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The interface between human behaviour and technology in youth with type 1 diabetes mellitus

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Date of Submission : August 2014

This thesis is submitted to National University of Ireland, Galway in accordance with the requirements for the Degree of Doctor of Medicine (MD).
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Summary of Contents

Utilisation of technology in the management of youth with type 1 diabetes has increased substantially over the past decade, however glycaemic results remain suboptimal for a significant proportion of users. Continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring systems (CGMS) represent cost-effective modalities, contingent upon achievement of target glycaemic control.

Controversy exists surrounding who to prioritise for these therapies, given current resource-limited healthcare systems. As metabolic control has been shown to correlate with amount of interaction at the user-technology interface, the premise of this work was the exploration of this human factor and the possibility of using personal characteristics to predict successful engagement with technology.

The first study in this work examined the impact on self-care parameters of CSII-automated blood glucose level (BGL) delivery versus the standard manual-entry method. This randomised crossover study displayed a mean increase of one BGL per day during the automated phase, but this did not translate to improvement in metabolic control, or other self-care behaviours.

Thereafter, I conducted a systematic review of the literature in order to identify reproducible demographic, inter- and intrapersonal characteristics robustly associated with, or predictive of, self-care or metabolic control. This examination of seventy empiric studies resulted in thirteen factors which were then coalesced into a questionnaire-based tool.

Finally, I conducted a clinical trial of this questionnaire in 97 youth with type 1 diabetes, 50 of whom subsequently commenced using
‘real-time’ CGMS and 47 of whom subsequently commenced CSII utilisation. The questionnaire resulted in a 92% accuracy in prediction of participant usage of CGMS and exhibited 95% accuracy in the CSII cohort.

This work advances our knowledge regarding the human element of diabetes-related technology and culminated in a pilot study of the first successful tool shown to be predictive of technology usage in children and adolescents with type 1 diabetes.
Preface

All of the work reported in the following thesis is entirely the product of my own original research, carried out in The Royal Children’s Hospital with the support of my supervisors Prof Fergus Cameron and Dr Michele O’Connell.

In the case of both clinical trials, I performed the role of principal investigator and was responsible initially for the production of the study protocol, grant funding applications and approval for trial commencement from the hospital Human Research Ethics Committee. Following on from this, I was responsible for participant recruitment, organisation of per-protocol investigations, data recording and analysis and reporting of all results.

In the case of the final clinical trial of the questionnaire-based tool, I acknowledge the assistance of Prof Timothy Skinner in carrying out the logistic regression analysis. I personally completed all of the education sessions for the fifty participants in the continuous glucose monitoring arm of this trial. The participants in the insulin pump arm had their education in continuous subcutaneous insulin infusion completed by the diabetes nurse educators in the Department of Endocrinology, as per standard hospital guidelines.

Data from this work were presented by myself at the annual meeting of the International Society for Pediatric and Adolescent Diabetes in Gothenburg, Sweden (Oct 2013).
Acknowledgements

This thesis reports research I conducted over the past three years and would not have been possible without the assistance of many people I have been fortunate enough to encounter over that period.

Firstly, I wish to extend my gratitude to my senior colleagues in the Department of Endocrinology at The Royal Children’s Hospital in Melbourne. Prof George Werther, as Head of Department, inspires an environment of intellectual enquiry and continual learning throughout the Unit, equally fostered by Prof Fergus Cameron, A/Prof Margaret Zacharin and Drs Michele O’Connell, Matt Sabin, Peter Simm, and Jacky Hewitt. I also had the pleasure of working alongside Prof Garry Warne briefly before his retirement. My experience within this Department was universally enjoyable and I have learnt an immeasurable amount both in terms of clinical and research knowledge and ‘non-clinical’ practicality thanks to you all.

Another privilege was to work with fabulous ‘fellow fellows’ Dr Jarod Wong and Dr Mary White to whom I thank for your constant encouragement, support and cups of tea. It was inspiring to work in an environment of such collegiality and within a triad with a great working relationship. Other members of the Department also deserve mention, in particular the diabetes nurse educators who provided support at all stages of my clinical trials, especially Lauren Foulds and Samantha Bridgland who selflessly sent through some final data after my departure from Australia. The support of other administrative staff was appreciated, such as Joanne Gurrisi, Ruki Gunaratne and Lee-Ann Jones, all of whom helped troubleshoot some secretarial aspects and most importantly helped solve the mystery of the missing pumps (and other stories).
Many thanks also to the staff of the Clinical Epidemiology and Biostatistics Unit (CEBU), who provided instruction regarding the nuances of STATA; most notably A/Prof Susan Donath who provided enormous help both at trial planning stages and in supervising my STATAnalyses, followed by support when foiled by an errant bracket or comma. Credit is also due to Poh Chua in the library for her ‘EndNote’ mentoring.

