidemiological studies suggesting a link between cardiac autonomic dysfunction and risk of severe hypoglycaemia (Stephenson *et al.*, 1996). Other risk factors may include the presence of microvascular complications and chronic kidney disease. The risk of hypoglycaemia has been shown to be higher in individuals with diabetes and chronic kidney disease. Indeed the risk of death in such individuals is increased within 48 hours of a hypoglycaemic event (Moen *et al.*, 2009).

If health care professionals were able to identify the clinical characteristics of patients who are not likely to respond to conventional interventions, then early consideration could be made to assessment of suitability for alternative interventions such as psychological / motivational approaches; or even more invasive treatments, such as beta cell replacement options including islet cell and whole pancreas transplantation.

4.2 Aims

The first aim was to characterise the phenotype of the group of people with type 1 diabetes recruited to the HypoCOMPaSS study, all of whom had impaired awareness of hypoglycaemia and were at high risk of severe hypoglycaemia.

The second aim was to perform secondary analyses of those who continued to experience IAH regardless of study intervention, to determine factors associated with absence of response.

This study was driven by the hypotheses that there would be two sub-groups:

1. Those in whom an absolute focus on avoidance of high glucose (evidenced from patient-reported outcome (PRO) measures) leads to continued biochemical hypoglycaemia despite the study goals;
2. Those with severe autonomic neuropathy (evidenced from clinical history) who are unable to recover autonomic warning symptoms of hypoglycaemia despite effective reduction in biochemical hypoglycaemia.

4.3 Research design and methods

Using the HypoCOMPaSS study population within the context of the randomised clinical controlled trial described in chapter 2, sub group analysis was undertaken of those who continued to experience IAH despite any study intervention.

4.3.1 Participants

All participants had c-peptide negative type 1 diabetes and had baseline Gold score ≥4, confirming impaired awareness of hypoglycaemia and increased risk of severe hypoglycaemia. All participants were randomised to one of four intervention groups as previously described for the 24-week RCT.

Intervention group 1:	CSII with RT
Intervention group 2:	CSII without RT
Intervention group 3:	MDI with RT
Intervention group 4:	MDI without RT

4.3.2 Characteristics on history and clinical examination

At the baseline study visit all participants had a detailed clinical history. In addition to baseline hypoglycaemia awareness status, details of the presence or absence of retinopathy, atherosclerotic disease, treated thyroid disease, symptoms of gastroparesis, bladder dysfunction, sweating regulation problems and sexual function were taken.

A clinical examination was carried out checking for features of peripheral neuropathy and postural hypotension. Peripheral neuropathy was checked for by an examination using a 10g monofilament, testing at four sites (1st, 3rd, and 5th metatarsal heads and plantar surface of distal hallux) on each foot. Loss of sensation at one or more site was taken as evidence of peripheral neuropathy (Boulton *et al.*, 2008).

Postural hypotension was undertaken by performing lying and standing blood pressures. Postural hypotension was considered present if a reduction in blood pressure (≥20 mm Hg in systolic, ≥10 mm Hg in diastolic) was sustained at or beyond three minutes (Parry and Tan, 2010).

4.3.3 Laboratory tests

A blood test was taken for creatinine concentration and a urine sample for microalbuminuria. Participants were given a sterile universal container for collection of a first morning void (Witte *et al.*, 2009). The blood and urine samples were analysed at all local site laboratories.

4.3.4 The hyperglycaemia avoidance scale

At the baseline study visit all participants were asked to complete the Hyperglycaemia Avoidance Scale (Singh and al, 2010) before study randomisation (Appendix 13).

4.3.5 The autonomic symptom profile questionnaire

At visit 4, prior to randomisation all participants were asked to complete the validated Autonomic Symptom Profile Questionnaire which takes approximately 15 minutes to complete (Suarez *et al.*, 1999). See section 2.14 for details on scoring. A copy of this questionnaire is included as Appendix 15.

4.4 Definitions of response and resolution

In the HypoCOMPaSS randomised control trial a range of interventions were used with the same common goal: avoid biochemical hypoglycaemia to regain hypoglycaemia awareness. Therefore I decided to look at the entire study cohort and determine who did and who did not manage to achieve this goal. To do this I compared awareness of hypoglycaemia as assessed by the Gold score in the entire study population at the end of the study against scores at baseline. This was used as a surrogate marker of 'response' to any intervention used in the study.

The population was compared firstly by responders vs non-responders and in a second analysis by resolution vs non-resolution.

1. Those who responded to any of the interventions used were defined by having 24-week Gold score < baseline Gold score.
2. Those who did not respond to any of the interventions used were defined by having 24-week Gold score ≥ baseline Gold score.
3. Those who had 'resolution' of IAH at 24 weeks were defined by having 24-week Gold score <4.
4. Those who did not have resolution of IAH at 24 weeks were defined by having Gold score ≥ 4.

4.5 Statistical analysis

Data were analysed on an intention-to-treat basis retaining ineligible participants and protocol violators in their randomised groups. Data were assessed for normality. Normally distributed variables are expressed as mean values (SD) with differences between groups analysed with parametric statistical tests (unpaired student's t-test). Categorical variables are expressed as proportions (%) with differences between groups analysed using Chi-squared test.

Data analysis took the form of a complete case analysis. Missing data were not deemed sufficient to justify imputation of values. Significance levels were set at $\alpha = 0.05$ throughout.

4.6 Results

4.6.1 Overall response and resolution

Of the 96 study participants who were randomised to one of the 4 study interventions complete data for these analyses was available for 85 individuals.

Fifty (58.8%) of the participants were defined as responders as defined as having a Gold score at 24-week study end point less than at study baseline.

Thirty three individuals (38.8%) were said to have had resolution of impaired awareness of hypoglycaemia as defined as 24-week gold score <4.

4.6.2 Clinical characteristics of the population

In the overall study population the mean (± SD) diabetes duration was 28.9 ± 12.4 years with a mean participant age of 48.6 ± 12·2 years.   The majority of the population (two thirds) had diabetic retinopathy with other micro- / macrovascular complications less common (Table 4.1). Injection site lipohypertrophy was frequent at 38% of the population. Postural hypotension was also frequent at 27% of the population.   29% had treated thyroid disease, 3% coeliac disease and one was taking corticosteroid replacement for primary adrenal insufficiency.

4.6.3 Clinical characteristics of responders

Analyses of responders vs non-responders can be seen in Table 4.1. Responders were younger than non-responders (45.0 ± 12.8 vs 53.3 ± 8.8 years) and also had shorter duration diabetes (26.7 ±12.1 vs 31.7 ± 12.8 years). Neither of these differences were found to be significant. Responders had a higher baseline HbA1c than non-responders (68 ± 13 mmol/mol, 8.4% vs 64 ± 10 mmol/mol, 8.0%), though again this was not statistically significant.

Baseline creatinine in the responders was lower than non-responders (70·3 ± 12.9 vs 80.0 ± 28.2), as was the frequency of microalbuminuria (18% of responders vs 31% non-responders) though these were both non-significant. There was no difference in rate of retinopathy but history of previous photocoagulation was lower in the responders group (18% responders vs 34% non-responders) though not significantly so.

4.6.4 Clinical characteristics of those with resolution of impaired awareness

Analyses of those with resolution of impaired awareness as compared to those without are seen in Table 4.2. In line with responders, those with resolution were younger (46.1 ±13.4 vs 49.8 ±10.9 years) and had shorter duration diabetes (25.9 ± 12.1 vs 30.5 ± 12.6 years) though neither of these differences were statistically significant. Frequency of retinopathy and baseline creatinine were both lower (non-significantly) in the resolution group (Table 4.2).

Table 4.1   Clinical characteristics: responders v non-responders

		Response (n=85)		P value*
		24-week Gold < Baseline		
	All (n=96)	No (n=35)	Yes (n=50)	
Baseline HbA$_{1c}$ (mmol/mol)	66±12	64±10	68±13	0.18
Age (years)	48·6 ±12·2	53·3 ±8·8	45·0 ±12·8	0.17
Male	35 (36%)	18 (51%)	13 (26%)	0.02**
Diabetes duration (years)	28·9 ±12·3	31·7 ±12·8	26·7 ±12·1	0.10
Body weight (kg)	74·7 ±14·2	76·6 ±14·5	73·7±14·8	0.62**
BMI (kg/m^2)	26·5 ±4·4	26·7 ±4·6	26·4 ±4·7	0.88**
Insulin dose (units/kg/24 hr)	0·64 ±0·23	0·69±0·29	0·63±0·19	0.32
Smoking status				0.65**
Current Smokers	21 (22%)	6 (17%)	11 (22%)	
Ex-smoker	26 (28%)	9 (26%)	15 (31%)	
Never smoked	47(50%)	20(57%)	23(47%)	
Alcohol consumers	62 (65%)	24 (69%)	32 (65%)	0.75**
Lipohypertrophy	35 (38%)	15 (45%)	17 (35%)	0.36**
Retinopathy	61 (64%)	23 (66%)	31 (63%)	0.82**
Laser photocoagulation	24 (25%)	12 (34%)	9 (18%)	0.09**
Microalbuminuria	22 (24%)	10 (31%)	9 (18%)	0.18**
Creatinine (micromol/L)	74·4 ±20·5	80·0 ±28·2	70·3 ±12·9	0.30
Peripheral neuropathy	18 (19%)	9 (26%)	7 (14%)	0.17**
Atherosclerotic disease	13 (14%)	7 (20%)	5 (10%)	0.19**
Treated thyroid disease	28 (29%)	12 (34%)	11 (22%)	0.21**
Postural Hypotension	26 (27%)	10 (29%)	14 (28%)	0.89**

Data are number of patients (%) or mean ± SD. *2-sample t-test (response v non-response)
**Chi square test (response v non-response).

Table 4.2   Clinical characteristics: resolution vs non-resolution

| | All (n=96) | Resolution (n=85) 24-week Gold < 4 | | P value* |
		No (n=52)	Yes (n=33)	
Baseline HbA$_{1c}$ (mmol/mol)	66±12	65±12	68±11	0.18
Age (years)	48·6 ±12·2	49·8 ±10·9	46·1 ±13·4	0.17
Male	35 (36%)	19 (37%)	12 (36%)	0.99**
Diabetes duration (years)	28·9 ±12·3	30·5 ±12·6	25·9 ±12·1	0.10
Body weight (kg)	74·7 ±14·2	74·3 ±14·3	75·9 ±15·5	0.62
BMI (kg/m^2)	26·5 ±4·4	26·5 ±4·4	26·6 ±4·6	0.88
Insulin dose (units/kg/24hr)	0·64 ±0·23	0·64±0·25	0·69±0·21	0.32
Smoking status				0.76**
Current Smokers	21 (22%)	9 (18%)	8 (24%)	
Ex-smoker	26 (28%)	15 (29%)	9 (27%)	
Never smoked	47 (50%)	27 (53%)	16 (49%)	
Alcohol consumers	62 (65%)	34 (67%)	22 (67%)	1.00**
Lipohypertrophy	35 (38%)	23 (47%)	9 (28%)	0.09**
Retinopathy	61 (64%)	35 (67%)	19 (59%)	0.46**
Laser photocoagulation	24 (25%)	13 (25%)	8 (24%)	0.94**
Microalbuminuria	22 (24%)	12 (25%)	7 (21%)	0.69**
Creatinine (micromol/L)	74·4 ±20·5	76·1 ±24·4	71·3 ±13·8	0.30
Peripheral neuropathy	18 (19%)	12 (23%)	4 (12%)	0.21**
Atherosclerotic disease	13 (14%)	9 (17%)	3 (9%)	0.29**
Treated thyroid disease	28 (29%)	16 (31%)	7 (21%)	0.33**
Postural Hypotension	26 (27%)	14 (27%)	10 (30%)	0.78**

Data are number of patients (%) or mean ± SD. *2-sample t-test (resolution v non-resolution) **Chi square test (resolution v non-resolution).

4.6.5 Hyperglycaemia avoidance scale (HAS)

The HAS score has a total score and four sub scales:

1. Worry about high glucose;
2. Immediate action for high glucose;
3. Preference for low blood glucose;
4. Action taken to avoid extremes.

The total (mean ± SD) score for the population was 39.9 ± 13.4. The total score for the non-responders was 38.2 ± 13.8 as compared to 41.1 ± 13.2 in the responders (Table 4.3). There were no significant differences in the sub-scale scores between responders and non-responders. Total and sub-scale scores were also similar in the resolution vs non-resolution analyses (Table 4.2).

Figure 4.1 shows a normal distribution of scores across the entire study population.

Figures 4.2 and 4.3 show the distribution of scores across the non-responders and responders respectively.

Figures 4.4 and 4.5 show the distribution of scores across the non-resolution and resolution groups respectively.

Table 4.3   Hyperglycaemia avoidance scale scores in responders vs non-responders and resolution vs non-resolution comparisons

	All (n=96)	Response (n=85) 24-week Gold < Baseline		P value*	Resolution (n=85) 24-week Gold < 4		P value*
		No (n=35)	**Yes (n=50)**		**No (n=52)**	**Yes (n=33)**	
Total score	39.9±13.4	38.2±13.8 (11.9-66.0)	41.1±13.2 (17.4-70.6)		39.7±14.5 (11.9-70.6)	40.3±11.8 (14.7-64.2)	
Worry about high glucose	25.0±9.2	23.5±9.8	25.6±8.7	0.29	24.5±9.9	25.1±8.1	0.79
Immediate action for high glucose	9.0±3.3	8.8±3.4	9.3±3.2	0.46	8.8±3.4	9.7±3.1	0.22
Low glucose preference	6.3±3.6	5.9±3.7	6.2±3.6	0.69	6.2±3.8	5.8±3.3	0.56
Avoid extremes	3.7±2.9	3.3±2.6	3.6±3.2	0.64	3.6±3.2	3.4±2.5	0.75

Data are mean ± SD and (range). * 2-sample t-test (response v non-response, resolution v non-resolution)

Figure 4.1   Histogram of hyperglycaemia avoidance scale total scores across the study population. The count is the number of individuals with a score within any given quantile.

Figure 4.2   Histogram of hyperglycaemia avoidance scale total scores across the non-responders. The count is the number of individuals with a score within any given quantile.

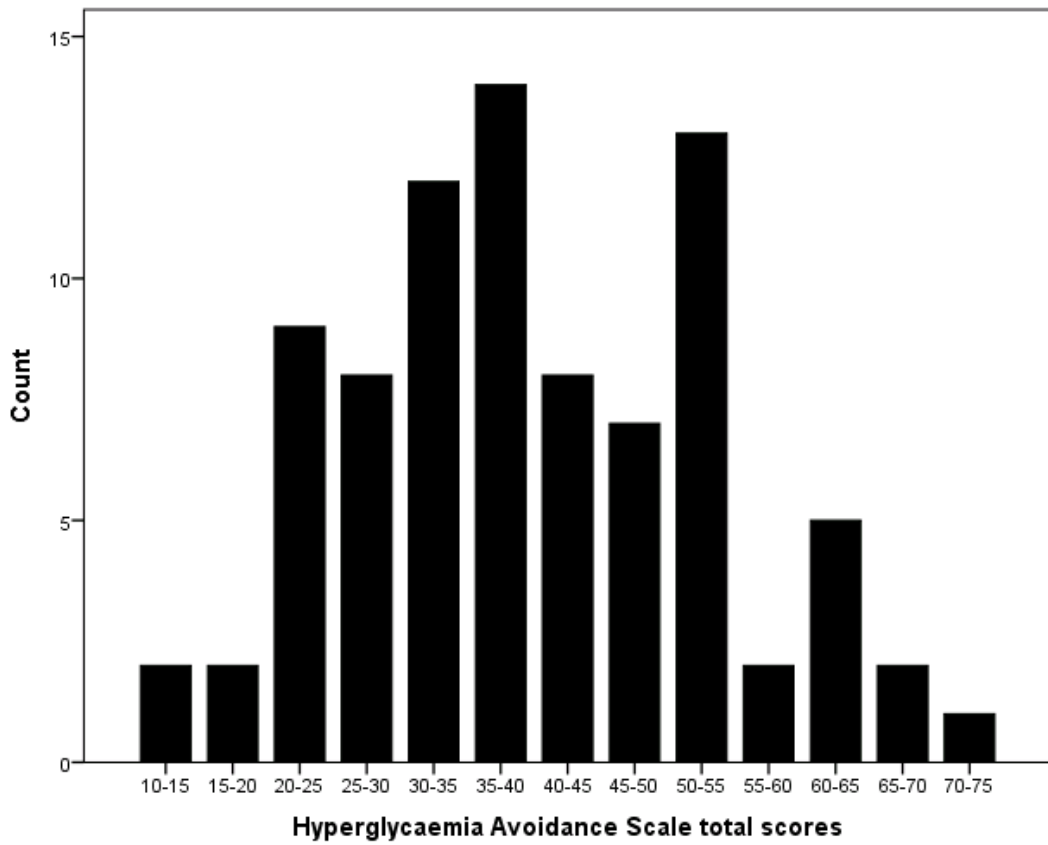**Figure 4.3   Histogram of hyperglycaemia avoidance scale total scores across the responders. The count is the number of individuals with a score within any given quantile.**

Figure 4.4 Histogram of hyperglycaemia avoidance scale total scores across the non-resolution group. The count is the number of individuals with a score within any given quantile.

Figure 4.5 Histogram of Hyperglycaemia Avoidance Scale total scores across the resolution group. The count is the number of individuals with a score within any given quantile

Figure 4.6   Histogram of hyperglycaemia avoidance scale worry subscale score across the study population. The count is the number of individuals with a score within any given quantile.

Figure 4.7 Histogram of hyperglycaemia avoidance scale worry subscale score across the responders. The count is the number of individuals with a score within any given quantile.
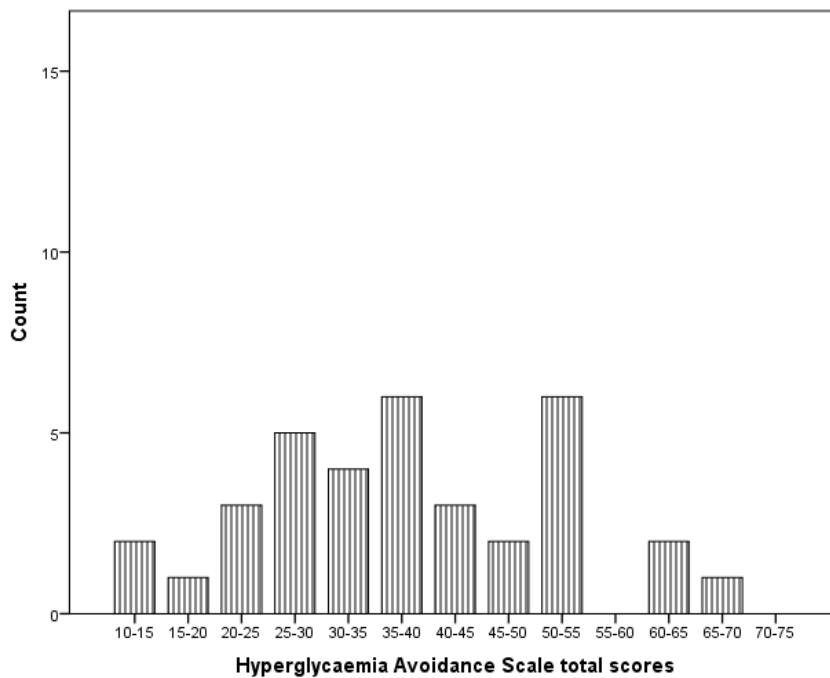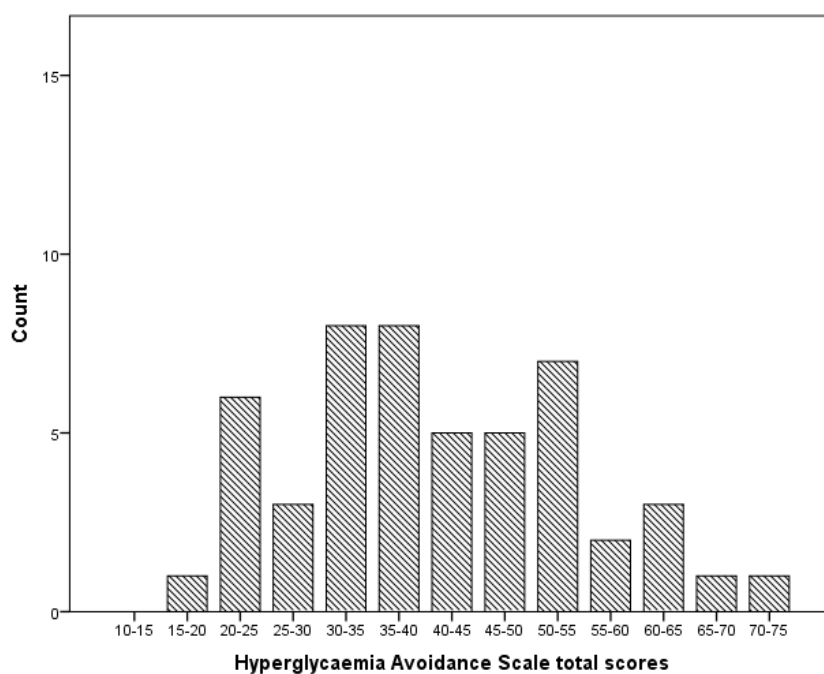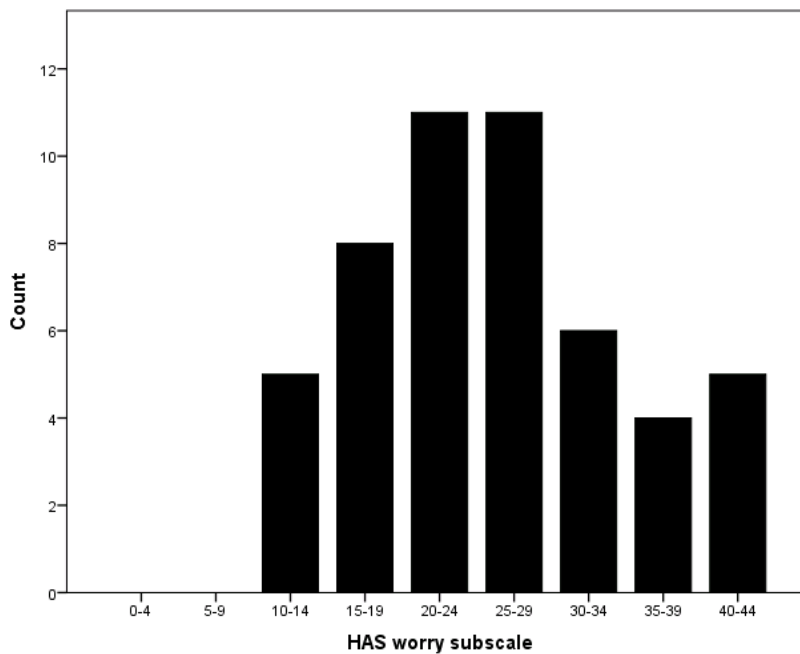

Figure 4.8 Histogram of hyperglycaemia avoidance scale worry subscale score across the non-responders. The count is the number of individuals with a score within any given quantile.
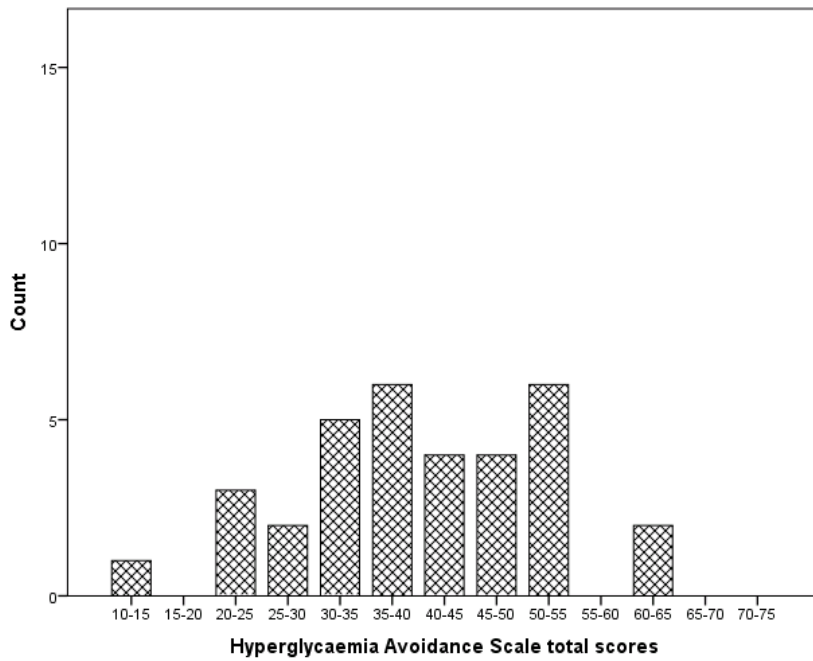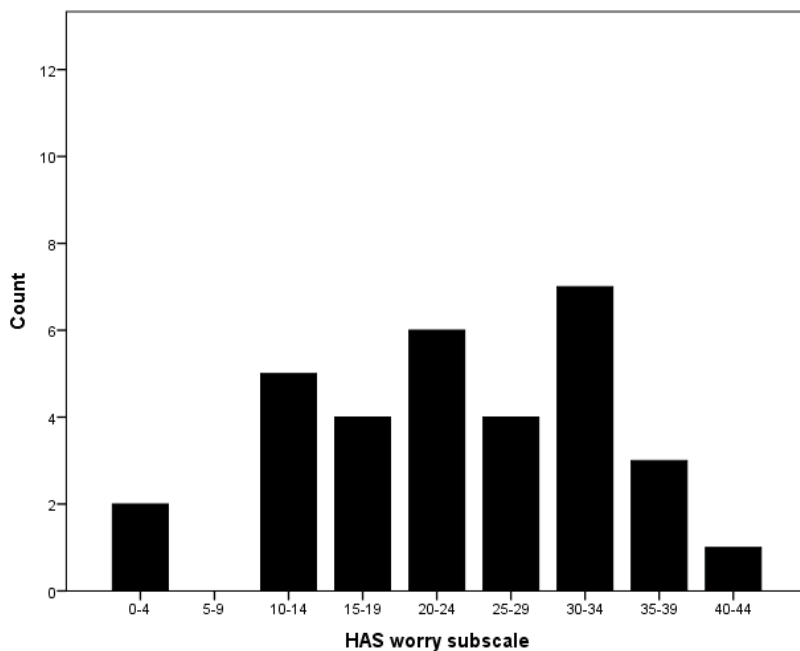
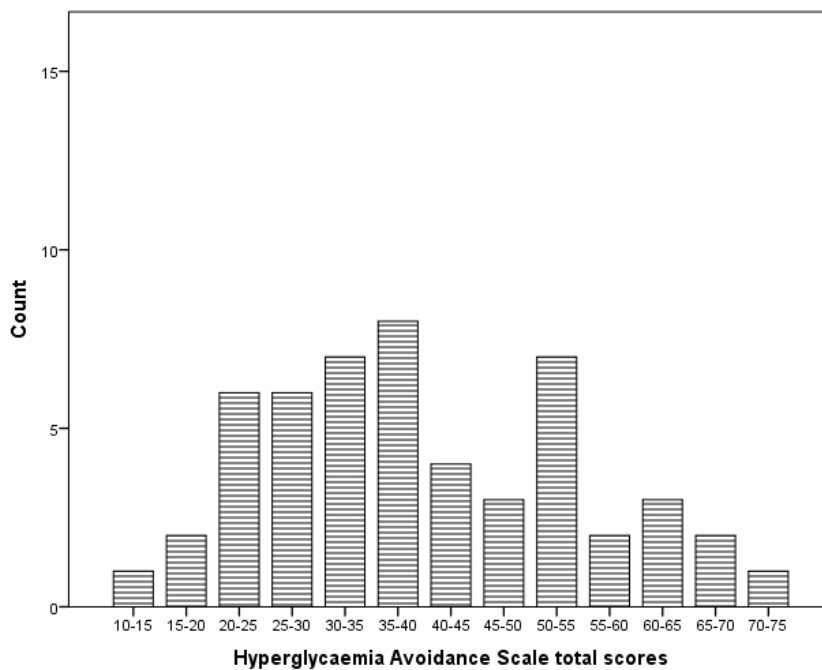**Figure 4.9   Histogram of hyperglycaemia avoidance scale low glucose preference subscale score across the study population. The count is the number of individuals with a score within any given quantile.**
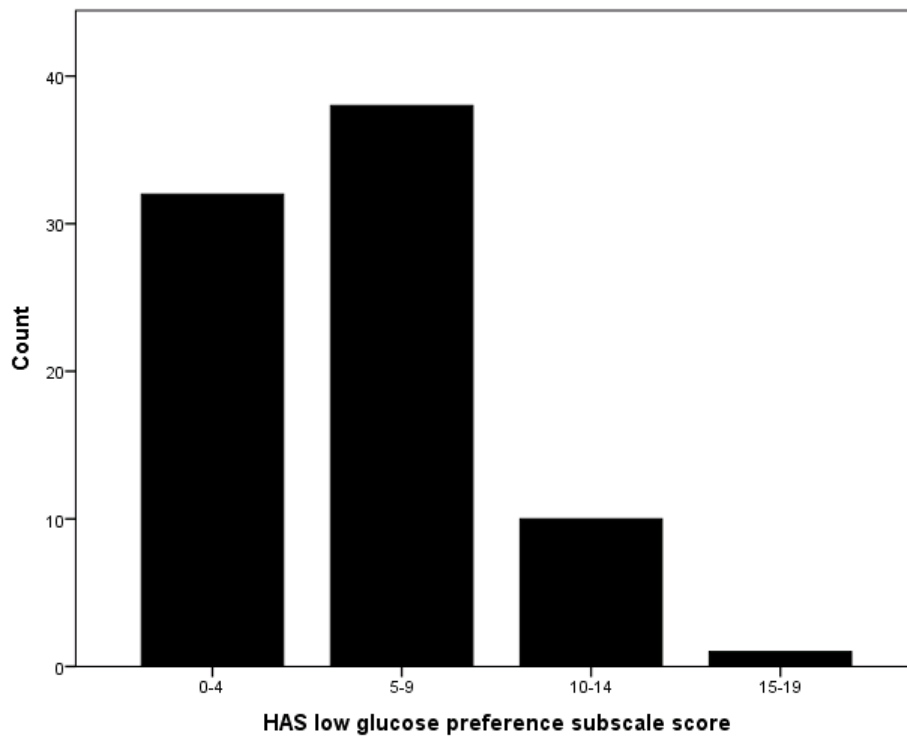
Figure 4.10 Histogram of hyperglycaemia avoidance scale low glucose preference subscale score across the responders. The count is the number of individuals with a score within any given quantile.
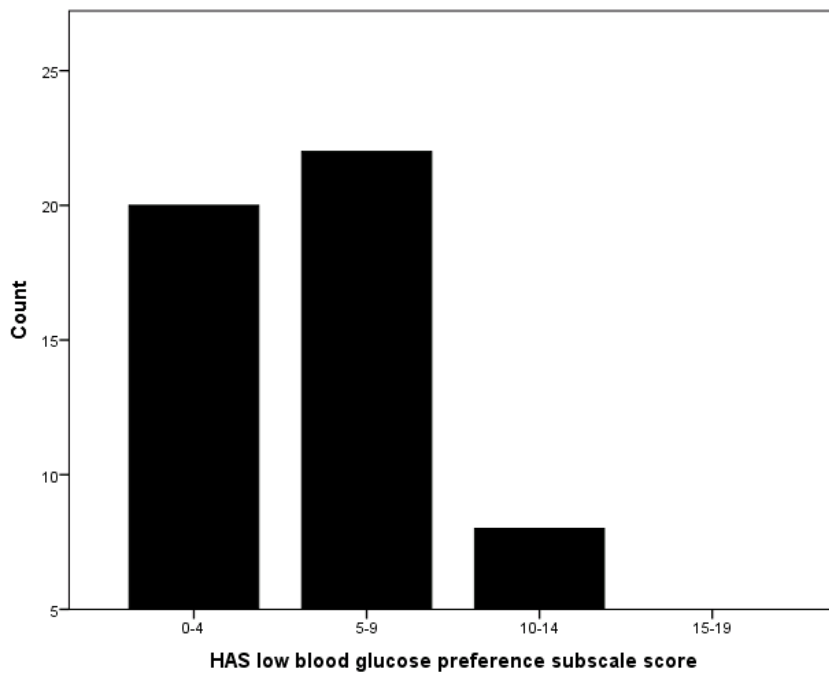
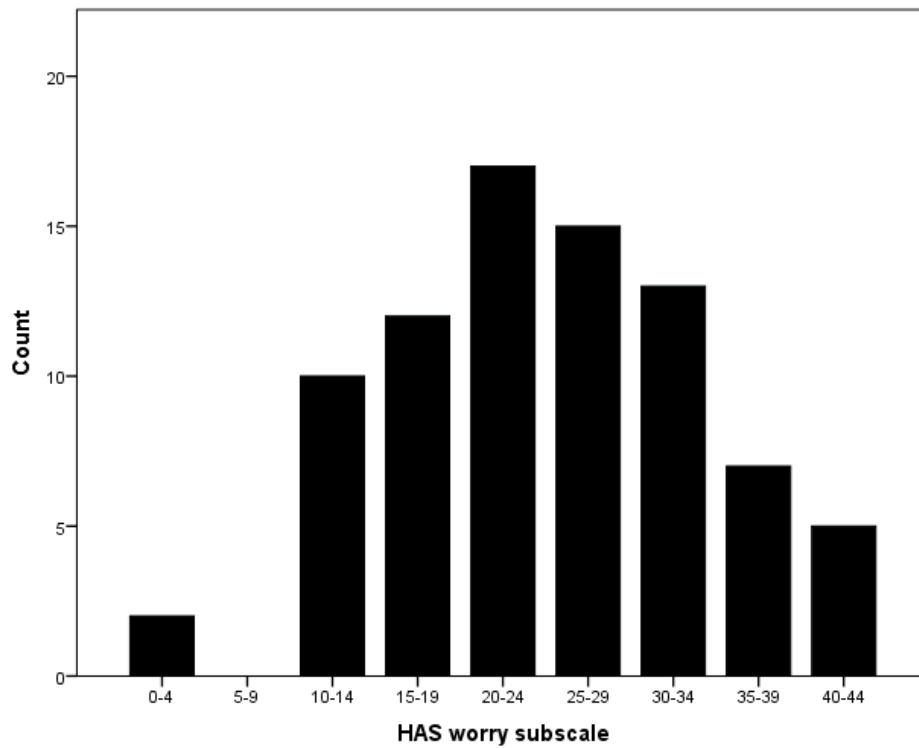**Figure 4.11 Histogram of hyperglycaemia avoidance scale low glucose preference subscale score across the non-responders. The count is the number of individuals with a score within any given quantile.**
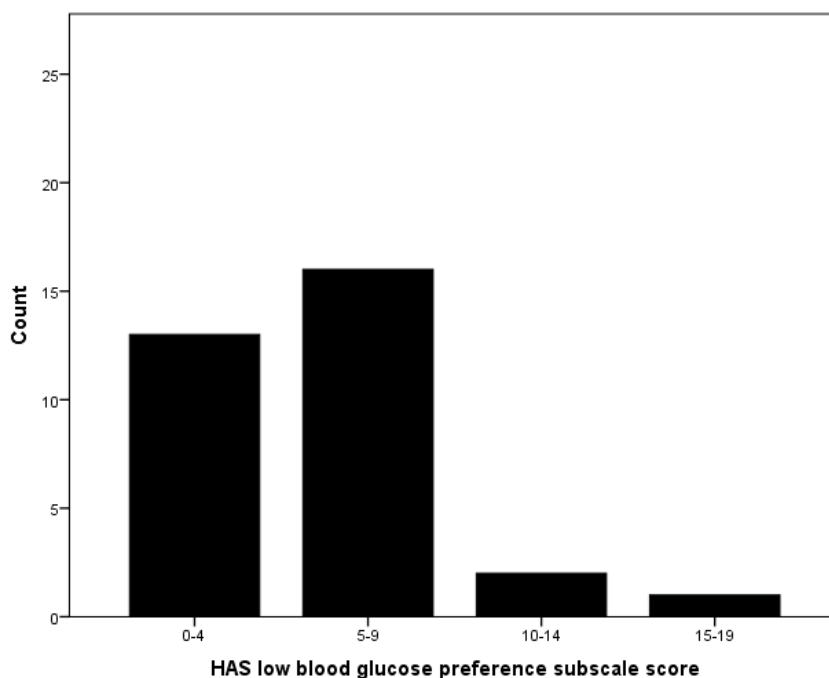
### 4.6.6   Autonomic symptom profile (ASP) results

The total scores for the non-responders and responders were (mean ± SD) 20.8 ± 17.7 and 21.2 ± 18.4 respectively. There were no differences between any of the subscale scores (Table 4.4). Total and sub-scale scores were similar for the resolution vs non-resolution analyses (Table 4.5). All groups scored highly on the orthostatic intolerance score, which is in keeping with the high frequency of postural hypotension as identified in Table 4.1.

Figure 4.12 is a histogram of the total ASP scores for the whole study population.

Figures 4.13 and 4.14 show the distribution of scores across the non-responders and responders respectively.

Figures 4.15 and 4.16 show the similar distribution of scores across the non-resolution and resolution groups respectively. Of note there was no one in the resolution group in the top 3 quantiles of ASP questionnaire score.

There was no correlation between ASP total scores and either participant age or diabetes duration as the histograms in Figures 4.17 and 4.18 respectively demonstrate.

Table 4.4   Autonomic Symptom Profile questionnaire scores:
responders v non-responders

	Response (n=85) 24-week Gold < Baseline		
	No (n=35)	Yes (n=50)	P*
Total	20.8±17.7	21.2±18.4	0.92
Orthostatic intolerance symptoms	9.1±9.3	8.8±9.5	0.91
Vasomotor symptoms	0.4±1.3	0.6±1.7	0.51
Secretomotor symptoms	2.1±3.0	2.4±2.9	0.70
Upper gastrointestinal symptoms	0.7±1.2	1.0±2.0	0.52
Autonomic diarrhoea symptoms	2.5±4.0	2.2±4.0	0.75
Constipation	0.9±1.8	0.9±1.8	0.87
Autonomic bladder dysfunction	2.1±2.9	2.4±3.3	0.67
Pupillomotor symptoms	1.3±1.3	1.1±1.2	0.58
Sleep disorder symptoms	1.1±1.3	1.5±1.6	0.23
Syncope symptoms	0.0±0.0	0.1±0.6	0.42
Erectile/Sexual dysfunction (Males only)	6.6±5.9	7.1±6.3	0.82

Data are mean ± SD. * 2-sample t-test (response v non-response)

Table 4.5   Autonomic symptom profile questionnaire scores resolution vs non-resolution

	Resolution (n=85) 24-week Gold < 4		
	No (n=52)	**Yes (n=33)**	**P***
Total	21.3±18.8	20.8±16.6	0.91
Orthostatic intolerance symptoms	8.7±9.7	9.3±9.1	0.77
Vasomotor symptoms	0.6±1.6	0.5±1.5	0.77
Secretomotor symptoms	2.4±3.1	2.2±2.7	0.75
Upper gastrointestinal symptoms	0.8±1.7	0.9±1.8	0.72
Autonomic diarrhoea symptoms	2.6±4.7	1.9±2.7	0.42
Constipation	0.8±1.7	1.0±1.8	0.62
Autonomic bladder dysfunction	2.7±3.5	1.6±2.4	0.15
Pupillomotor symptoms	1.2±1.2	1.1±1.2	0.75
Sleep disorder symptoms	1.4±1.6	1.3±1.3	0.86
Syncope symptoms	0.0±0.0	0.1±0.7	0.22
Erectile/Sexual dysfunction (Males only)	5.9±6.1	8.0±5.7	0.37

Data are mean ± SD. * 2-sample t-test (resolution v non-resolution)

Figure 4.12 Histogram of the autonomic symptom profile questionnaire scores for the entire study population. The count is the number of individuals with a score within any given quantile.
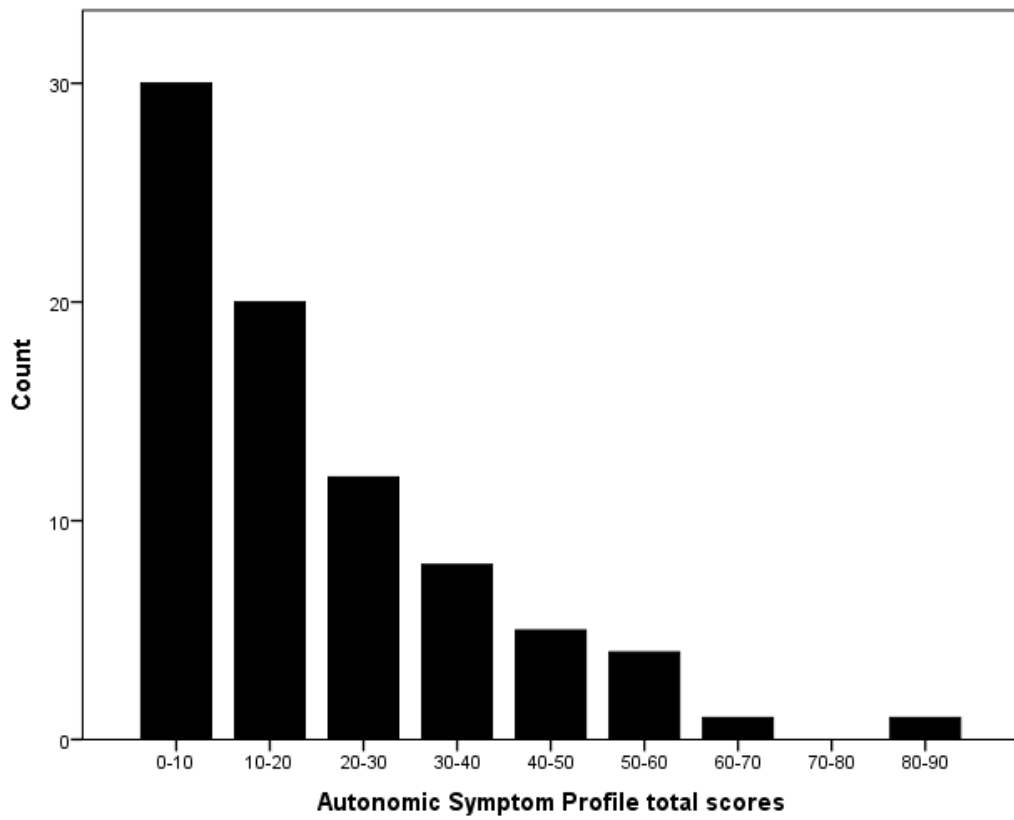
Figure 4.13 Histogram of the autonomic symptom profile questionnaire scores for the non-responders. The count is the number of individuals with a score within any given quantile.