Of course none of this work would have taken place without the children, adolescents and their families who volunteered participation in the two clinical trials conducted. I am immensely thankful for their time and assistance.

Principally, I am exceptionally indebted to my supervisors - Prof Fergus Cameron and Dr Michele O’Connell - for your example of critical thinking, continuous encouragement and patient whittling back of my ‘Joycean tendencies’. I have learnt an incredible amount in terms of clinical and research skills from you both and will always be appreciative of this. Another individual who acted in a supervisory capacity was Prof Timothy Skinner, to whom I am most grateful for his psychological expertise, statistical mentoring and enthusiasm for the research topic. Prof Gerard Loftus also provided essential support from Galway and subsequent to his retirement I am very grateful to Dr Edina Moylett for kindly filling this role.

Finally, I wish to dedicate this work to my family – to my parents Benny and Patsy for their constant love and encouragement, parents-in-law Gertie and Paul Mockler, and above all to my ever patient husband Gerry and children Meadbh and Donnacha, with which we have been blessed.
Publications arising from this work:

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**OM Neylon**, MA O’Connell, TC Skinner, FJ Cameron  
“Demographic, Inter- and Intrapersonal Predictors of Metabolic Control and Self-Care in Youth with Type 1 Diabetes Mellitus: a systematic review” *Diabetes Metab Res Rev.* 2013 May;29(4):257-72. doi: 10.1002/dmrr.2392. PMID:23364787
Major Abbreviations used throughout the text

ΔHbA\textsubscript{1c} : Change in Glycated Haemoglobin

ACS : Adolescent Coping Scale

ACTRN : Australian Clinical Trial Registration Number

AIHW : Australian Institute of Health and Welfare

ANZCTR : Australian New Zealand Clinical Trial Registry

BGL : Blood Glucose Level

BMI : Body Mass Index

BMI-SDS : Body Mass Index – Standard Deviation Score

CGMS : Continuous Glucose Monitoring System

CSII : Continuous Subcutaneous Insulin Infusion

DCCT : Diabetes Control and Complications Trial

DFBC : Diabetes Family Behaviour Checklist

DFCS : Diabetes Family Conflict Scale

DFRQ : Diabetes Family Responsibility Questionnaire

EDIC : Epidemiology of Diabetes Interventions and Complications

ENDIA : ENvironmental Determinants of Islet Autoimmunity

HbA\textsubscript{1c} : Glycated Haemoglobin

HLA : Human Leukocyte Antigen

HREC : Human Research Ethics Committee
ICER : Incremental Cost-Effectiveness Ratio
IDSRQ : Insulin Device Satisfaction Rating Questionnaire
IFCC : International Federation of Clinical Chemistry
IQR : InterQuartile Range
JDRF : Juvenile Diabetes Research Foundation
MARD : Mean Absolute Relative Difference
MDI : Multiple Daily Injections
NICE : National Institute for Clinical Excellence
QALY : Quality-Adjusted Life Years
RCH : Royal Children’s Hospital
ROC : Receiver Operating Characteristic
SAP : Sensor-Augmented Pump
SD : Standard Deviation
SEIFA : Socio-Economic Indexes For Areas
SES : Socio-Economic Status
SMBG : Self-Monitored Blood Glucose
T1DM : Type 1 Diabetes Mellitus
T2DM : Type 2 Diabetes Mellitus
TDD : Total Daily Dose
TEDDY : The Environmental Determinants of Diabetes in the Young
Declaration

I declare that the work reported in this thesis was carried out in accordance with the regulations of the National University of Ireland, Galway. This thesis comprises only my original work and no part of the dissertation has been submitted for any other degree.

SIGNED: ......................................

DATE: ......................................
CHAPTER 1 : INTRODUCTION
1.1 OVERVIEW OF TYPE 1 DIABETES MELLITUS

Type 1 diabetes mellitus (T1DM) is a disorder characterised by autoimmune destruction of the pancreatic beta cells, culminating in insulinopenia with resultant hyperglycaemia. It is one of the commonest chronic disorders diagnosed in childhood and has the 4th highest hospitalisation rate of all chronic childhood disorders, after asthma, childhood cancer and epilepsy (AIHW, 2002b). Hence, T1DM also constitutes a significant economical burden, with an estimated $14.4 billion (11.5 – 17.3) annual cost in the United States attributed to a combination of acute care costs and loss of income (Tao, Pietropaolo et al. 2010). Another report from the American Diabetes Association (ADA), which included other indirect and intangible costs estimated the total national cost of both type 1 and 2 diabetes in the US in 2007 at $174 billion (2008).