Figure 4.14 Histogram of the autonomic symptom profile questionnaire scores for the responders. The count is the number of individuals with a score within any given quantile.

Figure 4.15   Histogram of autonomic symptom profile questionnaire scores for the non-resolution group. The count is the number of individuals with a score within any given quantile.

Figure 4.16   Histogram of autonomic symptom profile questionnaire scores for the resolution group. The count is the number of individuals with a score within any given quantile.

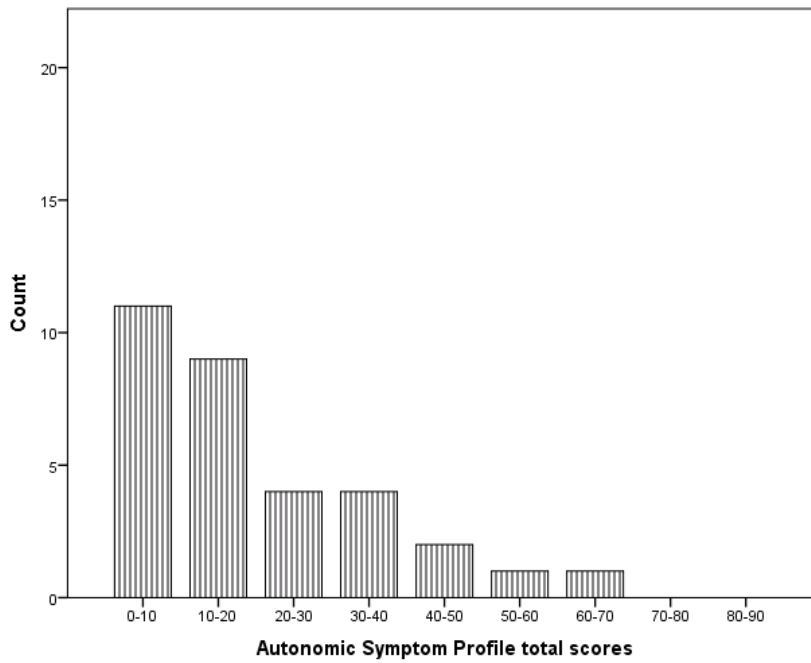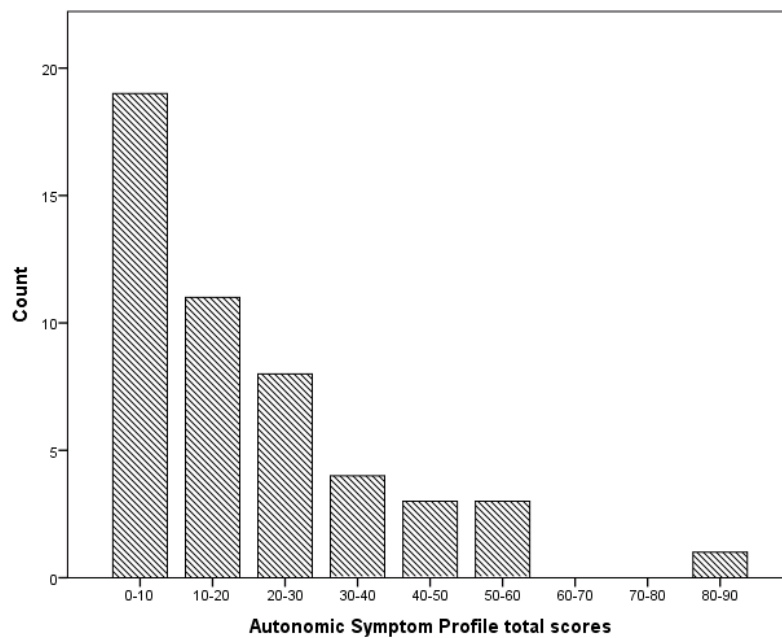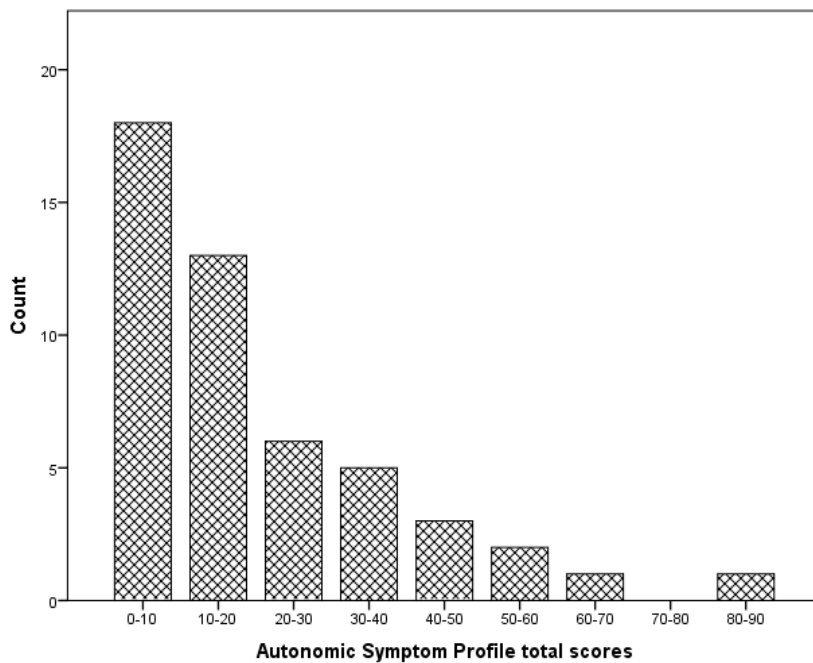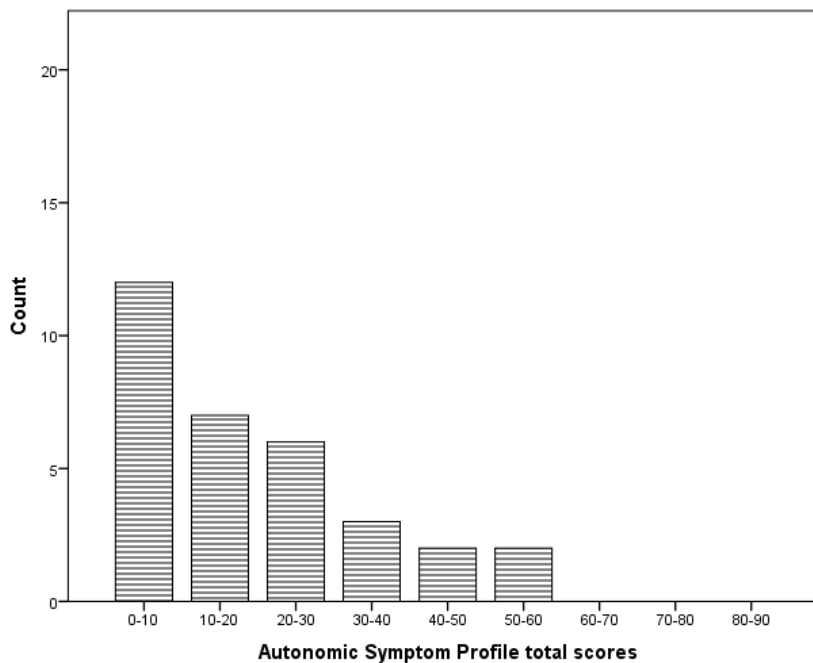152

Figure 4.17 Scatter plot of participant age (years) and ASP questionnaire total scores
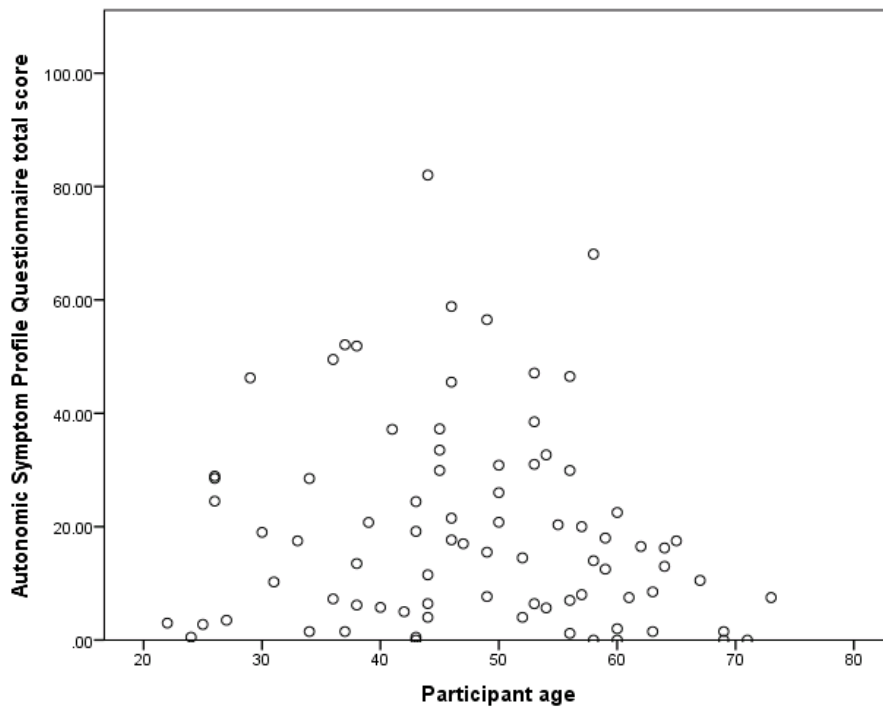

Figure 4.18 Scatter plot of diabetes duration (years) and ASP questionnaire total scores
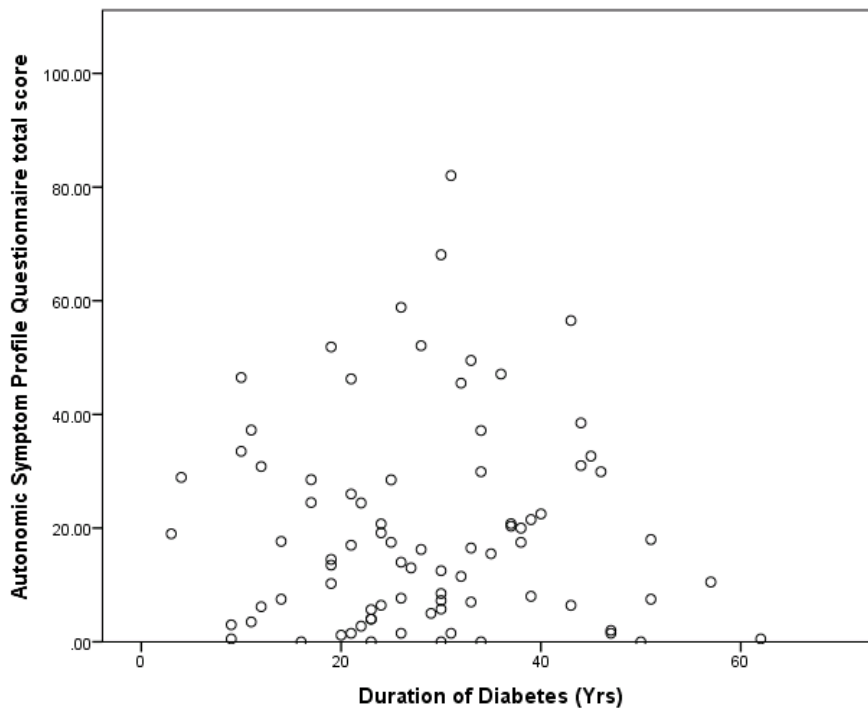
4.7 Discussion

These results show that while there were no significant differences in the clinical characteristics of those who responded as compared to those who did not respond, there was a suggestion that longer duration diabetes and advanced age may impair the ability to regain awareness. Of interest was that the creatinine level was also higher in the non-responders and non-resolution groups. It is known that people with chronic kidney disease (CKD) are more at risk of hypoglycaemia due to multiple factors such as impaired renal gluconeogenesis, reduced degradation of insulin in peripheral tissues (Snyder and Berns, 2004) and poor nutrition, leading to reduction in glycogen stores (Horst *et al.*, 1968). These factors, in conjunction with the failure to replicate the physiological replacement of insulin, make it even more difficult for people with CKD to avoid biochemical hypoglycaemia as necessary to improve their awareness of hypoglycaemia.

The reason why people with longer duration diabetes and advanced age may be less likely to respond was not answered by this study. The study's hypothesis that there would be a group of people identified who were not able to regain awareness with severe autonomic neuropathy, as evidenced by clinical symptoms, has not been proven. It may be that the methods used in this study (the autonomic symptom profile questionnaire) were not good enough to identify those with true diabetic autonomic neuropathy. Further work is required in identifying why age and diabetes duration may impair ability to respond to the interventions.

The autonomic symptom profile questionnaire, at the time of undertaking the study, was the only validated measure of autonomic symptoms available. While it is a comprehensive validated measure consisting of 169 items in 11 domains, and does relate findings to an established protocol of autonomic tests (Suarez *et al.*, 1999), it has a fairly complex layout and weighted scoring system. In previous validation studies of this questionnaire symptoms in people with diabetes (type 1 and type 2) have been significantly higher than control populations (Low *et al.*, 2004). The symptoms identified in the subscales of this questionnaire are clinically relevant and important to identify in a diabetes review consultation. For example the orthostatic intolerance domain identifies

symptoms of cerebral hypoperfusion on standing independently or after meals, physical exertion or with additional heat. The secretomotor sub-scale identifies symptoms of heat intolerance, specific and general changes in body sweating and dryness of eyes and mouth. The urinary sub-scale identifies symptoms of impaired voiding or control. The subscales focusing on gastrointestinal symptoms evaluate gastroparesis (bloating/nausea/vomiting) as well as diarrhoea and constipation. The pupillomotor subscale identifies symptoms such as photophobia, difficulty focusing and blurring in order to detect impaired neural control of the pupils.

However there are no previous publications on the scores of the ASP questionnaire in a population with impaired awareness of hypoglycaemia. It is therefore of some interest that the orthostatic intolerance subscale scores were noticeably higher in the population described in this study as compared to data on other populations with type 1 diabetes published by other groups (mean standardised score 0.13) (Low *et al.,* 2004).

The Hyperglycaemia avoidance scale scores were also similar between the different groups. There were individuals identified with high scores who may have excessive worry about high glucose levels. However in this study even some of these high scorers were responders, suggesting that people with excessive worry should not be excluded from trying the different insulin and glucose monitoring regimens used in this RCT as a mechanism to reduce biochemical hypoglycaemia and improve awareness.

The Gold score was used as a surrogate marker of 'response' and 'resolution'. This has its weaknesses. It is known that the Gold score is insensitive to change and is subject to variability around the score of 4 (Geddes *et al.*, 2007b). Nevertheless it is the current most widely accepted measure of awareness (out-with experimental hypoglycaemia clamp studies). The new measure of hypoglycaemia awareness, the HypoA-Q, may be a measure more sensitive to change. For this reason I plan to reanalyze the data concerning response and non-response once this score's validation studies have been published.

This study was not powered to detect differences between groups. Larger studies need to be carried out in this high-risk population.

Chapter 5

Discussion and Future Research

5.1 Introduction

In recent years there has been an increasing body of literature seeking to elucidate the underlying pathophysiology and risk factors for severe hypoglycaemia (DCCT, 1997; Cryer, 2005; Dunn *et al.*, 2007). While patients, relatives and physicians are aware of the anguish caused by severe hypoglycaemia there has been a lack of interventional trials in high risk populations with the specific goals of addressing these factors, reducing risk and preventing further severe events.

Contemporary approaches to type 1 diabetes management include structured education; psychosocial behavioural strategies supporting self-management; optimised insulin multiple daily injection regimens; CSII therapy; real-time CGM; SAP systems; and beta-cell replacement strategies (pancreas or islet transplantation). Although these have all been justified, at least in part, by their potential impact on reducing severe hypoglycaemia, there is little adequately powered RCT evidence supporting these claims.

5.2 Rationale of the studies in thesis

Of high clinical importance to clinicians providing care for people with T1DM is the lack of randomised control trials comparing widely used analogue multiple daily insulin injection regimens and insulin pump therapy. Previous studies comparing CSII and MDI, arguably have not been optimally designed to assess impact on severe hypoglycaemia. Furthermore there is a possibility that those randomised to pump therapy have received additional 'non-pump' education (Pickup and Sutton, 2008). Despite several trials assessing the impact of real-time CGM, at the time these studies were initiated no previous trials investigating this intervention had recruited high risk populations with IAH, or been powered around their potential to reduce risk of severe hypoglycaemia.

The unique studies in this thesis have investigated the potential for the currently widely available insulin regimens and different methods of monitoring glucose to improve impaired awareness of hypoglycaemia and reduce risk of severe hypoglycaemia in a high risk population. As set out in the methods chapter the RCT in chapter 3 was designed meticulously to provide identical levels of education and professional support to all intervention groups. The study in

chapter 4 has explored the characteristics of a previously under-studied population: one with impaired awareness of hypoglycaemia. The study investigated factors potentially increasing resistance to conventional interventions. This information, if available, could help clinicians develop more holistic care plans, tailored to the needs of the patient.

5.3   Comparison of MDI and CSII

The RCT in chapter 3 compared the outcomes of CSII and MDI in a high-risk population. Baseline rates of severe hypoglycaemia were high and few participants had used pump therapy before. All participants were given equivalent education and support and uniquely those randomised to MDI had access to the same bolus calculator as used by those randomised to CSII. There were no differences in the primary endpoint of Gold score at 24 weeks (MDI 4.1 ± 1.6 vs CSII 4.2 ± 1.7, p=0.76). Nor were there any differences in the secondary markers of glycaemic control including biochemical hypoglycaemia (% time spent ≤3.0 mmol/L: MDI 1.4 ± 2.5 vs CSII 2.0 ± 4.9, p=0.48), 8 point SMBG mean (MDI 8.9 ± 1.6 mmol/L vs CSII 8.7 ± 2.2 mmol/L, p=0.80) and HbA1c (MDI 67 ± 11 mmol/mol vs CSII 64 ± 9 mmol/L, p=0.26). In keeping with other studies treatment satisfaction was higher in those randomised to pump therapy (DTSQ: MDI 29 ± 6 vs CSII 32 ± 3, p<0.001).

5.4   Comparison of RT and SMBG

The factorial design of the RCT in chapter 3 allowed for the comparison of RT and conventional SMBG. Crucially, all participants randomised to these interventions were also given equivalent education and support with identical visit schedules and investigator contact time. There was no difference in the primary endpoint of Gold scores at 24 weeks (SMBG 4.3 ± 1.6 vs RT 4.0 ±1.7, p=0.42). There were no differences in the secondary endpoints of glycaemic control including biochemical hypoglycaemia (% time spent ≤ 3.0mmol/L SMBG 1.3 ± 2.1 vs RT 2.1 ± 5.1, p=0.36), 8 point SMBG mean (SMBG 9.1 ± 2.2 mmol/L vs RT 8.5 ± 1.6 mmol/L, p=0.80) and HbA1c (SMBG 65 ± 9 mmol/mol vs RT 66 ± 11 mmol/mol, p=0.80). In contrast to the comparison between MDI and CSII treatment satisfaction scores were similar between these groups (SMBG 30 ± 5 vs RT 30 ± 5, p=0.79).