1.1.1 Definition of Diabetes Mellitus

Diabetes mellitus is a group of metabolic diseases characterised by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both (Craig, Hattersley et al. 2009). The abnormalities in carbohydrate, fat, and protein metabolism that are found in diabetes are due to deficient action of insulin on target tissues. Type 1 diabetes mellitus accounts for 5-10% of diagnoses of diabetes overall, but is responsible for ~90% of diabetes diagnosed in the paediatric age-group (Vandewalle, Coeckelberghs et al. 1997; Thunander, Petersson et al. 2008). Diagnosis of diabetes can be made on demonstration of any of the following three criteria: the commonest is exhibition of typical symptoms (polydipsia, polyuria and weight loss) with a corresponding random plasma glucose of ≥11.1 mmol/l (200 mg/dl), or a fasting plasma glucose of ≥7.0 mmol/l (126 mg/dl) (Craig, Hattersley et al. 2009). The third criterion by which diagnosis can be made is a plasma glucose level of ≥11.1
mmol/l two hours post-glucose load during an oral glucose tolerance test, as described by the World Health Organisation (1999).

1.1.2 Epidemiology

In 1990 the World Health Organisation initiated the Multi-National Project for Childhood Diabetes (DiaMond Study) to ascertain and monitor the patterns of incidence of T1DM. A total of 19,164 cases were diagnosed in youth <14 years old across 100 centres during the period 1990 – 1994, involving 50 countries (Karvonen, Viik-Kajander et al. 2000). Considerable variability in incidence was demonstrated, with highest rates recorded in Sardinia and Finland (37/100,000 per year) and lowest rates in China and Venezuela (0.1/100,000 per year). In the Republic of Ireland, incidence has been calculated as medium-high at 16/100,000 (Roche, Menon et al. 2002), with a higher rate again calculated in Australia at 22.8/100,000 (AIHW 2010). Significant variation in incidence rates were demonstrated in countries in close geographic proximity, such as between Estonia and Finland. Overall, countries with high proportions of Caucasoid populations exhibited higher incidences, and South-East Asian countries demonstrated the lowest. Seasonality of incidence in children <15 years of age has also been postulated, with peaks in incidence in Autumn and Winter demonstrated in both hemispheres (Moltchanova, Schreier et al. 2009).

Since original incidence reports, it is apparent that T1DM is now the fastest growing chronic childhood condition worldwide. Prospective national and large international registries (EURODIAB) have established increasing incidence trends, particularly amongst the younger age groups [<5 years old] (Gale 2002; Shaltout, Moussa et al. 2002; Carrasco, Perez-Bravo et al. 2006; Soltesz, Patterson et al. 2007; Newhook, Grant et al. 2008). In Australia, T1DM is estimated to be increasing at a rate of 3% per year and incidence rates are predicted to increase by 50% by 2020 (Craig, Howard et al. 2000;
Haynes, Bower et al. 2004). Corresponding data from the Irish National Paediatric Diabetes Register has suggested an increase in incidence of 5% per year (Roche 2014). These data infer a worrying change in the demography of type 1 diabetes, with a linear increase in disease incidence.

1.1.3 Aetiology

Current understanding of the pathogenesis of T1DM is that it develops in a genetically susceptible individual, exposed to an environmental trigger which initiates autoimmune destruction of beta cells via autoreactive T-cells (Todd 2010). This theory is supported in part by studies on immigrant populations, repeatedly showing that when individuals relocate from areas of low to high T1DM incidence, they acquire the higher risk of T1DM associated with their new environment (Siemiatycki, Colle et al. 1988; Cataldo 2005). Pairwise discordance (13-33%) has been demonstrated among monozygotic twins (Barnett, Eff et al. 1981; Kaprio, Tuomilehto et al. 1992); however if followed for a longer duration, overall concordance has been shown to approach 50-60% (Redondo, Yu et al. 2001).

Much research effort has been directed towards identification of this environmental trigger. Both retrospective and prospective studies have proposed associations using multivariate analyses (Visalli, Sebastiani et al. 2003; Haynes, Bower et al. 2007; Algert, McElduff et al. 2009) and a large 15-year prospective multicentre study [TEDDY] is currently underway in an attempt to identify environmental determinants of disease (Group 2008), along with a similar study inherent to the Australian population [ENDIA].

Emphasis has been placed on a possible viral causative role, with molecular mimicry implicated as mediating confusion between self and foreign antigens. Increased incidence of T1DM has been shown after viral epidemics, such as recent H1N1 influenza (Nenna, Papoff
et al. 2011). However, the most commonly implicated viral pathogens are the enterovirus group (Diaz-Horta, Baj et al. 2012), with higher antibody levels demonstrated amongst children with T1DM autoimmunity (Sadéharju, Lonnrot et al. 2001) and enterovirus RNA found more frequently in the gut mucosa of affected children compared to control children (Oikarinen, Tauriainen et al. 2012) as well as in sera, temporally related to onset of autoimmunity (Lonnrot, Korpela et al. 2000). The immunomodulatory role of vitamin D has led to some cross-sectional and birth-cohort studies associating vitamin D deficiency with T1DM risk (Hypponen, Laara et al. 2001; Sorensen, Joner et al. 2012), but other large prospective analysis has refuted this (Simpson, Brady et al. 2011).

Dietary constituents have also been associated with an increased risk, with a particular focus on cow’s milk protein (Muntoni and Muntoni 2006; Luopajarvi, Savilahti et al. 2008; Mericq, Piccardo et al. 2010; Virtanen, Uusitalo et al. 2011). The first dietary primary prevention trial (TRIGR) is underway, designed to establish whether weaning to a highly hydrolysed formula (versus standard cow’s milk) in infancy subsequently reduces risk (Group, Akerblom et al. 2011). There appears to be a weak association of increased risk with advancing maternal age and conflicting results regarding birth order (Bingley, Douek et al. 2000; Sipetic, Vlajinac et al. 2004; Polanska and Jarosz-Chobot 2006). Studies have robustly demonstrated that partaking in the childhood immunisation schedule does not confer an increased risk of T1DM (Hviid, Stellfeld et al. 2004). Interactions between the gut microbiome and T-helper cells are also being explored (Gravitz 2012).

From a genetic perspective T1DM is a polygenic disorder, but various well-defined HLA subtypes are strongly associated with either susceptibility to [HLA-DR3-DQ2 & DR4-DQ8] or protection from [HLA-DQ6 & DQB1] disease development (Gale 2005; Sanjeevi, Sedimbi et al. 2008).
A subclinical prodrome period of varying duration exists before the overt metabolic decompensation of clinical diabetes. Several trials are currently underway examining the prospect of intervention and/or immunomodulation at this stage as part of an overall diabetes prevention strategy (Skyler and Ricordi 2011; Sosenko, Skyler et al. 2011).

1.1.4 History of T1DM

Records of individuals consistent with a type 1 diabetes phenotype are found in ancient texts and historical documents, where it was described as “the melting down of flesh and limbs into urine” (Arateus). Until 1851 diagnosis was based on detection of the sweet taste of an individual’s urine; subsequent to this, enhanced availability of biochemical urine testing emerged and diagnosis increased (Gale 2002). By 1923, urinary glucose measurement was available in many pharmacies at the affordable cost of 1¢ per test (Joslin 1923). Prior to the development of insulin, medical care centered around dietary restriction of extreme degree, scientifically adjusted to deliver 70% fat and 8% carbohydrate (Westman, Yancy et al. 2006). The outcome of this therapy mirrored the bleakness of the diet and quality of life.

All changed upon injection of ‘thick brown muck’ to a moribund Leonard Thompson on 11th January 1922 (Bliss 1983). This insulin extract prepared by Banting & Best required further refinement using the bench skills of Collip and daily injections began 12 days later on 23rd January, dramatically changing the boy’s condition (Banting, Best et al. 1922). Reports that a pancreatic extract had demonstrated life-saving effects were initially met with scepticism, but acceptance quickly followed upon translation of the discovery into a fully effective therapy available to thousands of people via utilisation of the resources of Eli Lilly (Holleman and Gale 2007). Refinement in
crystallisation technique was demonstrated by Abel in 1926, followed by long-acting stabilisation using protamine by Hagedorn in 1936, rendering insulin less soluble at an alkaline pH (Hagedorn, Jensen et al. 1936). Further retardation of the action of insulin was achieved by chemists at Novo in Denmark with the addition of zinc, which amalgamated insulin dimers into hexamer crystals of varying size that released insulin more slowly after administration (Jorpes 1943). Improvements in the predictability of insulin action were contrasted with often severe localised insulin reactions. The latter was alleviated with the introduction of recombinant human insulin in 1982. The recombinant DNA technology produced the alpha and beta chains of the insulin molecule separately through transfection of Escherichia Coli with requisite genetic fragments (Burge and Schade 1997). These chains were then biochemically linked to yield the intact insulin molecule (Burge and Schade 1997). Enzymatic conversion of porcine insulin to the human insulin sequence was achieved in the same year, by substitution of an alanine with a threonine residue at position B29 (Joslin 2004).

1.2 T1DM COMPLICATIONS AND GLYCAEMIC CONTROL

1.2.1 Complications of T1DM

Complications of type 1 diabetes can be short or long-term, with the former relating to the immediate effect on the individual of perturbations in blood glucose levels.