5.5 Improvement in awareness of hypoglycaemia and reduction in biochemical and severe hypoglycaemia

While few differences were seen between the intervention arms of the study in chapter 3 the outcomes of the study population as a whole are striking. There was a 10-fold reduction in severe hypoglycaemia events (baseline 8.9 ± 13.4 vs endpoint 0.8 ± 1.9 events/participant/year, p<0.001), with 20% of participants experiencing severe events during the RCT in comparison to 77% over the preceding 6 months and 92% in the preceding year. All measures of hypoglycaemia awareness improved with the Gold score improving from 5.1 ± 1.1 at baseline to 4.1 ± 1.6 at endpoint (p<0.001). Given the lack of a control group these findings need to be treated with some caution. However the immediate and sustained reduction in biochemical hypoglycaemia (% time <3.0mmol/L) falling from 3.7 ± 4.4 at baseline to 1.7 ± 3.9 (p<0.01) and the reduction in severe hypoglycaemia events suggest that the improvement in IAH scores is real.

5.6 Reduction in insulin doses

Across the study population the total daily insulin dose (units/kg) fell from 0.64 ± 0.23 at baseline to 0.53 ± 0.17 at endpoint (p<0.001). Previous studies have reported a reduction in insulin dose with CSII compared to MDI to achieve equivalent glycaemic control (DeVries *et al.*, 2002; Thomas *et al.*, 2007). However a striking finding of the study in chapter 3 is that both the CSII and MDI groups showed equivalent reductions in insulin total daily dose. At study endpoint the total daily insulin dose (units/kg) in the CSII group was 0.55 ± 0.18 as compared to 0.51 ± 0.15 in the MDI group (p=0.31). Importantly, these equivalent dose reductions were not associated with worsening of glycaemic control.

5.7 Fear of hypoglycaemia

While there was an overall significant reduction in Fear of Hypoglycaemia scores across the study population (baseline 58 ± 26 vs endpoint 45 ± 24, p<0.001), the study in chapter 3 demonstrated equivalent reduction in fear of hypoglycaemia in all groups. This is a novel finding as previous studies have tended to favour technology over MDI / SMBG regimens (Rubin *et al.*, 2012).

5.8 The Hypo awareness questionnaire

Due to recognised relative insensitivity of the Gold score to change, a newly designed measure of awareness was included. This showed a much greater magnitude of clinical improvement at study end-point with the score falling from 13.4 ± 3.4 at baseline to 9.1 ± 4.2 at endpoint ($p<0.001$). In keeping with the Gold score comparisons there was no difference in the Hypo-Q score between MDI and CSII (8.9 ± 4.3 vs 9.4 ± 4.2, $p=0.601$) or between SMBG and RT (9.2 ± 4.1 vs 9.0 ± 4.4, $p=0.83$). Validation studies for the HypoA-Q have been undertaken in Newcastle and in Edinburgh and once these are published this questionnaire may become more widely applicable.

In the study in Chapter 4 the Gold score was used as a marker of response to intervention. A one step improvement in Gold score cannot be a good discriminator, and therefore future analyses with a validated HypoA-Q score, which potentially will be more sensitive to change, is planned.

5.9 My hypo compass

The relative impact of the standardised education tool used in the study cannot be assessed. However as discussed in chapter 1 much of the most convincing previous evidence for improved hypoglycaemia awareness has accrued from structured educational programmes (Hermanns *et al.*, 2007; McIntyre *et al.*, 2010). As will be discussed in section 5.13.2 there have been new data recently published suggesting that both established structured educational interventions and novel psychosocial interventions may have a crucial role in reducing severe hypoglycaemia and improving IAH in high risk populations.

5.10 Clinical characteristics of non-responders

While there was a trend towards those with longer duration diabetes and higher age being less likely to demonstrate improved awareness of hypoglycaemia these findings were not significant. It is known that people with chronic kidney disease are at higher risk of severe hypoglycaemia and again there was a trend towards higher creatinine indicating less chance of response. While there

5.11 Autonomic symptoms and hyperglycaemia avoidance

There is evidence that impaired awareness of hypoglycaemia is reversible even in long-standing type 1 diabetes (Cranston *et al.*, 1994), but there may be sub-groups in whom this is particularly difficult to achieve with conventional medical management. One such sub-group includes those who are prepared to accept recurrent hypoglycaemia as a necessary encumbrance for avoiding high glucose levels and thus risk of chronic hyperglycaemia-induced complications. Another may include those with long-standing autonomic dysfunction in whom restoration of autonomic symptoms cannot be achieved solely by short-term absolute avoidance of hypoglycaemia. Neither of these groups were identified in this study which used the autonomic symptom profile questionnaire and hyperglycaemia avoidance scale as outcomes.

5.12 Optimised collection of biomedical glucose data

In the design of the study paper diaries were used for SMBG recording. This was to enable the glucose values to be collected in conjunction with data on what activity/task the glucose measurement related to (i.e. before meals, after meals and before bed). While it may be considered a weakness not to have downloaded the blood glucose meters this would not have provided any context to why the blood glucose measurement was taken.

While those participants randomised to RT were encouraged to use the sensors for at least 3 days every week, this was not mandated. This was to improve the relevance of the results of the study to real life clinical practice. However this may be deemed a limitation of the RCT in chapter 3.   While a potential weakness may have been not to collect all the data from the RT devices, a strength of the study was the equivalent methods of collecting continuous glucose monitoring data from all groups by use of the professional / blinded CGM. In this way the burden of all biochemical hypoglycaemia could be assessed using % time under a range of values across the entire study population.

5.13 Advances in the field

5.13.1 Real-time CGM

As discussed in chapter 1 when these studies were initiated there was little evidence that RT significantly reduced severe hypoglycaemia. Factors for this include the low baseline rates of hypoglycaemia amongst the participants randomised in previous trials, and in keeping with studies investigating the impact of analogue insulins, excluded those at highest risk. There is also evidence from studies that participants have slept through the low glucose alarms on the RT CGM devices overnight (Buckingham *et al.*, 2005).

However since the studies in this thesis were undertaken the first two randomised control trials investigating the use of insulin pump therapy with automated insulin suspension (termed 'low glucose suspend') have been published (Bergenstal *et al.*, 2013; Ly *et al.*, 2013). The low glucose suspension function enables insulin delivery to be stopped automatically for up to 2 hours when sensor glucose falls below a pre-set threshold.

In the first study published by a group in Australia (Ly *et al.*, 2013), which was partly funded by Medtronic, 95 individuals who were all pump users pre-study, were randomised to either continuing standard CSII therapy or to CSII therapy with the low glucose suspend feature (LGS). As an example of the non-standardised way hypoglycaemia is reported in clinical trials, in this study moderate hypoglycaemia was defined as an event requiring the assistance of another person whereas severe hypoglycaemia was classified as a hypoglycaemic seizure or coma.

All individuals randomised to the LGS group received an additional education session before commencing this intervention, a visit not matched in the standard pump therapy arm. Furthermore those using LGS system were advised to upload their data weekly to Medtronic's online software for data analysis, whereas those randomised to standard pump therapy continued under their pre-study clinical team for standard clinical review.

This study attempted to recruit those at high risk of severe hypoglycaemia by including the need for IAH as defined by the Gold score as an eligibility criteria. However although the participants recruited all had Gold and Clarke scores ≥ 4

at recruitment, unlike the participants of the studies in this thesis, the baseline rates of severe and moderate hypoglycaemia were low. The reason for the low baseline rate of severe hypoglycaemia may be that the participants were all much younger (range 4-50 years, mean <20 years) and had shorter duration diabetes (mean <13 years) as compared to mean of 28.9 years in the studies of this thesis. Of note, in each of the randomised groups fifteen of the participants were less than 12 years old. The study did show a significantly bigger reduction in combined severe and moderate hypoglycaemia rates with LGS than with standard pump therapy.

The second randomised controlled trial which has reported is the ASPIRE study, also published in 2013 (Bergenstal *et al.*, 2013). This multicentre study evaluated the effect of LGS compared to sensor augmented pump therapy (CSII with RT CGM). Potential participants were excluded from this study if they had history of more than one episode of severe hypoglycaemia (defined as coma, or seizure or requiring medical assistance) within the previous six months. Mean diabetes duration was longer than the Ly study at > 26 years and the visit schedule for the study was identical for both intervention groups. Of note, this study was also sponsored by Medtronic and representatives of the study performed data collection and provided editorial assistance to early versions of the manuscript.

In this study there was a two-week run in phase, during which time participants had to use the sensors at least 80% of the time, and have at least 2 episodes of nocturnal hypoglycaemia to be eligible for randomisation. Nocturnal hypoglycaemia was defined as 3.6 mmol per litre or less between 10pm and 8am for more than 20 consecutive minutes. 247 patients were randomised and included in the intention to treat analysis. The primary efficacy endpoint in the study was the area under the curve (AUC) for nocturnal hypoglycaemic events. The study reported that the AUC (mean ± SD) for nocturnal hypoglycaemia in the low glucose suspend group was 37.5% less than that of the control group (54.4 ± 66.6 mmol per litre x minutes vs 87.0 ± 110.7 mmol per litre x minutes, p<0.001). There were no severe hypoglycaemia events in the low glucose suspend group and four severe hypoglycaemia events in the sensor augmented pump group. This was a relatively short study at 3 months duration and

therefore the long term outcomes of the low glucose suspend feature are not yet known.

While these have been the first randomised studies evaluating LGS, non-randomised studies have shown reduced nocturnal hypoglycaemia with this technology.

5.13.2 Structured education and motivational approaches

The impact of the 'my hypo compass' tool (Little *et al.*, 2012a) cannot be assessed in the these studies. It was included as a way to ensure that all investigators were providing standardised advice on hypoglycaemia avoidance and treatment in a multicentre study. However given the immediate reduction in biochemical hypoglycaemia upon randomisation it may be that this tool played a significant role. Indeed as discussed in chapter 1 much of the most convincing previous evidence for improved hypoglycaemia awareness has accrued from structured educational programmes.

Since these studies were undertaken the DAFNE group have published new data. In an audit of participants attending courses in one year, 43% of those with impaired awareness at course entry (40% of the total) had restored awareness at one year (Hopkins *et al.*, 2012). In the same study there was also a significant reduction in the severe hypoglycaemia rate from 1.7 ± 8.5 to 0.6 ± 3.7 episodes/person/year (p <0.001), within one year of undertaking the programme.

Recently the DAFNE group have developed a new intervention which uses motivational interviewing and cognitive behavioural techniques to help individuals with impaired awareness of hypoglycaemia regain awareness. DAFNE HART is a 6 week course involving a 2 day workshop and weekly supervision which was in person, by telephone and by email, and involves input from a clinical psychologist.

In a recent pilot study 23 participants with confirmed Gold score ≥4 and mean diabetes duration 30.7 ± 11.9 years completed the programme (de Zoysa *et al.*, 2014). The severe hypoglycaemia rate (median, (range)) fell from 3.0 (0-104) to 0 (0-3) events per patient per year (p<0.0001). There was also a significant reduction in the Gold score, which fell from 5.6 ± 1.4 at baseline to 4.5 ± 1.9 at

12 months (p<0.029). It is notable that perhaps because the Gold score is insensitive to change, the 12-month mean Gold score was still within the 'unaware' range despite the improvement. There was a significant reduction in Clarke scores (mean ± SD) from 5.4 ± 1.2 at baseline to 3.8 ± 1.8 at 12 months (p<0.001). The endpoint mean Clarke score was in the 'aware' range. This pilot study also assessed hypoglycaemia avoidance scale (HAS) scores before and after the intervention. There were significant reductions in the behaviour and worry sub scale scores 12 months following the intervention,

This was an uncontrolled pilot study but the evidence of increased awareness, reduced severe hypoglycaemia events and interestingly reduced HAS scores suggest that the motivational approaches may be very relevant to this high risk population – a population very similar to that in HypoCOMPaSS.

5.13.3 Islet cell transplantation

Data has recently been published regarding the metabolic outcomes of the UK's nationally funded integrated islet transplant program (Brooks *et al.*, 2013). In this study the results of 20 individuals who had undergone a total of 25 islet cell infusions are provided. Severe hypoglycemia was reduced from 20 (7-50) episodes/patient-year pre-transplant to 0.3 (0 - 1.6) episodes/patient-year post-transplant (p<0.001). Resolution of impaired hypoglycemia awareness was confirmed [pretransplant: Gold score 6 (5 - 7); 24 (13.5 - 36) months: 3 (1.5 - 4.5); p< 0.03]. Beta-cell replacement through transplantation of whole pancreas or isolated islets can undoubtedly prevent recurrent severe hypoglycaemia. Unfortunately, for as long as there is an on-going requirement for full systemic immunosuppression, transplantation can only be considered for the minority with truly life threatening hypoglycaemia or those who have previously had another type of transplant.

5.14 Future work

5.14.1 Follow up study

An 18 month follow up study to the 24-week RCT is ongoing to assess the sustainability of the interventions. At the end of the RCT participants returned to routine clinical care with those randomised to CSII able to continue using this

if they so wished as NICE criteria had been met upon recruitment. Those randomised to RT were not provided with more sensors. All participants of the RCT will be invited 6, 12 and 18 months after the end of the study for repeat blinded CGM profiles, data collection on severe hypoglycaemia incidence and 8 point SMBG, repeat questionnaire completion including Gold, Clarke, Hypo-Q, DTSQ and HAS. Given the relatively short 24-week duration of the RCT it crucial to assess the longer-term impact of the study interventions.

5.14.2 Cardiac autonomic function data

As part of the HypoCOMPaSS study cardiac autonomic function tests were undertaken. This data will be analysed by colleagues in Sheffield. I plan to investigate the correlation of the autonomic symptom profile questionnaire with the cardiac autonomic function test results in the unique HypoCOMPaSS study population.

5.14.3 HypoCOMPaSS sub study

The population in HypoCOMPaSS was a unique sub-group of the population with type 1 diabetes. A control group is needed to compare the same outcomes in individuals with type 1 diabetes but with intact awareness. This study is taking place with fellow investigators from Sheffield. They are recruiting individuals with type 1 diabetes and intact awareness of hypoglycaemia as confirmed by a Gold score ≤ 3 at baseline. The participants will be undertaking cardiac autonomic function testing, completing the ASP questionnaire and undertaking hypoglycaemic hyperinsulinaemic clamp studies.

5.14.4 A study to investigate the impact of 'my hypo compass'

The study undertaken in chapter 3 highlights the need to undertake a randomised control trial of impact of the 'my hypo compass' intervention in individuals with T1DM and IAH. In the RCT 'my hypo compass' was carried out over a single 1-2 hour session and was facilitated by the site investigator. Although brief training on its use had been had been provided at the site initiation visit, educators did not have psychology qualifications. It may therefore be a more accessible intervention than the 6-week DAFNE HART intervention (described in section 5.13.2).

5.14.5 Further analyses of psychosocial measures

The hyperglycaemia avoidance scale was completed by all participants at baseline and at endpoint. While the hypothesis in the study in Chapter 4 was driven by the baseline phenotype, I plan to investigate whether the use of the biomedical interventions in this thesis impacted on behaviours such as having a 'low glucose preference' by analysing paired questionnaire scores.

As part of the HypoCOMPaSS study a range of other validated and non-validated psychosocial measures were recommended from Kings College London and included in the study protocol. I plan to use these measures to further investigate whether there are any subtle correlates with non-response to the interventions studied.

5.14.6 Correlating neuroimaging with phenotype

The increasing body of literature assessing the neuroimaging with IAH and risk of severe hypoglycaemia are of great interest. However it is yet to be seen how these people can be identified in routine clinical practice. It would be of interest to undertake neuroimaging of the HypoCOMPaSS study population and correlate this with the phenotypes described in the study in chapter 4 of this thesis.

5.14.7 Potential role of c-peptide microsecretion

As discussed in chapter 1 the presence of c-peptide was shown in the DCCT study to protect against severe hypoglycaemia through an as yet unidentified mechanism (DCCT, 1997). Recently there has been improvement in the sensitivity of c-peptide assays. A recent study has shown that in a group of 74 individuals with type 1 diabetes (as defined as diagnosis <30 years old or diagnosed >30 years old with positive islet autoantibodies), c-peptide was detectable (>3.3 pmol/L) in 54 (73%) (Oram *et al.*, 2014). The phenotype of this group including status of hypoglycaemia awareness is not known. Therefore further research is needed to characterise apparent non-responders from responders in terms of c-peptide micro secretion. A further study is planned to invite all HypoCOMPaSS participants for a mixed meal tolerance test to have c-

peptide serum analysis using an electrochemiluminescence immunoassay with a reported limit of detection of 3.3 pmol/L.

5.15   Conclusions

Awareness of hypoglycaemia can be improved and recurrent severe hypoglycaemia prevented in people with long duration type 1 diabetes without relaxing HbA1c. Similar biomedical outcomes can be attained with conventional MDI and SMBG regimens compared with CSII and RT. All individuals may benefit from biomedical interventions aimed at improving awareness of hypoglycaemia. Disease duration and age did not correlate with degree of autonomic dysfunction symptoms in this research, though there is a suggestion that those with the highest scores were less likely to respond. This research provides a basis for further studies investigating impact of new technologies on IAH, severe hypoglycaemia and behaviour change. This research underlines the importance of tailoring treatment to avoid biochemical hypoglycaemia without relaxing overall control.

Appendices

6.1 Appendix 1: The hypoglycaemia awareness questionnaire (HypoA-Q)

The Hypo Awareness Questionnaire

These questions are about your recent experience of hypoglycaemia, also known as low blood glucose, having a 'hypo' or going 'low'. Please tick the one box ☑ on each line that best describes your experience. There are no right or wrong answers. We just want to know about your experiences.

1. In the past week, how often have you had any hypo (mild or severe, day or night)? ____ times (please enter a number)

2. In the past 6 months, how often did you have a hypo where …

   a) … you needed help / were unable to treat yourself? ____ times (please enter a number)

   b) … emergency services were called to help you? ____ times (please enter a number)

   c) … you were taken to hospital (A&E) for treatment? ____ times (please enter a number)

   d) … you were admitted to hospital (overnight or longer)? ____ times (please enter a number)

A. 'Hypos' when you are awake

	Never	Once or twice	Three or four times	About once or twice a month	About once a week	More than once a week
3. In the past 6 months, how often have you had any 'hypo' when awake?	☐	☐	☐	☐	☐	☐

4. In the past 6 months, how often have you had any 'hypo' when awake where you …	Never	Once or twice	Three or four times	About once or twice a month	About once a week	More than once a week
a) … had symptoms and were able to treat yourself?	☐	☐	☐	☐	☐	☐
b) … had symptoms and were unable to treat yourself?	☐	☐	☐	☐	☐	☐
c) … needed someone else to give you sugar by mouth (e.g. a drink, carbohydrate, glucose gel)?	☐	☐	☐	☐	☐	☐
d) … needed someone else to give you a glucagon injection?	☐	☐	☐	☐	☐	☐

5. In the past month, have you had blood glucose readings (in mmol/l) …			If yes, how often did you have hypo symptoms?				
			Never	Rarely	Sometimes	Often	Always
a) … 3.5 to 3.9?	Yes ☐ No ☐ Don't know ☐		☐	☐	☐	☐	☐
b) … 3.0 to 3.4?	Yes ☐ No ☐ Don't know ☐		☐	☐	☐	☐	☐
c) … 2.5 to 2.9?	Yes ☐ No ☐ Don't know ☐		☐	☐	☐	☐	☐
d) … less than 2.5?	Yes ☐ No ☐ Don't know ☐		☐	☐	☐	☐	☐

6. How low does your blood glucose usually need to be before you feel any of the following symptoms?	4.0mmol/l or above	3.5-3.9 mmol/l	3.0-3.4 mmol/l	2.5 -2.9 mmol/l	Below 2.5mmol/l	I do not have these symptoms
a) Trembling, shakiness, pounding heart, warmth, sweating, hunger	☐	☐	☐	☐	☐	☐
b) Weakness, lack of coordination, confusion, dizziness, inability to concentrate, difficulty speaking, blurred vision, drowsiness, tiredness, irritability, odd behaviour	☐	☐	☐	☐	☐	☐
c) Nausea, tingling, headache	☐	☐	☐	☐	☐	☐

	Never	Rarely	Sometimes	Often	Always
7. I have symptoms when my blood glucose is low	☐	☐	☐	☐	☐
8. I 'just know' when I am going hypo by the way that I feel	☐	☐	☐	☐	☐
9. I check my blood glucose level if I feel 'low'	☐	☐	☐	☐	☐
10. Other people recognise I am hypo before I do	☐	☐	☐	☐	☐

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
11. I am less aware of my hypos coming on than I used to be	☐	☐	☐	☐	☐
12. I have lost symptoms I used to have when my blood glucose is low	☐	☐	☐	☐	☐
13. In the past 6 months, I have been more aware of my hypos coming on than I used to be	☐	☐	☐	☐	☐

14. Is there anything else you would like to mention about your hypos or your awareness of hypos when you are awake? If so, please write it in this box.