1.2.1.1 Short-term complications

Hypoglycemia is often accompanied by signs and symptoms of autonomic (adrenergic) activation and/ or neurological dysfunction (neuroglycopenia). Children may also exhibit behavioural or mood changes when their blood glucose level falls rapidly but remains
within the normal range (Clarke, Jones et al. 2009). Symptoms include diaphoresis, tachycardia, tremor, and slurred speech with possible progression to confusion, loss of consciousness, seizures and death. The absolute blood glucose level at which signs and symptoms begin to occur may vary among individuals and within the same individual at different times and in different situations (Cox, Gonder-Frederick et al. 1993). A value of ≤3.9 mmol/l (70 mg/dL) has been suggested as the definition of hypoglycaemia for research purposes by the American Diabetes Association and is taken as the recommended lower target for blood glucose levels in individuals with T1DM (2005). Hypoglycaemia and fear of hypoglycaemia remain significant barriers towards optimisation of glycaemic control and represent the main limiting factors towards the success of intensification of therapy (Cryer 2002; Hawkes, McDarby et al. 2014). Conversely, hyperglycaemia can be associated with visual disturbance, irritability, difficulty concentrating, thirst, osmotic diuresis and may progress to ketosis or ketoacidosis. In individuals diagnosed with T1DM, this commonly results from intercurrent illness, insulin omission, or excessive carbohydrate. Extra insulin therapy may be recommended, particularly if associated with ketosis (Brink, Laffel et al. 2009).

1.2.1.2 Long-term complications

Long-term vascular complications of T1DM include microvascular disease (retinopathy, nephropathy, neuropathy) and macrovascular disease (Donaghue, Chiarelli et al. 2009). The outcomes are:

- visual impairment and blindness due to diabetic retinopathy
- renal failure and hypertension due to diabetic nephropathy
- pain, paraesthesiae, muscle weakness and autonomic dysfunction due to diabetic neuropathy
- cardiac disease, peripheral vascular disease and cerebrovascular accident secondary to macrovascular disease.
Pathogenesis of diabetes-associated complications is multifactorial, but relates to the duration and degree of hyperglycaemic exposure encountered by the individual (discussed further in section 1.2.3), compounded by genetic determinants of individual susceptibility and independent accelerating factors such as hyperlipidaemia, cigarette smoking or hypertension (Brownlee 2005). Various molecular pathways are proposed to explain the damage incurred secondary to hyperglycaemia at a cellular level: increased oxidative stress via increased flux through the polyol pathway, intracellular production of advanced glycation end-product precursors, activation of protein kinase C isoforms and increased hexosamine pathway flux with consequent overmodification of proteins by N-acetylglucosamine (Brownlee 2005).

1.2.1.3 Incidence and outcomes of T1DM complications

A declining incidence of long-term complications has been recorded in some specialist T1DM clinics (Mohsin, Craig et al. 2005), however this has occurred in the context of major changes to treatment regimens and goals - as described later in this section - and is not necessarily the case in areas where access to care, funding or glycaemic outcomes remain disadvantageous. A recent retrospective review of young adults with T1DM in the West of Ireland has revealed suboptimal mean HbA\textsubscript{1c} levels (9.6% or 81 mmol/mol) and a high complication prevalence of 32% (Casey, O'Hara et al. 2014). Poor engagement with healthcare services was demonstrated in this cohort.

Life-expectancy of individuals with T1DM has been shown to be reduced when compared with the general population; original estimations from 1975 concluding a 27 year difference (Goodkin 1975). However, studies since then have paralleled the declining complications incidence, with recent work from the Pittsburgh
Epidemiology of Diabetes Complications cohort demonstrating a 15 year increment in life expectancy between persons born between 1950-64 versus 1965-80 (53.4 [50.8–56.0] Vs 68.8 [95% CI 64.7–72.8] years, respectively) \((P < 0.0001)\); this difference persisted regardless of sex or pubertal status at diagnosis (Miller, Secrest et al. 2012). Another contemporary study of almost 25,000 individuals with T1DM from the Scottish Care Information – Diabetes Collaboration Database confirms narrowing gaps in life expectancy across all age brackets between those with T1DM and the general population (Livingstone and Colhoun 2013).

Although functional impact from complications is rare in childhood and adolescence, early functional and structural abnormalities may be present a few years after the clinical onset of the disease (Donaghue, Craig et al. 2005; Eppens, Craig et al. 2006; Rabago Rodriguez, Gómez-Díaz et al. 2007). This implies that attempts should be made from the time of diagnosis to optimise modifiable factors impacting upon an individual’s future complication risk. As well as the considerable personal healthcare burden of diabetes-related complications, the presence of micro- and macrovascular complications has been shown to double the annual cost of treatment in a recent economic analysis of adults with T1DM involving 58 diabetes centres (Franciosi, Lucisano et al. 2013).