6.2

B. 'Hypos' when you are asleep

		Never	Less than one a month	About once or twice a month	About once a week	About twice a week	Most days
15.	In the <u>past 6 months</u>, how often have you had a hypo <u>during your sleep</u>?	☐	☐	☐	☐	☐	☐

		Never	Less than one a month	About once or twice a month	About once a week	About twice a week	Most days
16.	In the <u>past 6 months</u>, how often have you had a hypo <u>during your sleep</u> …						
	a) … and were <u>unable</u> to treat yourself when you woke up?	☐	☐	☐	☐	☐	☐
	b) … and someone else gave you sugar by mouth (e.g. a drink, carbohydrate, glucose gel)?	☐	☐	☐	☐	☐	☐
	c) … and someone else gave you a glucagon injection?	☐	☐	☐	☐	☐	☐
	d) … which led to a major problem (e.g. a fit, tongue biting, fall, collapse, incontinence)?	☐	☐	☐	☐	☐	☐
	e) … where you stayed asleep and only later realised that you had been hypo?	☐	☐	☐	☐	☐	☐

During my sleep...	Never	Rarely	Sometimes	Often	Always	Not Applicable
17. … I have symptoms which wake me when my blood glucose is low	☐	☐	☐	☐	☐	
18. … other people recognise that I am hypo before I do	☐	☐	☐	☐	☐	☐
19. … my insulin pump / monitoring device wakes me when my blood glucose is low	☐	☐	☐	☐	☐	☐

20. Is there anything else you would like to mention about your hypos or your awareness of hypos when you are <u>asleep</u>? If so, please write it in this box.

Thank you. Please check that you have answered all the questions.

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6.2 Appendix 2: Participant handbook for my hypo compass

Hypo C✦MPaSS
Comparison of Optimised MDI versus Pumps with or without Sensors in Severe Hypoglycaemia

My Hypo Compass
Participant Handbook

Name:

Date:

My hypo compass ✦

Aims

In this session ('my Hypo Compass'), we aim to help you to identify successful ways to avoid severe hypoglycaemia (very low blood glucose). We will do this by referring to four key issues (matching the four points of the compass).

Before starting, please take a few moments to think about what you would like to achieve from this session to help you develop ways of preventing future hypos.   Write your own aims in the box below.

My aims from this session

Do you have any questions for the facilitator or do you have any issues about avoiding low blood glucose? Please make a note of any issues in the box below. You will be able to reflect on these at the end of the session. If your aims, questions and issues are not addressed during the session, there will be time at the end to discuss them with the facilitator.

My questions / issues about avoiding low blood glucose

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The hypo compass

Now!
No delay

Wary even
While asleep

Establish your
Extra risks

Scan for
Subtle
Symptoms

Section 1

**Now!
No delay**
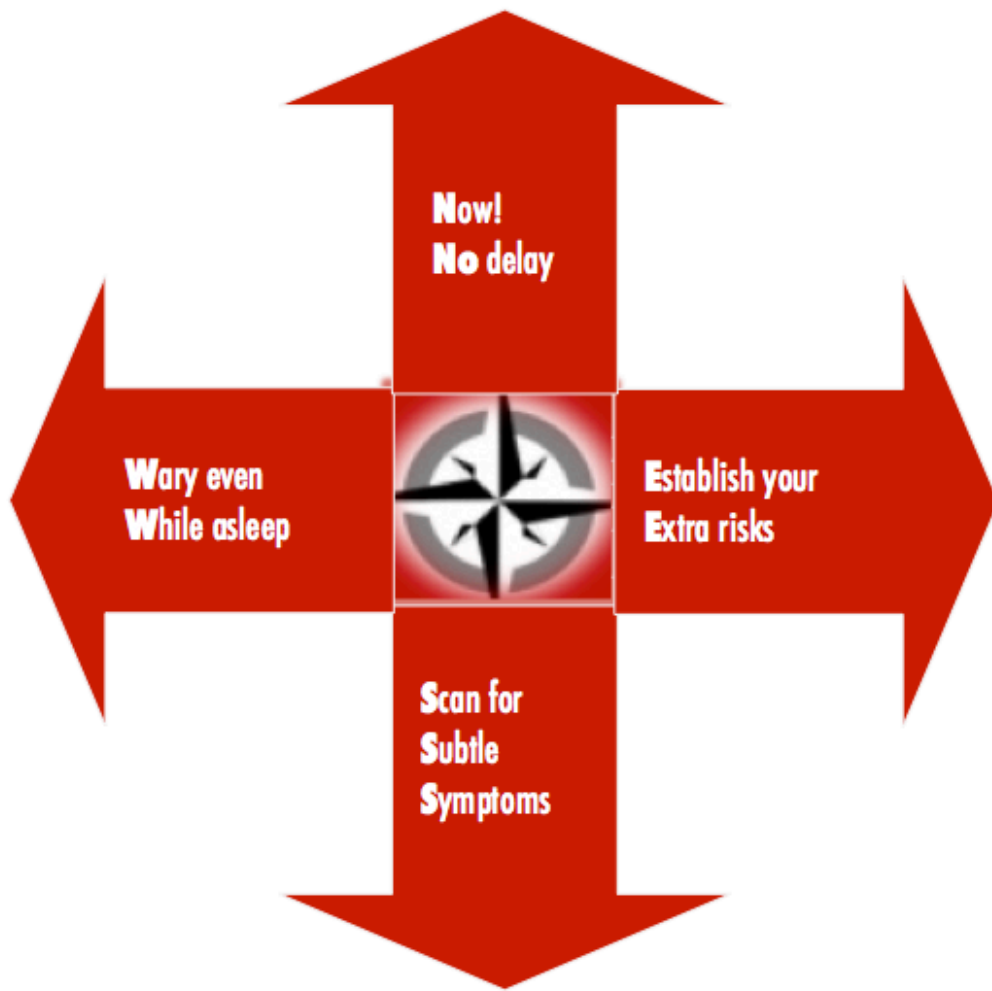
At what blood glucose level would you treat yourself for being 'hypo' (even if there are no symptoms)?

Sometimes, people don't treat a hypo straight away.
Have you ever **not** treated a hypo as soon as you recognised it?
If so make a list of the reasons for this here.

What do you currently use to treat your hypos?

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What do you dislike / like about your hypo treatment?

Dislikes	Likes

What do you think is the best treatment for a hypo?

Where do you keep your hypo treatment?

Can you think of any other places to keep your hypo treatment? (think of places where you've had hypos previously)

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At the end of this section, after discussion with the facilitator complete the following table.

When treating hypos in the future:

What is the lowest blood glucose I would want before treating?	
How will I avoid delays to treatment?	
What will I use to treat a hypo?	
Where will I keep my hypo treatment?	

Key messages in Section 1

- 'Don't ignore a glucose less than 4' - treat any blood glucose <4mmol/L to avoid hypos and rebound high glucose levels

- Never delay treatment of low blood glucose.

- Use rapid acting carbohydrates (e.g sugary drink) to treat your hypo most effectively.

- Identify your own preferred treatment for a hypo.

- Keep your treatment close at hand at all times – including bedside.

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Section 2

Establish your Extra risks

When are you most at risk of having a hypo?

Are there any activities which increase your risk of having a hypo?

Have you had any hypos that have been directly related to food or drink?

Have you ever had any hypos that you think have been due to your insulin acting more strongly than normal? Why do you think this was?

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Have you ever been frustrated at how long it has taken for your blood glucose to fall after eating and therefore given extra insulin, only to a have hypo later?

When else do you think you are at extra risk of having a hypo?

Key Messages in Section 2

- Look for hypo patterns (When? Where? Why?).

- Identify times when you are more likely to have low blood glucose.

- Avoid Insulin Stacking.

Section 3

Scan for
Subtle
Symptoms

Even if you have lost most of the symptoms of hypoglycaemia that you used to have, you may still be able to identify some subtle signs. You may also have your own way of trying to recognise symptoms (e.g. noticing that you are typing the wrong keys on a computer keyboard or that you can't do some simple maths in your head). Make a list of any of any symptoms you experience in the box below.

All symptoms can change over time. Each person with diabetes has their own unique warning signs. You may find that you experience different symptoms of hypoglycaemia from other people with diabetes. You may also find that each hypo event (or episode) has its own symptoms and signs.

Have a look at the table on the next page. Do you have any of these symptoms when you have a hypo? Please circle any symptoms that apply to you.

My hypo compass participant handbook version 3.0

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How do you feel physically?	How do you feel emotionally?	What is your performance like?
Trembling	Sad	Feel sluggish
Pounding heart	Relaxed	Unexplained sleepiness
Flushed face	Confident	Difficulty concentrating
Sweating	Energetic	Slowed thinking
Warm hands	Uneasy	Difficulty finding right word
Numb lips/mouth	Happy	Light headedness
Fast pulse	Worried	Slurred speech
Blurred vision	Nervous	Making more mistakes
Queasy stomach	Distressed	Doing things more slowly
Heavy breathing	Irritated	Taking more effort than usual
Headache	Frustrated	
Heavy legs	Angry	
Feeling cold	Stubborn	
Weakness/Fatigues		
Dilated pupils		
Deep hunger		
Tingling in legs		

Make a note here of any more subtle symptoms or feelings you may experience at the beginning of a hypo, that you could watch out for in future and that might remind you to treat a hypo early.

Key Messages in Section 3

- Be aware of subtle symptoms or signs that suggest you may be having a hypo.

- At times of high risk of if you think you might be hypo, scan your body for any symptom or sign.

- Make this into a routine but do it especially if you suspect any mismatch between your insulin, food and physical activity.

- Make a note of how you would check or test yourself to see if you might be hypo.

Section 4

Do you ever have hypos at night?

Wary even While asleep

Do you ever wake up in the morning with symptoms of headache / feeling hung-over / lethargy or just feel as though you're not functioning properly?

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Have you ever found your blood glucose levels to be variable (or even erratic) first thing in the morning?

Is there anything you could do to make it easier for you to check your blood glucose?

Section 4 Key Messages:

- You may be at increased risk of hypoglycaemia overnight when asleep. Consider setting an alarm to check blood glucose at night.

- Be wary of hypoglycaemia at any time of day and night – if in doubt check!

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Summary

1. 'Don't ignore a glucose less than 4' – treat any blood glucose <4 mmol/L to avoid hypos.

2. Never delay treatment of low blood glucose.

3. Use rapid acting carbohydrates (e.g. sugary drink) to treat your hypo most effectively.

4. Identify your own preferred treatment for a hypo.

5. Keep your treatment dose at hand at all times – including bedside.

6. Look for hypo patterns (When? Where? Why?)

7. Identify times when you are more likely to have low blood glucose.

8. Avoid insulin stacking.

9. Be aware of subtle symptoms or signs that suggest you may be having a hypo.

10. At times of high risk or if you think you might be hypo, scan your body for any symptom or sign.

11. Make this into a routine but do it especially if you suspect any mismatch between your insulin, food and physical activity.

12. Make a note of how you would check or test yourself to see if you might be hypo.

13. You may be at increased risk of hypoglycaemia overnight when asleep. Consider setting an alarm to check blood glucose at night.

14. Be wary of hypos at any time of day and night – if in doubt check!

Now that you have completed the session, go back to the front page. Has this session achieved your personal aims? Have your questions and issues been addressed? If you have any outstanding queries, please ask your facilitator about them now.

Finally, you might find it useful to complete the summary on the final page to use in the future as an aide memoire.

My key reminders

Now!
No delay

Wary even
While asleep

Establish your
Extra risks

Scan for
Subtle
Symptoms
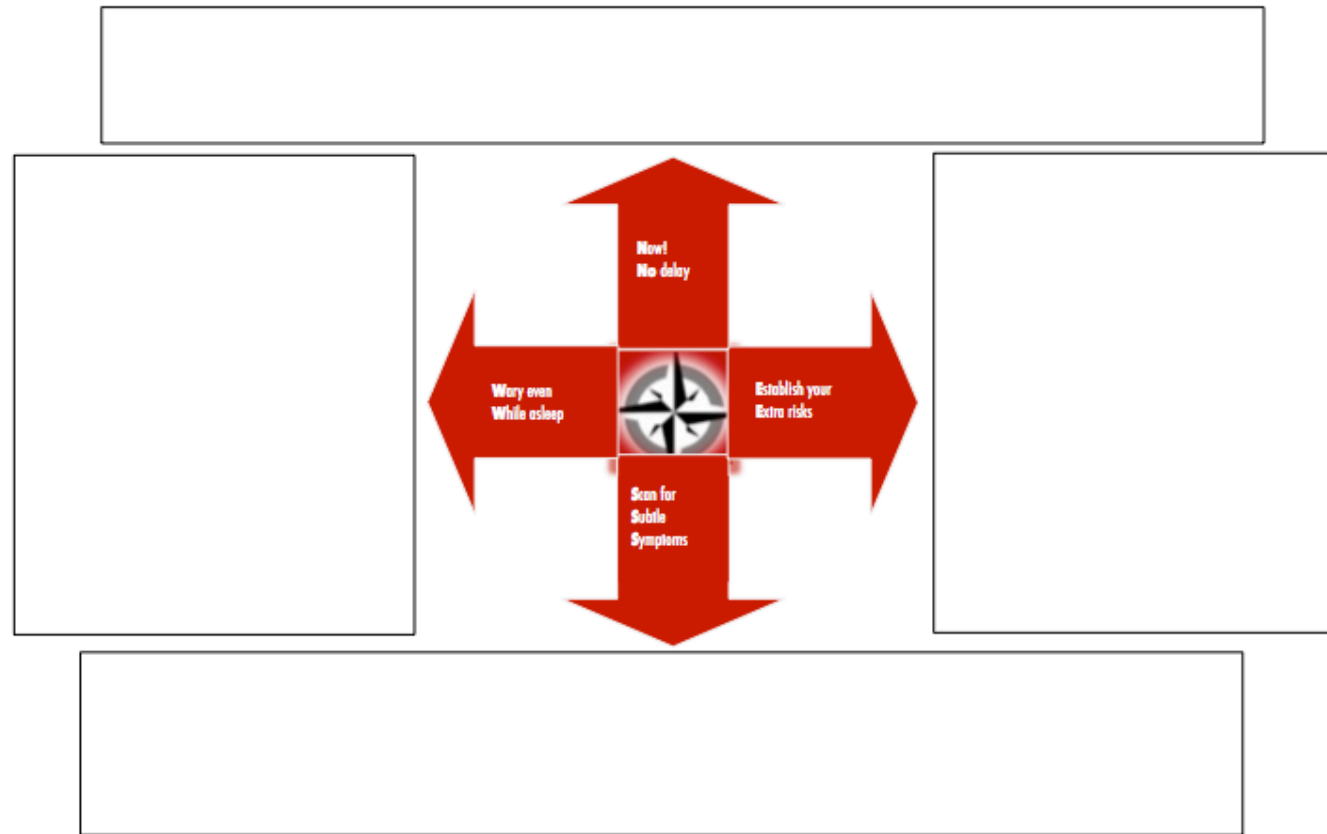
6.3   Appendix 3: Facilitator handbook for 'my hypo compass'

Hypo C⊕MPaSS
Comparison of Optimised MDI versus Pumps with or
without Sensors in Severe Hypoglycaemia

My Hypo Compass
Facilitator Handbook

My hypo compass ⊕

Philosophy and Principles of My Hypo Compass

As healthcare professionals, we have expert knowledge about hypoglycaemia and its associated risk factors. However, we readily acknowledge that only our patients have expertise about their own diabetes and their own lives. It is our responsibility to help our patients explore their own expertise to highlight their own unique risk factors for hypoglycaemia and the obstacles which can prevent optimal treatment.

People are responsible for their own self management. As healthcare professionals we can only ever have limited responsibility and influence over a person's diabetes outcomes. We are responsible for providing up to-date evidence-based information, ensuring people are aware of their risks and helping them to identify successful strategies for minimising those risks. We need to support people in the development of their own strategies for preventing and managing hypoglycaemia.

Hypoglycaemia remains one of the most feared complications of insulin treatment, as it can lead to blackouts, seizures and collapse without warning. However, in the real world there are many barriers to optimal self management, which may hamper the individual's efforts to achieve optimal outcomes or change their motivational focus. As healthcare professionals, we need to acknowledge these barriers with empathy at all times.

My Hypo Compass – Session timetable

Section	Time needed in minutes
Introductions	5
Aims	10
Section 1:Treatment of hypoglycaemia	30
Section 2: Risk factors for hypoglycaemia	30
Break	20
Section 3: Identifying hypoglycaemia	30
Section 4: Being wary about hypoglycaemia	30
Summary including Questions and Answers	10

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The Hypo Compass

There are four main sections to this fully interactive session: treatment, risk factors, identification and being wary about hypoglycaemia. These correspond to the four points of the hypo compass (Figure 1).
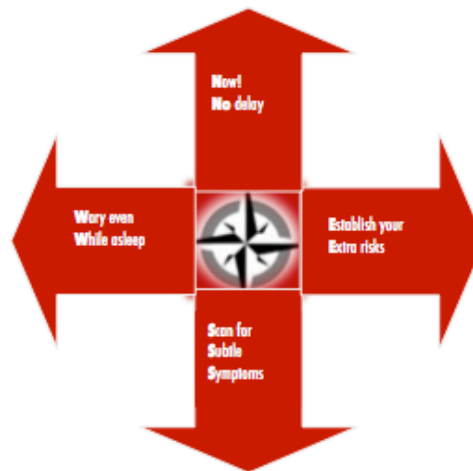
Figure 1: The Hypo Compass

Participants are encouraged to write down their answers to the questions raised in the participant handbook. The participant can then reflect on these answers, and with the facilitator, can formulate individualised 'take home messages'.

Each section has key learning outcomes and specific facilitator activities, such as asking certain questions, and discussing and emphasising particular points. Each section may also require the facilitator to elicit or provide key information to help achieve the learning outcomes. This is all outlined on the following pages.

Materials Needed

You will need:
- Whiteboard / flipchart & pens
- Your own copy of the Participant Handbook
- One copy of Participant Handbook and pens per participant
- Post-it notes
- One 'HypoCompass' poster (and some blu-tack or other means of fixing it)

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Aims of My Hypo Compass

Learning Outcomes	Facilitator Activities	Section plan
Understand that the overall aims of 'My Hypo Compass' are to: 1. Identify the obstacles which may prevent optimal management and develop strategies to overcome them. 2. Identify own risk factors for having a hypo which will help to minimise them. 3. Identify any subtle symptoms of a hypo which may lead to earlier treatment. 4. Recognise the importance of being wary of hypos at all times of the day and night.	**Questions** 1. Ask what the person's own objectives are from the session. 2. Ask the person to write down any questions or issues they may have about avoiding low blood glucose. **Explain** If any questions / issues raised are not addressed during the session, there will be time at the end to discuss them. **Illustrate** Using the 'My Hypo Compass' poster show how the learning outcomes for the session will be met by discussion around the four points of the compass	Start by explaining the principles of 'my hypo compass' as outlined in the introduction. Elicit what the participants hope to achieve using the facilitator questions. Some participants may be concerned that avoiding lows will lead to higher blood glucose levels and increase risk of future complications. Reassure that many questions are likely to be answered during the session and objectives covered but there will be an opportunity for any outstanding issues to the discussed at the end. Give the participants some time to look at the hypo compass poster and then discuss as a group how each learning outcome links with each point of the compass.

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Section 1: The Treatment of Hypoglycaemia

Now!
No delay

Learning Outcomes	Facilitator Activities	Section plan
1. Understand that any blood glucose less than 4mmol/L requires treatment to avoid a 'hypo' – 'don't ignore a glucose less than 4'. 2. Understand that the treatment of low blood glucose should never be delayed. 3. Understand that rapid acting carbohydrate should be used for the most effective treatment. 4. Identify own preferred treatment of a hypo. 5. Understand that every attempt should be made to ensure that this treatment is easily accessible at all times.	**Question 1** At what blood glucose level would you treat yourself to avoid a 'hypo' (even if there are no symptoms)? **During discussion emphasise:** • 'Don't ignore a glucose less than 4' (even if there are no symptoms.) • The need to always consider treatment of a blood glucose less than 4mmol/L (even if there are no symptoms.) **Question 2** Have you ever not treated a hypo as soon as you recognised it? **Discussion Points** • The identification of reasons for possible delayed treatment. Examples may include: I. a lack of carbohydrate / food available at the time II. occurring at a socially inconvenient time (eg in cinema, theatre, meeting, work place / while doing housework etc) III. Didn't want to deal with it just then – 'I'll finish off what I'm doing'. IV. Lack of perceived urgency / something else more important taking attention. V. When having a hypo just before a planned meal and thinking that you will be OK until the meal is ready ('dinner's in the oven'). **Emphasise** • Emphasise that everyone has their own reasons (conscious or unconscious) and no-one will judge them for whatever their reason is for delaying treatment. • Every attempt should always be made to never delay the treatment. **Question 3** What do you currently use to treat your hypos? **Discussion Points** (use the whiteboard to make a list) • What are effective treatments? • What doesn't work so well and why not?	**Key information for participant to know by end of this section:** Treating low blood glucose quickly is important as it is very easy for the glucose level to fall quickly to a point where you may not be able to self-treat. Low blood glucose must be raised as quickly as possible by taking approximately15 grams of rapid acting carbohydrates (4-5 glucose tablets, half a tube of hypostop, 90mls of fruit juice, cola, lemonade, or Lucozade). Certain sweets like jelly beans and jelly babies (4 jelly babies are equivalent to about 4 glucose tablets) are also very quick acting and easy to carry around. Treatment for hypoglycaemia should be easily portable. Do not wait for the blood sugar to get lower or for symptoms to appear before starting treatment.

My hypo compass facilitator handbook v3.0

- Are long acting carbohydrates useful as a follow-up treatment?

Question 4
What do you like / dislike about your hypo treatment?

Discussion Points
- Some people may not like taste or 'mouth-feel' of suggested treatments, e.g. glucose tablets or Lucozade.
- Alternative options which may better suit different individuals
- Some people like the taste of certain foods (e.g. sweets, chocolates, cakes) and use the hypo as an excuse for a 'reward' / 'treat'.
- Much better to see the hypo treatment as necessary (a 'medicine') rather than a reward or an excuse for an unhealthy treat.

Question 5
What do you think is the best treatment for a hypo?

Discussion Points
- What are the participants' individual experiences of different treatments ie which are fast and which are slow.

Question 6
Where do you keep your hypo treatment?

Discussion Points
- The pros and cons of the suggestions offered (e.g. why might people not keep some treatment by the side of their bed?)

Question 7
Can you think of any other places you could keep your hypo treatment?

Discussion Points
- The places people have hypos.
- Is it practical to keep treatment in these places?

End of section task
- Ask participants to complete table in handbook

Check your blood glucose level 10-15 minutes later and ensure that the level is on the rise.

If the blood glucose level remains <4.0 mmol/L more rapid acting carbohydrate should be taken as above. There may be a role for long acting carbohydrate in some circumstances
Reinforce the message that no foods are off limits for people with diabetes, so there is no need to use hypos as an excuse to eat 'forbidden foods'. Discuss the fact that fat slows absorption of glucose, so biscuits, chocolate etc are not ideal first line treatments

Always keep rapid acting carbohydrates in pocket, car, workplace, exercise bag, bed-side table or any other place that you often go

Hint
At the end of this section use the white board to facilitate the end of section task. Completion of this will reinforce the key learning outcomes.

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Section 2: The Risk Factors for Hypoglycaemia

Establish your Extra risks

Learning Outcomes	Facilitator Activities	Section Plan
To look for hypo patterns (When? Where? Why?) To identify times when you are more likely to have low blood glucose	**Question 1** When are you most at risk of having a hypo? **Discussion Points** • After giving too much insulin. • After inaccurately carbohydrate counting. • When distracted. • The key information on exercise. • The key information on alcohol. **Question 2** Are there any activities which increase your risk of having a hypo? **Discussion Points** • Possible examples include housework, dog walking, D.I.Y, running to catch the bus etc. **Question 3** Have you had any hypos that have been directly related to food or drink? **Discussion Points** • After alcohol – key information on alcohol to be discussed. • If meals are not finished after already taking insulin. • When stomach is not emptying properly (gastroparesis). • Not treating a hypo because thinking will be OK until next meal. • When having a lighter meal than normal and getting insulin dose wrong.	**Key information for participants to know by end of this section** *Exercise:* • Exercise can lower blood glucose levels during the activity, immediately after or up to 24 hours after exercise. • You may need to reduce your pre- and post-exercise insulin. • You may need to eat more carbohydrate during and following exercise. • Monitor your blood glucose frequently and use this information to adjust your food and exercise accordingly. • Avoid injecting pre-exercise insulin into any area of working muscle eg thigh before a jog or arm before ironing/DIY etc (it may get absorbed much more quickly than usual if you do). *Alcohol:* • Alcohol can cause late hypoglycaemia, with events often not occurring until the next day. • Ensure you monitor your glucose levels frequently in the 24 hours after drinking alcohol and • remember you may need to reduce your insulin dosage in the 24 hours after drinking alcohol

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Question 4

Have you ever had any hypos that you think have been due to your insulin acting more strongly than normal? Why do you think this was?

Discussion Points
- Insulin acting more rapidly than usual after injecting into exercising muscle.
- Having a hypo while/after having a warm bath/shower.
- Using a different injection site.
- Key information on insulin action.

Question 5

Have you ever been frustrated at how long it has taken for your blood glucose to fall after eating and therefore given extra insulin, only to a have hypo later?

Discussion Points:
- The key information on insulin stacking.

Question 6

When else do you think you are at extra risk of having a hypo?

Discussion Points
- Related to menstrual cycle.
- When on holiday (different routine)
- When busy with other activities (e.g. distracted while Watching television / working at computer or relaxed and not noticing symptoms / warning signs).
- When travel plans delayed (eg on trains / at airports)
- When unwell and taking more insulin than normal.

Insulin Action:
(It might be helpful to use the whiteboard to illustrate these points)

- Rapid acting insulins (eg aspart / lispro) usually start working after 5-10 minutes.
- Their peak action may be at 30-90 minutes after injecting but they can be active for up to 4 hours.
- Peak action means the time that the insulin is most active.
- Long acting insulin (such as glargine) starts working after about 1 hour but can be active for between 12-28 hours with peak at 8-10 hours.
- When too much of this insulin is taken or not followed up with enough food it may cause delayed episodes of hypoglycaemia.

Insulin stacking:

- Hypoglycaemia can occur after insulin stacking.
- Stacking is when rapid acting insulin is given between meals to correct for hyperglycaemia but there is already rapid acting insulin from a previous injection waiting to be absorbed.
- When rapid acting insulin is used it is important to think about how much insulin taken before hand may still be waiting to be absorbed.
- Don't stack! Only give extra insulin at meal times if BG is high (not in between meals).

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Section 3: Identifying Hypoglycaemia

Learning Outcomes	Facilitator Activities	Section plan
1. To be aware of subtle symptoms or signs which suggest being 'hypo'. 2. To consider scanning your body for any symptom or sign that may indicate a hypo. 3. To consider scanning as a routine, especially if any mismatch between insulin, food and physical activity is suspected. 4. To think about a way of testing/checking yourself to identify a hypo.	**Discuss** • Even if people have lost most of the symptoms of hypoglycaemia that they used to have, they may still be able to identify some subtle symptoms. • People may have their own way of trying to recognise symptoms (e.g. noticing that you're typing the wrong keys on a computer keyboard or that you can't do some simple maths in your head). **Emphasise** • It may still be possible to identify subtle symptoms of hypoglycaemia. **Task** • Ask participants to make a list of any of the symptoms they experience when having a hypo. **Discuss** • How symptoms can change over time. Explain that each person with diabetes may experience different symptoms of hypoglycaemia. Sometimes each episode may result in different symptoms and signs. **Task** • Ask participant to look at the table of symptoms provided in the participant handbook and to identify any of the symptoms applicable to them.	**Hint** Using a whiteboard or flip chart may be helpful during this section. .

Section 4: Being wary of Hypoglycaemia

**Wary even
While asleep**

Learning Outcomes	Facilitator Activities	Section plan
1. To understand you may be at increased risk of hypoglycaemia overnight when asleep. 2. To consider setting an alarm to check blood glucose at night. 3. To be wary of hypoglycaemia at all times – if in doubt check!	**Question 1** Do you ever have hypos at night? **Question 2** Do you ever wake up in the morning with symptoms of headache / feeling hung-over / lethargy or just feel as though you're not functioning properly? **Question 3** Have you ever found your blood glucose levels to be variable or even erratic first thing in the morning? **Discussion Points** • Nocturnal hypos and how to improve prevention of these. • Where to keep treatment for hypos. • Key information. **Question 4** Is there anything you could do to make it easier for you to check your blood glucose? **Discussion Points** • The importance of being able to check your BG at all times. • Keeping a blood glucose meter by side of bed. • Ensuring partner / family member / friends can use your blood glucose meter. • BG checking is the only way to be sure about not being hypo. • Ensuring availability of functioning spare glucose meter. • Consider packing 2 meters in separate bags when going on holiday.	**Key information for participant to know by end of this section** If you find that your blood glucose levels are particularly variable or even erratic first thing in the morning this may suggest you are having hypoglycaemic episodes overnight. If this is the case you could consider reducing your insulin dose (or basal rate if using a pump). The only way to be absolutely certain that you are not having a hypoglycaemic episode is to test your blood glucose. Be wary of hypoglycaemia at all times and if ever in doubt check your blood glucose level remembering 'don't ignore a glucose less than four'. Key checkpoints are 2 hours after meal bolus/ short-acting analogue injection; 8-10 hours after glargine injection (before evening meal for morning injection and before breakfast for bedtime injection). There is an increased risk of developing hypoglycaemia overnight when you are asleep as blood glucose levels can fall without you being aware. Some people who do experience an episode of hypoglycaemia overnight and are awoken may not remember the event the next morning.

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Section 5: Summary including Questions and Answers

Facilitator Activities	Section plan
Question 1: Has this session achieved your personal aims? Have the questions and concerns you recorded on the first page been addressed? **Discuss** Ensure each participant has had all questions and concerns addressed.	Invite participants to review their own post-it notes and ask if any objectives or questions remain outstanding. After addressing all questions and concerns, invite participants to complete the summary page of their handbook using the notes they made during the session. Advise them that it would be helpful to them to keep that summary handy, to reflect on over the coming weeks and months.

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6.4 Appendix 4: Guy's and St Thomas' minimally modified Clarke hypoglycaemia survey

Study Centre: Today's date: / /   (dd/mm/yy)

Patient ID #:   Patient DOB: / /   (dd/mm/yy)

Guy's and St Thomas' Minimally Modified Clarke Hypoglycaemia Survey

1.   Tick the category that best describes you (tick one only):

0   I always have symptoms when my blood sugar is low

0   I sometimes have symptoms when my blood sugar is low

0   I no longer have symptoms when my blood sugar is low

2.   Have you lost some of the symptoms that used to occur when your blood sugar was low?

0   Yes   0   No

3.   In the past 6 months, how often have you had hypoglycaemic episodes, where you might feel confused, disorientated, or lethargic and were unable to treat yourself?

0   Never   0   Once or twice   0   Every other month

0   Once a month   0   More than once a month

4.   In the past year, how often have you had hypoglycaemic episodes, where you were unconscious or had a seizure and needed glucagon or intravenous glucose?

0   Never   0 5 times   0 10 times

0   1 time   0 6 times   0 11 times

0   2 times   0 7 times   0 12 or more times

0   3 times   0 8 times

0   4 times   0 9 times

5.   How often in the last month have you had readings <3.5mmol/l with symptoms?

0   Never   0 1-3 times   0 1 time/week

0   2-3 times/week   0 4-5 times/week   0 Almost daily

6.   How often in the last month have you had readings <3.5mmol/l without any symptoms?

0   Never   0 1-3 times   0 1 time/week

0   2-3 times/week   0 4-5 times/week   0 Almost daily

7.   How low does your blood sugar need to go before you feel symptoms?

0   3.4-3.9mmol/l   0 2.8-3.3mmol/l   0 2.2-2.7mmol/l

      0 <2.2 mmol/l

8.   To what extent can you tell by your symptoms that your blood sugar is low?

0   Never   0 Rarely   0 Sometimes   0 Often   0 Always

6.5 Appendix 5: Edinburgh hypoglycaemia survey including the Gold score

1. Please score the extent to which you experience the following symptoms during a typical daytime hypoglycaemic episode (circle a number for each symptom)

	Not present						Present a great deal
Confusion	1	2	3	4	5	6	7
Sweating	1	2	3	4	5	6	7
Drowsiness	1	2	3	4	5	6	7
Weakness	1	2	3	4	5	6	7
Dizziness	1	2	3	4	5	6	7
Warmth	1	2	3	4	5	6	7
Difficulty Speaking	1	2	3	4	5	6	7
Pounding heart	1	2	3	4	5	6	7
Inability to concentrate	1	2	3	4	5	6	7
Blurred vision	1	2	3	4	5	6	7
Hunger	1	2	3	4	5	6	7
Nausea	1	2	3	4	5	6	7
Anxiety	1	2	3	4	5	6	7
Tiredness	1	2	3	4	5	6	7
Tingling lips	1	2	3	4	5	6	7
Trembling	1	2	3	4	5	6	7
Headache	1	2	3	4	5	6	7

2. Do you know when your hypos are commencing? Please circle a number:

	Always aware						Never aware
Awareness	1	2	3	4	5	6	7

Comments:

6.6 Appendix 6: Standard operating procedure for stepped hyperinsulinaemic hypoglycaemic clamp in the HypoCOMPaSS study

Exclusion Criteria for clamp study

All participants from the hypo COMPASS trial will be asked to consider participating in the clamp study unless they meet any of the following exclusion criteria:

- Age >60

- History of Epilepsy (seizures not primarily induced by hypoglycaemia)

- Known Ischaemic Heart Disease

- Other significant disease which in the judgement of the investigators which would increase the risks associated with taking part in the study

Day before Study

Subjects will have been fitted with a retrospective CGM sensor to be worn for the 7 days preceding the study day. This will be downloaded on the morning of the study to determine whether any antecedent biochemical hypoglycaemia occurred over the 24-hour period prior to the clamp. Studies will be postponed to another day if any CGM and/or self-monitored capillary glucose below 3.0mmol/l are detected during 24 hours prior to the study. If this is the case, participants will be asked to be fitted for a further 72 hours CGM and to reduce their basal insulin by 25% if on Detemir insulin (this applicable only to clamp studies carried out before the intervention period) and by 50% if on glargine on the night before the rescheduled clamp study, in addition to making other targeted self-management adjustments to absolutely prevent glucose levels <3.0mmol/L over the preceding 24 hours.

Day of Study

Participants will be admitted to the research unit at 0700Hrs on the study day following an overnight fast from 10 pm. An intravenous cannula will be inserted in the antecubital vein of the non-dominant arm and another retrogradely sited

in a vein on the dorsum of the hand on the same side using local anaesthetic. From 7am to 10. 30am, blood glucose will be stabilized with sliding scale insulin infusion aiming initially for blood glucose reading of 6.0 – 7.0 mmol/l, but bringing down to between 5 and 6 mmol/L between 10.30 and 11 am for start of clamp.

The retrograde cannula will be used for sampling, both during initial stabilization and during clamp study. A slow intravenous infusion of saline will be used as needed to keep the sampling line patent. During this period of stabilization, participants will be shown how to perform the brain (cognitive) function tests and asked to practice the tests till they achieve consistent results (typically 5 practice sessions). The distal non-dominant hand will be heated using hot box starting at least 30 min prior to start of clamp (10.30 am at latest) and continued throughout study.

Clamp

At 11 am, a primed infusion of 60 mU/m^{-2}/min actrapid insulin will be started via the non-dominant antecubital vein catheter.

To do this, insulin will made up between 10.00am and 11 am using either:

1) total volume 50mls if using syringe driver: normal saline with 2mls of autologous blood (add saline first then blood and insulin last)
2) total volume 100ml in bag if using infusion pump: remove volume of saline from 100 ml bag, add 4 mls of autologous blood then insulin last!

The insulin dose will be calculated and will be run through the side arm of a 3-way tap. Priming rates are

(i)   insulin infusion at 48 mls/hr from 0 to 4 min
(ii)   insulin infusion at 32 ml/h from 4 to 7 min
(iii)   insulin infusion at 16 ml/hr from 7 min onwards

20% glucose will also be infused via the same antecubital cannula (best through "straight" arm of 3 way tap at a variable rate to keep the blood glucose at the desired level. This is varied but a "typical" starting protocol might be:

0 min   0   mg/kg/min

4 min   2   mg/kg/min

7 min	2.5	mg/kg/min
9 min	3	mg/kg/min
11 min	4	mg/kg/min

<u>Plasma</u> glucose will be sampled from sample drawn from retrograde cannula every 5 minutes (2ml dead space drawn, then the sample for analysis and then dead space sample returned), spun rapidly and assayed using Yellow Springs glucose analyzer. Dextrose infusion rates will be adjusted as needed aiming for stabilization at 5.0mmol/l at 40mins and lowered in a step wise manner by variable glucose infusion to 3.8mmol/L, 3.4mmol/l 2.8mmol/l and 2.4mmol/l. Each step will consist of 40 min allowing 20 minutes to fall to target and 20 minutes for stabilization at that level. Participants will be blinded to glucose levels throughout the study.

In addition to samples for plasma glucose, additional arterialised venous blood samples for insulin, catecholamines, growth hormones, glucagon and cortisol will be drawn spun and stored at 0,10,20,30 and 40 minutes at start of clamp. Thereafter, these extra samples will be drawn at 20 minute intervals. Sampling details/ collection are detailed below. Also heart rate and BP recorded every 20 minutes so easiest for timings to have a consistent time pattern of recording HR, draw samples and then inflate BP cuff as flushing line. Suggested pattern of activity for each glucose step (other than 0 to 40 min where additional basal hormone sampling) in figure 1 below:
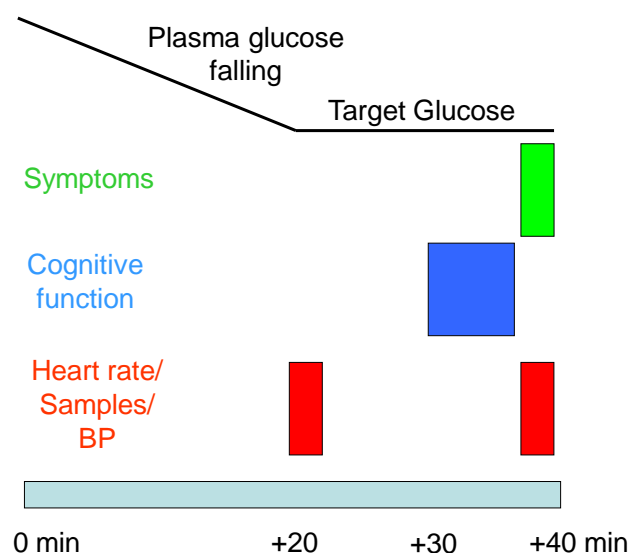
Figure 1: Pattern of activity for each clamp step

Following Clamp

At the end of the study, dextrose infusion will be increased to raise blood glucose to euglycaemia, and then tapered off gradually during meal (typically halved halfway through eating then discontinued at end of meal). For insulin;

> (1) for pump patients, the iv insulin infusion will be reduced to approximate basal infusion rates and pump reconnected with meal bolus as below but allowing 30 minutes overlap for pump site to kick in before stopping iv insulin (halve iv insulin infusion rate after 15 minutes)
> (2) For MDI patients, iv insulin infusion will be reduced to approximate basal infusion rates and meal injection given as below. Allow 30 mins overlap between bolus and stopping iv insulin (halve iv insulin infusion rate after 15 minutes).

A carbohydrate rich meal will be consumed with 80% of usual prandial insulin bolus given. Frequent blood glucose measurements will be made (every 10 minutes) until glucose levels are stable (at least 45 minutes after end of meal).

Participants will be discharged home with advice about their subsequent insulin dose. Specifically (1) warned increased risk of hypo during subsequent 24-48 hour period (2) MDI patients warned that it may take up to 3 days to restabilise baseline, to monitor frequently and to make small corrections only.

Measures

Blood:

Plasma glucose will be analysed by Yellow Springs analyser (Yellow Springs, Ohio, USA).

Hormone analysis of samples from all centres will be performed in the quality assured Diabetes Research Laboratory at Newcastle University.

Blood samples for insulin will be collected as 3ml samples in EDTA tubes, and centrifuged at 2500 rpm for 2 minutes. Equal volumes of a polyethylene glycol (PEG) buffer will be added, samples vortexed and then spun for 30 minutes to remove the precipitated globulin fraction. The supernatant will be frozen for

assay (stored at -20) and free insulin measured by double-antibody immunoassay.