1.2.2  **Glycated Haemoglobin**

Glycated (formerly Glycosylated) haemoglobin, or HbA\(_{1c}\), is a glycoprotein formed in a non-enzymatic glycation pathway by irreversible post-translational changes at the N-terminal of the beta chain of the haemoglobin molecule (Abraham, Huff et al. 1978). As the plasma glucose concentration increases, the proportion of glycated haemoglobin increases, serving as a marker of overall metabolic control during the 120-day lifespan of the erythrocyte. Results can be adversely affected in patients with concurrent...
haemoglobinopathies or membranopathies, in a method-dependent manner (Schnedl, Krause et al. 2000). There are currently four principal glycohaemoglobin assay techniques (ion-exchange chromatography, electrophoresis, affinity chromatography and immunoassays) and over 20 methods that measure different glycated products. Attempts are currently underway to globally standardise HbA₁c reporting since the publication of the DCCT (see below) using a working group established by the International Federation of Clinical Chemistry (IFCC) (Hanas and John 2010).

1.2.3 Importance of metabolic control and complications

After initial acknowledgement of the potential usefulness of HbA₁c, it was unknown whether or not it had value in predicting diabetes-associated complications, either micro- or macrovascular (McDonald and Davis 1979). This question was definitively answered upon the publication of the Diabetes Control & Complications Trial (DCCT), a study conducted from 1983 to 1993 in 29 centres across the USA and Canada and funded by the National Institute of Diabetes and Digestive and Kidney Diseases. This randomised clinical trial was designed to compare intensive with conventional diabetes therapy with regard to their effects on the development and progression of early vascular and neurologic complications of insulin-dependent diabetes mellitus. The intensive therapy arm was intended to achieve blood glucose values as close to normal as possible and used ≥3 injections per day or continuous subcutaneous insulin infusion (CSII), adjusted regularly according to self-monitoring of blood glucose (SMBG). Participants in this group visited their study centre every month and frequent telephone contact was maintained between visits. Conventional therapy consisted of one or two insulin injections per day, routine diet and exercise advice and did not usually include regular dose adjustment.
1.2.3.1 DCCT outcomes

Retinopathy was chosen as the primary marker of microvascular complication risk and two cohorts were studied: those without any evidence of retinopathy (establishing primary prevention risk) and a cohort with evidence of early retinopathy (secondary intervention benefit in mild-to-moderate nonproliferative retinopathy). Participants were recruited between the ages of 13-39 years old and of the 1,441 patients recruited, 195 were in the adolescent age-range. The entire cohort was followed for a mean of 6.5 years (range 3-9yrs) and overall, the average percentage of time spent receiving the assigned treatment was 97%, with 99% of participants completing the study.

HbA₁c reached a nadir at 6 months in the intensive treatment arm and despite the rigorous nature of follow-up, the target level of 6.05% was achieved by 44% of participants at least once, but <5% maintained an average value in this range. However, HbA₁c differed significantly between treatment arms from 3 months until trial completion, with the overall mean for the intensive arm at 7.4±1.1% versus 9.1±1.5% in the conventional arm. Quarterly seven-point glucose profiles were also measured and differed significantly between arms (8.6 ± 1.7 mmol/l intensive versus 12.8 ± 3.1 conventional; p<0.001) during the complete course of the study.

1.2.3.1.1 Effect on Primary Prevention of Retinopathy

Retinopathy was assessed 6-monthly by seven-field stereoscopic fundoscopy. Incidence curves began to separate between the two groups at 36 months. During a mean of 6 years follow-up, retinopathy developed in 23 participants in the intensive arm and in 91 participants in the conventional arm. Intensive therapy was calculated to reduce the adjusted mean risk of retinopathy by 76% (95% confidence interval, 62-85%).
1.2.3.1.2 Effect on Secondary Prevention of Retinopathy

During the first year of the study, participants in the intensive-therapy group had a higher cumulative incidence of progression of retinopathy than the conventional-therapy group, but a lower cumulative incidence beginning at 36 months and continuing for the remainder of the study. Overall, intensive therapy reduced the average risk of retinopathy progression by 54% (95% confidence interval, 39-66%).

1.2.3.1.3 Effect on Other Microvascular Complications

Microalbuminuria was defined as urinary albumin excretion of ≥40mg per 24 hours and was measured annually. Albuminuria was defined as a urinary albumin excretion of ≥300mg per 24 hours. Intensive therapy reduced the risk of albuminuria by 56% and microalbuminuria by 34% in the primary prevention cohort and by 43% in the secondary prevention cohort. Neuropathy was defined as the presence of peripheral sensorimotor neuropathy plus either abnormal nerve conduction in at least 2 peripheral nerves, or unequivocally abnormal autonomic nerve testing. In the primary-prevention cohort, intensive therapy reduced the appearance of neuropathy by 69%. In the secondary-prevention group, intensive therapy reduced the appearance of clinical neuropathy at 5 years by 57%. All three components of the definition of neuropathy were reduced equally.

1.2.3.1.4 Adverse Events

Mortality did not differ significantly between treatment arms and overall was less than expected from population-based mortality studies. However, the incidence of severe hypoglycaemia was 3 times higher in the intensive-therapy group versus the conventional group. Despite this, there was no difference between the two therapy groups in the occurrence of changes in neuropsychological function.
There were also no differences between groups in quality-of-life scores. Participants in the intensive therapy group did gain more weight, with a 33% increase in the mean adjusted risk of becoming overweight (>120% of ideal bodyweight). No difference in rates of diabetic ketoacidosis (DKA) were shown between treatment groups.

1.2.3.2 Adolescent Subgroup

Adolescents (13-17 years old) comprised 13.5% of the DCCT cohort (n=195), with 125 adolescent participants recruited to the primary prevention cohort and 70 to the secondary prevention cohort (1994). Adolescent participants were followed for a mean of 7.4 years and target metabolic control was more difficult to achieve in this age-group. The intensive-therapy adolescent group had a mean HbA1c of 8.1% versus a mean of 9.8% in the conventional-therapy group. In the primary prevention cohort, intensive therapy decreased the risk of having retinopathy by 53% (95% confidence interval, 1% to 78%; \( p = 0.048 \)) in comparison with conventional therapy. In the secondary intervention cohort, intensive therapy decreased the risk of retinopathy progression by 70% (95% confidence interval, 25% to 88%; \( p = 0.01 \)) and the occurrence of microalbuminuria by 55% (95% confidence interval, 3% to 79%; \( p = 0.042 \)) (1994). Motor and sensory nerve conduction velocities were faster in intensively treated subjects. Similar to the overall cohort, the major adverse event experienced with intensive therapy was a nearly threefold increase of severe hypoglycaemia. It was concluded that the adolescent subgroup experienced the same benefit afforded to the entire DCCT cohort from intensive therapy and that the intensive treatment option should be offered to all.

1.2.4 Similar studies to the DCCT

Other studies have also confirmed the strong correlation between development of microvascular complications and duration of
Introduction

glycaemic exposure over time. The Stockholm Diabetes Intervention Study evaluated 96 participants with T1DM in a similar manner to the DCCT and resulted in a HbA$_1c$ differential of 7.2±0.1% vs. 8.7±0.1% in the intensive and conventional arms respectively. At 5 years from commencement, a beneficial effect was clearly displayed in the intensive-therapy arm on rates of retinopathy, urinary albumin excretion and nerve conduction studies (Reichard, Berglund et al. 1991). Akin to the findings of the DCCT, increased rates of hypoglycaemia and increased weight were seen in the intensive group.

This effect has also been demonstrated in a large prospective study of individuals with type 2 diabetes mellitus (T2DM) – the UK Prospective Diabetes Study (UKPDS) – providing further evidence of the correlation of hyperglycaemic exposure with development of complications. This controlled trial randomised 5,102 patients with newly-diagnosed T2DM to intensive (median HbA$_1c$ 7.0%) or conventional (median HbA$_1c$ 7.9%) diabetes control. This was conducted in 23 centres across the UK between 1977 and 1991. Overall, the microvascular complication rate was decreased by 25% in the intensive-therapy arm (1998). The effect of intensive hypertension management was also shown to be favourable for all outcomes, both macro- and microvascular.

1.2.5 Epidemiology of Diabetes Interventions and Complications (EDIC)

1.2.5.1 Overview of EDIC

The relative youth of participants in the DCCT precluded the assessment of macrovascular outcomes, hence 97% of the surviving original DCCT cohort agreed to participate in a follow-up study which ran from 1994 to 2005. The aim of this study was also to provide longer-term follow-up regarding microvascular complication risk and
93% of the original cohort remained in the EDIC study until completion. During the EDIC observational extension study, the methods used in the DCCT were continued, although with reduced frequency of contact, and participants’ diabetes care was returned to their own health-care providers. HbA$_{1c}$ was measured annually, along with an annual electrocardiogram and fasting lipid levels and renal function on alternate years (1999).