For glucagon, 2.5ml blood will be collected in a tube containing 0.25ml aprotinin (trasylol) and EDTA which will have been stored in a refrigerator. A sequential radioimmunoassay will be used for Glucagon assay.

Blood samples for cortisol will be collected as 2.5ml samples in glass white topped tubes. ADVIA Centuar Cortisol assay will be used to measure cortisol in the serum samples.

For catecholamines 4 mls of whole blood will be drawn into a Lithium Heparin tube. A non competitive enzyme linked immunosorbent assay kit will be used to measure epinephrine or norepinephrine in plasma.

Blood samples for growth hormone assays will be collected as 3ml samples in EDTA tubes. GH will be measured using a Nichols Advantage assay using a two-site chemiuminescence immunoassay procedure.

Physiological measurements

Electrocardiograph monitoring will be performed continuously throughout the clamp studies using three electrodes. One electrode will be placed on either side of the sternum and one in the V5 position. The signal will be amplified and displayed on a monitor with the integrated heart rate displayed digitally.

Heart Rate, blood pressure and 2 minutes ECG trace will be formally recorded every 20 minutes.

In some studies, monitoring of skin perspiration and limb tremor will be undertaken intermittently using non-invasive previously validated sensors. This is not expected to cause any added discomfort or inconvenience for the recipient.

Hypoglycaemia Symptom Score

The participants will complete a symptom questionnaire at the end of each glucose step (i.e. every 40 minutes). Each symptom will be graded on a visual analogue scale (1-7).

Hypoglycaemia symptoms will be classified into 3 groups:

Autonomic: palpitations, sweating, shaking and hunger

Neuroglycopenic: confusion, drowsiness, odd behaviour, speech difficulty and inco-ordination

Non-specific: nausea and headache

Cognitive function

Participants will undertake three cognitive function tests at the end of each step of the clamp study (and practiced at least 5 times as described above prior to start of clamp between 7 and 11 am- the practice data will also be recorded to show that performance is stable), consisting of 4CRT (4 Choice Reaction Time), N-back and SWM (Spatial Working Memory) performed always in this order:

Four choice reaction time:

Four-choice reaction time is a test of attention, discrimination and motor speed reaction. In this test, the subject is presented with a computer screen divided into four quadrants. A computer-generated signal appears randomly in one quadrant at a time and the subject has to clear it by pressing a corresponding button on a box. Up to 500 signals are presented in 5 min. The mean time of the reactions and accuracy (the percentage of correct responses) are recorded. The measures of speed and accuracy used in this test have previously been demonstrated to change by less than 1% on repeated measures at euglycaemia (Maran A, 1993)

N-back:

In this task, the subject is shown a rapid series of randomly chosen letters and responds when the letter presented is the same as either the last or the next to last or the previous to the next to last letter in the series.

Spatial Working Memory:

Spatial Working Memory (SWM) task involves searching for a token hidden behind a circle by pressing a touch sensitive computer screen. Once the token is found, a new trial will start and participants are informed that another token is hidden behind a different circle, therefore they should avoid touching the circle where the previous token was found. The SWM test has been shown to be sensitive to hormonal manipulations. For example, chronic administration of cortisol to healthy subjects leads to an increase in the within-search errors and impairs the use of appropriate cognitive strategies *(Young, AH; Sahakian BJ; Robbins TW; Cowen PJ (1999). "The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers." Psychopharmacology 145(3): 260-266).*

More recently, a more challenging SWM test has been developed in Newcastle and this has been found to be sensitive to acute cortisol administration demonstrating a detrimental effect of cortisol on the within-search task, an effect that was attenuated by a selective serotonin reuptake inhibitor pre-treatment (Alhaj, HA; Arulnathan, VE; Gallagher, P; Marsh, RA; Massey, AE; Pariante, CM; McAllister-Williams, RH (2009). "Citalopram Modulation of the Effects of Cortisol on Attention and Memory." Journal of Psychopharmacology 23(6): TE18.).

This is an in house adaptation of the SWM task from the CANTAB battery of cognitive tests. See www.camcog.com/camcog/default.as

6.7   Appendix 7: Blood glucose targets

The blood glucose targets (for all patients in both CSII and MDI groups) were as follows:

Fasting blood glucose (FBG):	5.0 - 7.0 mmol/l
Pre-prandial blood glucose:	4.5 - 7.0 mmol/l
Post-prandial glucose*:	6.0 – 8.0 mmol/l
Bedtime blood glucose**:	6.0 – 8.0 mmol/l
4am blood glucose:	5.0 – 7.0 mmol/l

*postprandial blood glucose: measurement made 2 hours after the start of a meal

**bedtime blood glucose: measurement made within 30 minutes of retiring to bed for the night.

6.8 Appendix 8: Glargine titration in MDI group

Insulin glargine was self-administered and the following titration protocol was followed:

- Take within 30 minutes of retiring to bed for night / no need for snack

- Aim for stable (not falling) glucose through the night

- Reduce dose if any hypoglycaemic episodes or glucose <5.0mmol/l between 4am and before breakfast

- Target glucose of 5-7mmol/l before breakfast – adjust dose by 1-2 units to maintain target if necessary with primary aim being absolute avoidance of biochemical hypoglycaemia)

- During periods of illness, basal insulin doses may need to be altered and this will be guided by SMBG levels.

Introduction of twice daily glargine

Participants randomised to MDI already on twice daily glargine continued on this from the outset of the RCT. In other MDI participants, if glucose was consistently >7mmol/l before evening meal or highly variable between breakfast and evening meal, a second dose of insulin glargine was added before breakfast. Initial dose was 4 units but was adjusted in light of participant's insulin doses. If glucose had been falling through the night, a 2-4 unit reduction in evening glargine dose was actioned before bed on the day of commencing the morning dose. The addition of a second daily glargine dose was considered for all participants in the MDI group. This was initiated between study visits if necessary, e.g. after telephone advice.

Morning insulin glargine was self-administered and adjusted as follows:

- Take within 30 minutes of rising from bed for the morning

- Aim for stable (not falling) glucose through the afternoon

- Reduce dose if any hypoglycaemic episodes or glucose <5mmol/l between 2 hours after lunch and evening meal

- Target glucose of 5-7mmol/l before evening meal – adjust dose by 1-2 units to maintain target if necessary with primary aim being absolute avoidance of biochemical hypoglycaemia

6.9 Appendix 9: Basal insulin titration in CSII group

The basal insulin delivery rate was titrated according to fasting, bedtime, pre-prandial and 4am glucose levels ensuring absence of recurrent low glucose levels at these times (checkpoints). Increased or decreased delivery was commenced from the previous basal insulin checkpoint level, i.e. if low at 4am – decreased from bedtime; if high fasting increased from 4am.

Mean fasting; bedtime; 4am and pre-prandial blood glucose:

• Within target: No change to basal delivery rate

• Above target: Increase basal insulin by 0.1U/hr from previous check point

• Below target or unexplained late post-prandial hypoglycaemia: Decrease basal insulin by 0.1U/hr from previous check point

During periods of illness, basal insulin rates may need to be altered and this will be guided by SMBG levels.

6.10 Appendix 10: Meal-time insulin bolus in all groups (CSII and MDI)

Carbohydrate counting skills and bolus dose adjustment in light of current blood glucose level / individualised insulin carbohydrate ratios was reviewed in all participants. Aspart or lispro was delivered either by subcutaneous injection or as a subcutaneous pump bolus before all meals and snacks with substantial carbohydrate content.

Insulin: carbohydrate ratios were calculated for all individuals using the '500 rule' and using total daily insulin doses pre-randomisation. The '500 rule' is:

500 divided by the TDD (Total Daily Dose of insulin) = grams of carbohydrate covered by one unit of aspart or lispro

In the event of high pre-prandial glucose levels corrective doses were also recommended with meals as part of the meal time bolus. This was calculated using the '100 rule' for estimation of Insulin Sensitivity Factor. The '100 rule' is

100 divided by the TDD (Total daily Dose of insulin) = glucose drop in mmol/l per 1 unit of aspart or lispro

This was presented to all participants as '1 unit of aspart/lispro will reduce your blood glucose by X mmol/l'.

Corrective doses with all pre-main meal boluses / prandial insulin injections were encouraged according to the 100 rule when glucose level was above target.
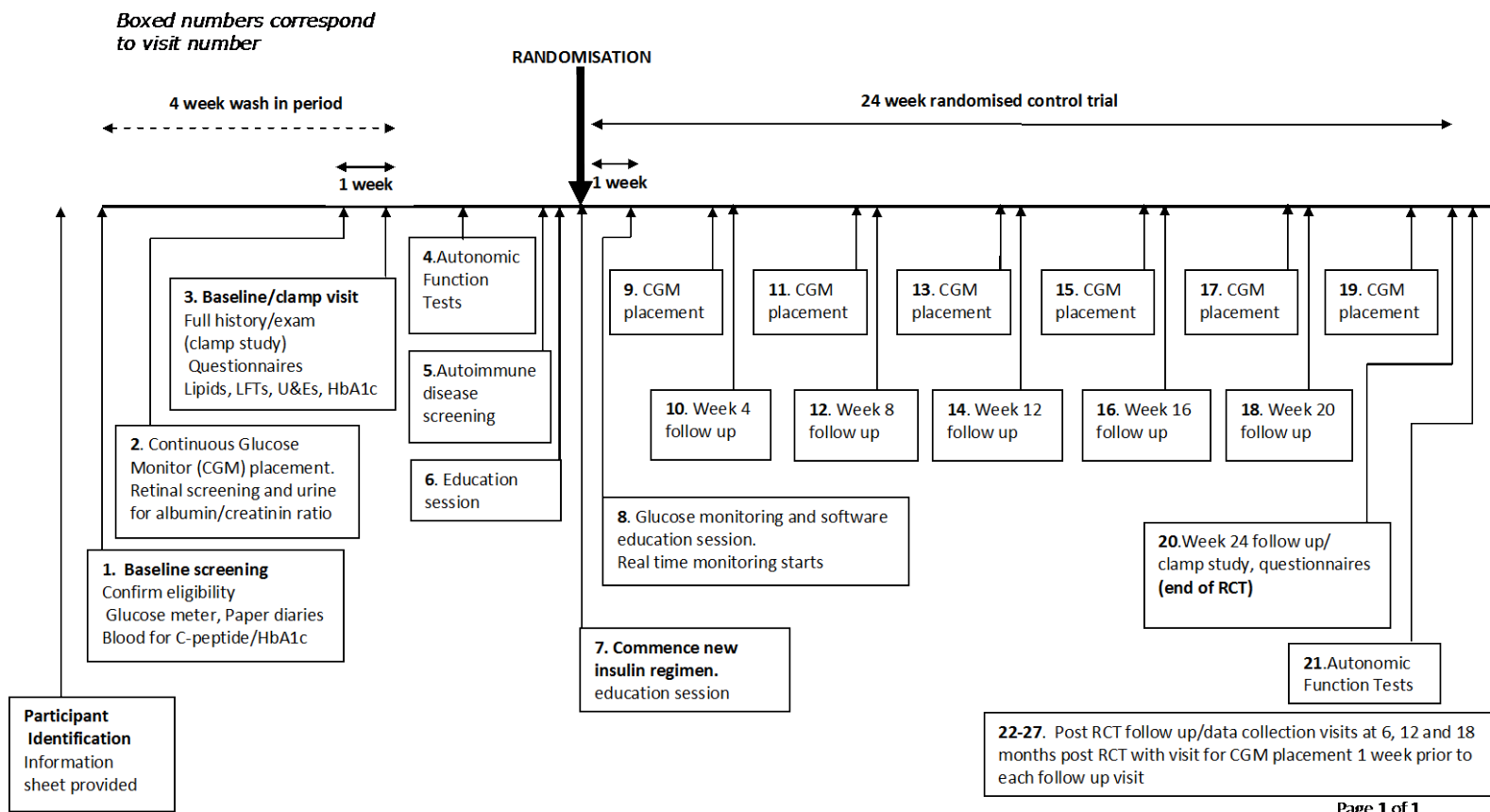
The insulin: carbohydrate ratio and Insulin Sensitivity Factor for that period of the day was adjusted accordingly in the event that:

- The glucose level was consistently below or above target 2 hours after a bolus / prandial insulin injection.

- If any unexplained hypoglycaemic event occurred 2 hours after a bolus / prandial insulin injection

6.11 Appendix 11: Study flow chart

Hypo C★MPaSS
Comparison of Optimised MDI versus Pumps with or
without sensors in Severe Hypoglycaemia

HypoCOMPASS Study Flowchart version 1.0 100909
REC Reference: 09/H0904/63

*Boxed numbers correspond
to visit number*

RANDOMISATION

4 week wash in period

24 week randomised control trial

1 week

1 week

3. Baseline/clamp visit
Full history/exam
(clamp study)
Questionnaires
Lipids, LFTs, U&Es, HbA1c

4. Autonomic
Function
Tests

9. CGM
placement

11. CGM
placement

13. CGM
placement

15. CGM
placement

17. CGM
placement

19. CGM
placement

5. Autoimmune
disease
screening

2. Continuous Glucose
Monitor (CGM) placement.
Retinal screening and urine
for albumin/creatinin ratio

6. Education
session

10. Week 4
follow up

12. Week 8
follow up

14. Week 12
follow up

16. Week 16
follow up

18. Week 20
follow up

8. Glucose monitoring and software
education session.
Real time monitoring starts

20. Week 24 follow up/
clamp study, questionnaires
(end of RCT)

1. Baseline screening
Confirm eligibility
Glucose meter, Paper diaries
Blood for C-peptide/HbA1c

**7. Commence new
insulin regimen.**
education session

21. Autonomic
Function Tests

**Participant
Identification**
Information
sheet provided

22-27. Post RCT follow up/data collection visits at 6, 12 and 18
months post RCT with visit for CGM placement 1 week prior to
each follow up visit

Page 1 of 1

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6.12 Appendix 12: The diabetes treatment satisfaction questionnaire

Diabetes Treatment Satisfaction Questionnaire: DTSQs

The following questions are concerned with the treatment for your diabetes (including insulin, tablets and/or diet) and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1. How satisfied are you with your current treatment?

   very satisfied   6   5   4   3   2   1   0   very dissatisfied

2. How often have you felt that your blood sugars have been unacceptably high recently?

   most of the time   6   5   4   3   2   1   0   none of the time

3. How often have you felt that your blood sugars have been unacceptably low recently?

   most of the time   6   5   4   3   2   1   0   none of the time

4. How convenient have you been finding your treatment to be recently?

   very convenient   6   5   4   3   2   1   0   very inconvenient

5. How flexible have you been finding your treatment to be recently?

   very flexible   6   5   4   3   2   1   0   very inflexible

6. How satisfied are you with your understanding of your diabetes?

   very satisfied   6   5   4   3   2   1   0   very dissatisfied

7. Would you recommend this form of treatment to someone else with your kind of diabetes?

   Yes, I would definitely   6   5   4   3   2   1   0   No, I would definitely
   recommend the   not recommend the
   treatment   treatment

8. How satisfied would you be to continue with your present form of treatment?

   very satisfied   6   5   4   3   2   1   0   very dissatisfied

Please make sure that you have circled one number on each of the scales.

6.13 Appendix 13: hyperglycaemia avoidance scale

High Blood Sugar Survey

PART 1: The items below describe things people may do in their daily diabetes management in order to avoid <u>high</u> blood glucose levels. Please <u>tick one box</u> ☑ <u>on each line</u> that best describes how often you do each of these in your diabetes management.

How often do you …	Never	Rarely	Sometimes	Often	Always
1. try to lower your blood glucose when it is higher than 10mmol/l?	☐	☐	☐	☐	☐
2. choose to take a little more insulin rather than risk taking too little?	☐	☐	☐	☐	☐
3. choose to under-treat low blood glucose rather than risk high blood glucose later?	☐	☐	☐	☐	☐
4. keep your blood glucose below 7mmol/l?	☐	☐	☐	☐	☐
5. give extra insulin when you know your blood glucose is above 7mmol/l?	☐	☐	☐	☐	☐
6. exercise to lower your blood glucose when you know it is high?	☐	☐	☐	☐	☐
7. avoid restaurants / social situations that tempt you to have food / drink which raise your blood glucose?	☐	☐	☐	☐	☐
8. miss meals when you know your blood glucose is high?	☐	☐	☐	☐	☐
9. avoid stressful situations that might raise your blood glucose?	☐	☐	☐	☐	☐
10. check your blood glucose more often when you think it is high?	☐	☐	☐	☐	☐
11. choose to keep your blood glucose low rather than risk being high?	☐	☐	☐	☐	☐
12. keep your blood glucose low because you want to avoid unpleasant symptoms?	☐	☐	☐	☐	☐

PART 2: The items below describe concerns and <u>feelings</u> you may have about <u>high</u> blood glucose. Please <u>tick one box</u> ☑ <u>on each line</u> that best reflects how often you feel that way.

How often do you ...	Never	Rarely	Sometimes	Often	Always
1. worry about complications of high glucose, e.g. blindness, kidney failure, amputation?	☐	☐	☐	☐	☐
2. worry that you might die early due to diabetes?	☐	☐	☐	☐	☐
3. worry about high blood glucose?	☐	☐	☐	☐	☐
4. feel upset (e.g. frustrated, distressed) when your blood glucose is too high?	☐	☐	☐	☐	☐
5. feel comfortable about being hypo if that is what it takes to avoid high blood glucose?	☐	☐	☐	☐	☐
6. worry about going into DKA (diabetic ketoacidosis)?	☐	☐	☐	☐	☐
7. worry about losing your health due to your diabetes?	☐	☐	☐	☐	☐
8. worry about not recognising when your blood glucose is high?	☐	☐	☐	☐	☐
9. feel annoyed at yourself when your blood glucose is high?	☐	☐	☐	☐	☐
10. worry about not knowing how to lower your blood glucose when it is high?	☐	☐	☐	☐	☐
11. worry about your doctor's reaction if your blood glucose is high?	☐	☐	☐	☐	☐
12. worry that you will experience unpleasant symptoms if your blood glucose is high?	☐	☐	☐	☐	☐

On a typical day, what is the highest blood glucose level that you would feel comfortable with?

_____ mmol/l *(please write a number)*

HbA_{1c} is a measure of average blood glucose over the past 6-8 weeks. What is the highest HbA_{1c} that you would feel comfortable with?

_____ % *(please write a number)*   OR   _____ mmol/mol *(please write a number)*

☐ I don't know

Thank you for completing this questionnaire.

6.14 Appendix 14: Hypoglycaemia fear survey

Fear of Hypoglycaemia Survey

<u>Behaviour:</u> Below is a list of things people with diabetes sometimes do in order to avoid low blood sugar and its consequences. Tick the box that best describes what you have done during the last 6 months in your daily routine to AVOID low blood sugar and its consequences (please do not skip any).

To avoid low blood sugar and how it affects me, I …	Never	Rarely	Sometimes	Often	Almost always
1. ate large snacks	☐	☐	☐	☐	☐
2. tried to keep my blood sugar 4mmol/L or above	☐	☐	☐	☐	☐
3. reduced my insulin when my blood sugar was low	☐	☐	☐	☐	☐
4. measured my blood sugar <u>six</u> or more times a day	☐	☐	☐	☐	☐
5. made sure I had someone with me when I go out	☐	☐	☐	☐	☐
6. limited my out of town travel	☐	☐	☐	☐	☐
7. limited my driving (car, truck or bicycle)	☐	☐	☐	☐	☐
8. avoided visiting friends	☐	☐	☐	☐	☐
9. stayed home more than I liked	☐	☐	☐	☐	☐
10. limited my exercise / physical activity	☐	☐	☐	☐	☐
11. made sure there were other people around	☐	☐	☐	☐	☐
12. avoided sex	☐	☐	☐	☐	☐
13. kept my blood sugar higher than usual in social situations	☐	☐	☐	☐	☐
14. kept my blood sugar higher than usual when doing important tasks	☐	☐	☐	☐	☐
15. had people check on me several times during the day or night	☐	☐	☐	☐	☐

Because my blood sugar could go low, I worried about...	Never	Rarely	Sometimes	Often	Almost always
16. not recognising / realising I was having low blood sugar	☐	☐	☐	☐	☐
17. not having food, fruit or juice available	☐	☐	☐	☐	☐
18. passing out in public	☐	☐	☐	☐	☐
19. embarrassing myself or my friends in a social situation	☐	☐	☐	☐	☐
20. having a hypoglycaemic episode while alone	☐	☐	☐	☐	☐
21. appearing stupid or drunk	☐	☐	☐	☐	☐
22. losing control	☐	☐	☐	☐	☐
23. no-one being around to help me during a hypoglycaemic episode	☐	☐	☐	☐	☐
24. having a hypoglycaemic episode while driving	☐	☐	☐	☐	☐
25. making a mistake or having an accident	☐	☐	☐	☐	☐
26. getting a bad evaluation or being criticised	☐	☐	☐	☐	☐
27. difficulty thinking clearly when responsible for others	☐	☐	☐	☐	☐
28. feeling lightheaded or dizzy	☐	☐	☐	☐	☐
29. accidentally injuring myself or others	☐	☐	☐	☐	☐
30. permanent injury or damage to my health or body	☐	☐	☐	☐	☐
31. low blood sugar interfering with important things	☐	☐	☐	☐	☐
32. becoming hypoglycaemic during sleep	☐	☐	☐	☐	☐
33. getting emotionally upset and difficult to deal with	☐	☐	☐	☐	☐

6.15 Appendix 15: Autonomic symptom profile questionnaire

Answer every question by darkening the appropriate oval. If you are unsure about how to answer a question, please give the best answer you can. Please darken the corresponding oval completely. Fill in the number in the box if provided. This is an American questionnaire – so some of the spellings are strange and the numbers erratic, please just ignore this and answer the questions as they appear. Many thanks.

18. In the past year, have you ever felt faint, dizzy or 'goofy' or had difficulty thinking soon after standing up from a sitting or lying position ?
    O 1   Yes *If you marked Yes go to question 19.*
    O 2   No *If you marked No go to question 37.*

19. When standing up, how frequently do you get these feelings or symptoms ?
    O 1   Rarely
    O 2   Occasionally
    O 3   Frequently
    O 4   Almost always

20. How would you rate the severity of these feelings or symptoms ?
    O 1   Mild
    O 2   Moderate
    O 3   Severe

21. For how long have you been experiencing these feelings or symptoms ?
    O 1   Less than 3 months
    O 2   3-6 months
    O 3   7 to 12 months
    O 4   13 months to 5 years
    O 5   more than 5 years
    O 6   as long as I can remember.

22. In the past year, how often have you ended up fainting soon after standing up from a sitting or lying position ?
    O 0   Never
    O 1   Once
    O 2   Twice
    O 3   Three times
    O 4   Four times
    O 5   Five or more times

23. How cautious are you about standing up from a sitting or lying down position ?
    O 1   Not cautious at all
    O 2   Somewhat cautious
    O 3   Extremely cautious

24. What part of the day are these feelings worst ? (check one only)
    O 1   Early morning
    O 2   Rest of the morning
    O 3   Afternoon
    O 4   Evening
    O 5   At night, when I get up after I've been sleeping
    O 6   No particular time is worst
    O 7   Other time, please specify ………………………………………

25. In the past year, have these feelings or symptoms that you have experienced:
    O 1   Got much worse
    O 2   Got somewhat worse
    O 3   Stayed about the same.
    O 4   Got somewhat better
    O 5   Got much better
    O 6   Completely gone.

Please rate the average severity you have experienced in the past year for each of the following symptoms.

	never had	Mild	Moderate	Severe
26. Rapid or increased heart rate (palpitations)	O 1	O 2	O 3	O 4
27. Sickness to your stomach (nausea) or vomiting ?	O 1	O 2	O 3	O 4
28. A spinning or swimming sensation ?	O 1	O 2	O 3	O 4
29. Dizziness ?	O 1	O 2	O 3	O 4
30. Blurred vision ?	O 1	O 2	O 3	O 4
31. Feeling of weakness ?	O 1	O 2	O 3	O 4
32. Feeling shaky or shaking sensation?	O 1	O 2	O 3	O 4
33. Feeling anxious or nervous ?	O 1	O 2	O 3	O 4
34. Turning pale ?	O 1	O 2	O 3	O 4
35. Clammy feeling to your skin ?	O 1	O 2	O 3	O 4

36. Do you have any biological (blood, natural) relatives among your patients, grand parents, brothers, sisters, or children who have frequent dizziness after standing from a sitting or lying position ?

O 1 Yes   O 2 No   If Yes, please list their names and relationships to you.

Name   Relationship
……………………..   …………………………….
……………………..   …………………………….
……………………..   …………………………….

In the past year, have you ever felt faint, dizzy, or 'goofy' or had difficulty thinking:

37. soon after a meal ?	O 1 Yes	O 2 No
38. after standing for a long time ?	O 1 Yes	O 2 No
39. during or soon after physical activity or exercise ?	O 1 Yes	O 2 No
40. during or soon after being in a hot bath, shower, tub or sauna ?	O 1 Yes	O 2 No
41. Have you ever felt dizzy or faint or actually fainted when you saw blood or had blood samples taken ?	O 1 Yes	O 2 No

In the past year, have you fainted:

42. while passing urine ?	O 1 Yes	O 2 No
43. while coughing ?	O 1 Yes	O 2 No
44. while pressing on your neck ?	O 1 Yes	O 2 No
45. before a public speech ?	O 1 Yes	O 2 No
46. any other time ?	O 1 Yes	O 2 No

If you checked Yes to any of these questions on fainting please describe circumstances.
………………………………………………………………………….
………………………………………………………………………….

47. In the past year, have you ever completely lost consciousness after a spell of dizziness ?

O 1 Yes   O 2 No

48. In the past year, have you had any seizures or convulsions ? O 1 Yes   O 2 No
       please describe circumstances ……………………………..

In the past 5 years how would you rate the amount of trouble, if any you have had:

	None	Some	A lot	Constant
49. with paralysis in parts of your face ?	O 1	O 2	O 3	O 4
50. with feelings of complete weakness all over your body ?	O 1	O 2	O 3	O 4
51. with attacks of uncontrollable movements of your arms and legs ?	O 1	O 2	O 3	O 4
52. with attacks in which you couldn't control your speech ?	O 1	O 2	O 3	O 4

53. Have you ever in your adult life had a spell of dizziness ?   O 1 Yes   O 2 No

54. In the past year, have you ever noticed colour changes in your skin, such as red, white or purple ?

     O 1 Yes   *If yes, continue with question 55.*   O 2 No *If no, go to question 65.*

What colour skin changes have occurred (check all that apply)

     55. O My skin turns red.

     56. O My skin turns white.

     57. O My skin turns purple.

     58. O Other, please specify ………………………………………………

What parts of your body are affected by these colour changes ? (check all that apply)

     59. O My hands.

     60. O My feet.

     61. O Other parts, please specify …………………………………………

     62. O Entire body.

     63. For how long have you been experiencing these changes in skin colour ?
         O 1   Less than 2 months
         O 2   3-6 months
         O 3   7-12 months
         O 4   13 months to 5 years
         O 5   More than 5 years
         O 6   As long as I can remember

64. Are these changes in skin colour:
         O 1   Getting much worse
         O 2   Getting somewhat worse
         O 3   Staying about the same
         O 4   Getting somewhat better
         O 5   Getting much better
         O 6   Completely gone

     65. In the past year, after a long hot bath or shower, have you ever noticed the pads on the ends of your fingers wrinkle up ?
     O 1 Yes   O 2   No

     66. In the past 5 years, what changes, if any, have occurred in your general body sweating?
     O 1   I sweat much more than I used to.

O 2 I sweat somewhat more than I used to.
O 3 I haven't noticed any changes in my sweating.
O 4 I sweat somewhat less than I used to.
O 5 I sweat much less than I used to.

67. In the past 5 years, what changes, if any, have occurred in the amount your feet sweat ?
O 1 They sweat much more than they used to.
O 2 They sweat somewhat more than they used to.
O 3 I haven't noticed any changes.
O 4 They sweat somewhat less than they used to.
O 5 They sweat much less than they used to.

68. In the past 5 years, what changes, if any, have occurred in facial sweating after eating spicy foods ?
O 1 I sweat much more than I used to.
O 2 I sweat somewhat more than I used to.
O 3 I haven't noticed any changes in my sweating.
O 4 I sweat somewhat less than I used to.
O 5 I sweat much less than I used to.
O 6 I avoid eating spicy foods because I sweat so much.
O 7 I avoid eating spicy foods for other reasons.

In the past 5 years, what changes, if any, have occurred in your ability to tolerate heat during a hot day, strenuous work or exercise, hot bath or shower, hot tub or sauna ? (check all that apply).

69. O I now get more overheated.

70. O I now get dizzy.

71. O I now get short of breath.

72. O Other changes, please specify …………………………………………..

73. O No change.

74. Do your eyes feel excessively dry ?
O 1 Yes O 2 No

75. Does your mouth feel excessively dry ?
O 1 Yes O 2 No

76. Do you have excessive amounts of saliva formation ?
O 1 Yes O 2 No

77. What is the longest period of time that you have had any one of these symptoms: dry eyes, dry mouth, or increased saliva production ?
O 0 I have not had any of these symptoms.
O 1 Less than 3 months.
O 2 3 to 6 months.
O 3 7 to 12 months.
O 4 13 months to 5 years.
O 5 More than 5 years.
O 6 As long as I can remember.

78. For the symptom of dry eyes, dry mouth, or increased saliva production that you have had for the longest period of time, is this symptom:
O 0 I have not had any of these symptoms.
O 1 Getting worse.
O 2 Getting somewhat worse.
O 3 Staying about the same.
O 4 Getting somewhat better.
O 5 Getting much better.
O 6 Completely gone.

79. What weight changes, if any, have you had over the past year ?
O 1 I have lost about ………………… pounds.
O 2 My weight has not changed.
O 3 I have gained about ……………..pounds.

80.   In the past year, have you noticed any changes in how quickly you get full when eating a meal ?
O 1   I get full a lot more quickly now than I used to.
O 2   I get full more quickly now than I used to.
O 3   I haven't noticed any change.
O 4   I get full less quickly now than I used to.
O 5   I get full a lot less quickly now than I used to.

81.   In the past year, have you felt excessively full or persistently full (bloated feeling) after a meal ?
O 1 Never   O 2   Sometimes   O 3   A lot of the time

82.   In the past year, have you felt like you had a persistent upset stomach (nausea) ?
O 1 Never   O 2   Sometimes   O 3   A lot of the time

83.   In the past year, have you vomited after a meal ?
O 1 Never   O 2   Sometimes   O 3   A lot of the time

84. In the past year, have you had a cramping or colicky abdominal pain ?
O 1 Never   O 2   Sometimes   O 3   A lot of the time

85. Are these pains usually after a meal ?   O 1 Yes   O 2 No

86. How long have you had these cramping or colicky abdominal pains ?
O 1   Less than 3 months
O 2   3 to 6 months
O 3   7 to 12 months
O 4   13 months to 5 years
O 5   More than 5 years
O 6   As long as I can remember

87.   In the past year, have you had any bouts of diarrhea ?
O 1 Yes   *If yes continue with question 88*   O 2 No *If no go to question 94*

88.   How frequently does this occur ?
O 1 Rarely   O 2   Occasionally
O 3   Frequently ………..times per month O 4   Constantly

89.   How severe are these bouts of diarrhoea ?
O 1   Mild   O 2   Moderate   O 3   Severe

90.   What part of the day do they seem to be worse ?
O 1   First thing in the morning
O 2   Rest of the morning
O 3   Afternoon
O 4   Evening
O 5   During the night
O 6   No particular time

91.   Do these bouts of diarrhoea usually occur after meals
     O 1   Yes   O 2   No

92.   Are these bouts of diarrhoea accompanied with lots of rectal gas (flatus)
O 1   NeverO 2   Occasionally   O 3 Frequently   O 4 Always

93.   Are your bouts of diarrhea getting:
O 1   Much worse
O 2   Somewhat worse
O 3   Staying the same
O 4   Somewhat better
O 5   Much better
O 6   Completely gone

94. In the past year, have you been constipated ?
 O 1 Yes *If Yes continue below with question 95* O 2   No *If No go to question 98.*

95. How frequently are you constipated ?
O 1 Rarely   O 2   Occasionally
O 3   Frequently ………..times per month O 4   Constantly

96. How severe are these bouts of constipation ?

O 1   Mild   O 2   Moderate   O 3   Severe

97. Is your constipation getting:
O 1   Much worse
O 2   Somewhat worse
O 3   Staying the same
O 4   Somewhat better
O 5   Much better
O 6   Completely gone

98. Overall, are your abdominal symptoms of vomiting, diarrhoea, constipation, or weight loss getting:
O 0   I have not had these symptoms.
O 1   Much worse
O 2   Somewhat worse
O 3   Staying the same
O 4   Somewhat better
O 5   Much better
O 6   Completely gone

99. Which one of the following symptoms have been most troublesome for you (check only one).
O 0   None
O 1   Vomiting
O 2   Diarrhoea
O 3   Constipation
O 4   Weight loss

100.How long have you had this most troublesome symptom.
O 0   I do not have any of these symptoms
O 1   less than 3 months
O 2   3 to 6 months
O 3   7 to 12 months
O 4   13 months to 5 years
O 5   more than 5 years
O 6   As long as I can remember

101 Is this most troublesome symptom getting:
O 0   I do not have any of these symptoms
O 1   Much worse
O 2   Somewhat worse
O 3   Staying the same
O 4   Somewhat better
O 5   Much better
O 6   Completely gone

102 In the past 5 years, how would you rate the amount of trouble, if any, you have had with difficulty swallowing.
O 1   No trouble
O 2   Some trouble
O 3   A lot of trouble
O 4   Constant trouble

103. In the past 5 years, how would you rate the amount of trouble, if any, you have had with everything you eat tasting the same.
O 1   No trouble
O 2   Some trouble
O 3   A lot of trouble
O 4   Constant trouble

Have you ever in your life:
104 Been nauseated or vomited   O 1 Yes   O 2   No

105 had a bout of diarrhea   O 1 Yes   O 2   No

106. lost your appetite for at least part of the day O 1 Yes   O 2   No

107. Felt discomfort or pain in the pit of the stomachO 1 Yes   O 2   No

108. In the past year, have you ever leaked urine or lost control of your bladder function ?
O 1 Never   O 2   Occasionally

O 3   Frequently ………..times per month O 4 Constantly

109. In the past, have you had difficulty passing urine ?
O 1 Never   O 2 Occasionally
O 3   Frequently ………..times per month O 4 Constantly

110. In the past year, have you had trouble completely emptying your bladder ?
O 1 Never   O 2 Occasionally
O 3   Frequently ………..times per month O 4 Constantly

111. How would you describe your current sexual desire ?
O 1 Completely absent   O 2 Greatly reduced
O 3   Somewhat reduced   O 4 About the same or more than in the past

IF MALE COMPLETE QUESTIONS 112 -123 . FEMALES GO TO QUESTION 124

112. Are you able to have a full erection ?
O 1   Never, under any circumstances
O 2   Much less frequently than in the past
O 3   Somewhat less frequently than in the past
O 4   The same, or more frequently, than in the past

Which of the following statements apply to your situation ? (Fill in all that apply)

113. O 1 My ability to have intercourse has not changed.

114. O 1 I have erections but am unable to have intercourse.

115. O 1 I can have intercourse only some of the time.

116. O 1 My erections are definitely impaired.

117. O 1 I am able to have intercourse, but am unable to ejaculate

118. O 1 I have 'dry' orgasms and afterward my urine looks milky.

119. O 1 I have been unable to have erections or they have been impaired since I started taking a medication called ………………………………………………………….

120. O 1 Other situation, please describe …………………………………………..

121. O 1 None of the above apply.

122. How long have you had difficulty with erectile function ?
O 0   I do not have this difficulty
O 1   Less than 3 months
O 2   3 to 6 months
O 3   7 to 12 months
O 4   13 months to 5 years
O 5   More than 5 years
O 6   As long as I can remember

123. Is this difficulty getting:
O 0   I do not have difficulty
O 1   Much worse
O 2   Somewhat worse
O 3   Staying the same
O 4   Somewhat better
O 5   Much better
O 6   Completely gone

124. In the past year, without sunglasses or tinted glasses, has bright light bothered your eyes ?
O 1 Never   O 2 Occasionally
O 3 Frequently   O 4 Constantly

125. How severe is the sensitivity to light ?
O 1 Mild   O 2 Moderate   O 3 Severe

126. In the past year, have you had trouble focussing your eyes ?
O 1 Never   O 2   Occasionally
O 3 Frequently   O 4   Constantly

127. How severe is this focusing problem ?
O 1   Mild   O 2 Moderate   O 3 Severe

128. In the past year have you had blurred vision ?
O 1 Never   O 2   Occasionally
O 3 Frequently   O 4   Constantly

129. How severe is the focusing problem
O 1   Mild   O 2 Moderate   O 3 Severe

130 In the past year, have you had difficulty seeing at night ?
O 1 Never   O 2   Occasionally
O 3 Frequently   O 4   Constantly

131. How severe is the focusing problem
O 1   Mild   O 2 Moderate   O 3 Severe

132 In the past year, has the same degree of light seemed:
O 1   Excessively dimmer   O 2   Much dimmer
O 3   About the same   O 4   Much brighter
O 5   Excessively brighter

133. Which one of the following eye symptoms is the most troublesome for you ?
O 0   None   O 1   Trouble focusing O 2   Blurred vision
 O 3   Difficulty seeing at night.

134. How long have you had this troublesome eye symptom ?
O 0   I don't have any of these symptoms
O 1   Less than 3 months
O 2   3 to 6 months
O 3   7 to 12 months
O 4   13 months to 5 years
O 5   More than 5 years
O 6   As long as I can remember

135. Is this most troublesome symptom with your eyes getting:
O 0   I don't have any of these symptoms
O 1   Much worse
O 2   Somewhat worse
O 3   Staying the same
O 4   Somewhat better
O 5   Much better
O 6   Completely gone

136. In the past year, have you ever noticed or been told that while sleeping you stop breathing for several seconds ?
O 1   Yes   O 2   No

137. In the past year, have you ever noticed or been told that while sleeping you snore loudly ?
O 1   Yes   O 2   No

Have you ever been told you have or been diagnosed as having :

138. Narcolepsy
     O 1 Yes   O 2 No   O 3 Don't know

139. Obstructive sleep apnoea
     O 1 Yes   O 2 No   O 3 Don't know

140. Abnormal or disordered sleep
Patterns
     O 1 Yes   O 2 No   O 3 Don't know

141. Currently, how refreshing and restorative is your sleep
O 1 Not at all restorative – derive no benefit

O 2 Some slight restorative value
O 3 Restorative, but not adequate
O 4 Relatively satisfactory
O 5 Very satisfactory – feel completely refreshed

142.   Compared with a year ago, how would you rate your own sleep over the last month ?
O 1 Last month was much worse than a year ago
O 2 Last month was slightly worse than a year ago
O 3 Last month was about the same as a year ago
O 4 Last month was slightly better than a year ago
O 5 Last month was much better than a year ago

143.   Have you ever in your adult life had difficulty getting to sleep or staying asleep once you were asleep?
O 1   Yes   O 2   No

144.   In the past year, have you ever noticed or been told that during the day you sometimes breathe very loudly (e.g. croup) ?
O 1   Yes   O 2   No

How would you describe your alcohol use of the past year (check all that apply)
145. O 1   I have not drunk any alcohol over the last year

146. O 1   I drink socially only.

147. O 1   I have used alcohol excessively in the past year.

148. O 1   I have been intoxicated one or more times in the past year.

149. O 1   I have passed out from drinking too much alcohol one or more times in the past year.

How would you describe your drug use over the past year ? (check all that apply)

150. O 1   I have not used any drugs in the last year

151. O 1   I have used drugs excessively in the last year

152. O 1   I have been intoxicated from drugs one or more times in the last year.

153. O 1   I have passed out from taking drugs one or more times in the last year.

154. Have you ever felt that you have used alcohol or drugs excessively ?   O 1 Yes   O 1 No

155. Have you ever been told or have you been diagnosed as having alcohol of drug dependency ?
O 1   Yes   O 2   No

156.   Have you received treatment for alcohol or other drug dependency
O 1   Yes   O 2   No   Please list the drugs involved including alcohol

   …………………………………………………………………..
Which of the following describe your cigarette smoking ? (check all that apply)
157. O 1   I have never smoked cigarettes

158. O 1   I have smoked cigarettes in the past but stopped: Date stopped :

163. O 1   I am currently smoking about ……………………… cigarettes per day.

166. In the past 5 years, how would you rate the amount of trouble, if any you have had with over sensitive hearing ?
O 1 None   O 2   Some   O 3   A lot   O 4 Constant

167. Have you ever in your adult life had difficulty keeping your mind on your job or task ?
O 1   Yes   O 2   No

What medications have you taken in the past month ?

Name of medication   How often do you take it   How much do you take each time

……………………..   …………………………………

…………………………………….

……………………..   …………………………………

…………………………………

…………………….   …………………………………

…………………………………….

……………………   ………………………227…………

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…………………….   …………………………………

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……………………..   …………………………………

…………………………………….

……………………..   …………………………………

……………………….................

We welcome below (or on a separate sheet) any comments you might have about what might have caused or been associated with your current illness or anything that might be helpful to us in understanding your current condition.

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