During the 11-year follow-up period, differences in the mean HbA$_{1c}$ values between treatment groups narrowed considerably ($8.0\pm1.2\%$ intensive-therapy versus $8.2\pm1.2\%$ conventional-therapy, $p=0.03$) and the absolute difference between groups by year 11 was only 0.1%. The risk of first occurrence of non-fatal myocardial infarction, stroke, or death from cardiovascular disease was reduced by 57% in the intensive-therapy group when compared to the conventional-therapy group (95% confidence interval 12 to 79%, $p=0.02$) (Nathan, Cleary et al. 2005). A slightly higher proportion of the conventional therapy group had micro- or overt albuminuria at conclusion of the DCCT, which increased the risk of cardiovascular disease by over 250%. However, the difference in cardiovascular disease outcomes between therapy groups remained significant after statistical adjustment for these factors. Hence it was concluded that intensive therapy in T1DM has long-term beneficial effects on cardiovascular disease risk. Further studies have also examined carotid intima-media thickness and progression of coronary artery calcification as markers of cardiovascular disease and displayed ongoing benefit in terms of both in the intensive-therapy cohort (Nathan, Lachin et al. 2003; Cleary, Orchard et al. 2006).

1.2.5.2 Long-term benefit on microvascular complications

Despite regression of HbA$_{1c}$ towards the mean in both treatment arms over the first 4 years of EDIC follow-up, continued differences in complication occurrence rate and progression were demonstrated
(odds reduction worsening retinopathy, 72% to 87%, P<0.001) (odds reduction microalbuminuria 59%) (2000; 2003). This phenomenon has been labelled "metabolic memory", proposed to suggest that hyperglycaemia contributes to the development of complications over an extended period of time (and conversely can take an extended period before benefit is shown with an improvement in control). Ten years on from DCCT completion, this effect was beginning to wane somewhat, with calculated retinopathy risk reduction in 1,211 of the original cohort attenuated to 53% (White, Sun et al. 2008).

1.2.5.3 Long-term benefit in adolescent group

Of the original 195 DCCT adolescent cohort, 156 individuals were evaluated at EDIC year 10. Compared to adults at DCCT baseline, the adolescent subgroup were more likely to be part of the primary prevention cohort, have a higher HbA1c (9.6% at baseline) and have milder retinopathy. At DCCT completion, they had a higher mean HbA1c during the trial period, a longer duration of follow-up, more severe retinopathy and higher albumin excretion rate.

During the ten years of follow-up, adolescent mean HbA1c did not differ significantly from adults, or by previous treatment group (8.2±1.3% ex-intensive-therapy group versus 8.2±2.1% ex-conventional-therapy, p>0.05). By DCCT year 10, the majority of participants (>90%) were using intensive insulin therapy. More than 55% of participants were SMBG ≥4 times per day, except the adolescent ex-conventional-therapy group (39%, p=0.018). However, after 10 years of EDIC follow-up, there was no longer overt evidence of metabolic memory in the adolescent subgroup, with 40% each of ex-intensive and ex-conventional groups exhibiting retinopathy progression (odds ratio 0%, -88 to 49%, p=0.95) (White, Sun et al. 2010). This finding was examined intensively, using separate Weibull models constructed with and without adjustment for mean HbA1c during DCCT and across the DCCT and EDIC combined. These
models showed that 79% of the metabolic memory difference between adults and adolescents was attributed to the difference in mean HbA\textsubscript{1c} level during the DCCT (8.9% adolescents vs. 8.1% adults) and 86% attributable to the mean HbA\textsubscript{1c} difference across DCCT and EDIC combined (8.4% vs. 8.0% for the combined adolescents vs. adults respectively). This inferred that the degree of lowered HbA\textsubscript{1c} achieved by the adult group was the likely driving force of the long-term durability of the benefits of intensive therapy. It was concluded that the metabolic memory phenomenon is largely driven by the prior levels of glycaemic control achieved, postulate to result from epigenetic mechanisms or accumulation of advanced glycation end-products (White, Sun et al. 2010).

1.2.6 Conclusions and Clinical Impact of DCCT/EDIC and related trials.

The trials as described above provided incontrovertible evidence of the causative link between the duration and degree of hyperglycaemic exposure and the development of micro- and macrovascular complications in diabetes. Notably, no glycaemic threshold for development of complications was displayed. Recommendations for target-related goals therefore moved towards using intensive therapy to maintain the lowest HbA\textsubscript{1c} possible, counterbalanced with the risk of severe hypoglycaemia. Large multicentre analyses from the post-DCCT era displayed this paradigm change, with a large shift towards use of multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) (de Beaufort, Swift et al. 2007).

It has been noted that none of these trials included children <13 years of age, hence there is some discrepancy between international diabetes associations in recommendation of suitable HbA\textsubscript{1c} targets. Concern regarding the inability of young children to effectively recognise and treat hypoglycaemia, along with the potential
possibility of increased neurocognitive impact upon the developing brain has led to the American Diabetes Association producing age-stratified glycaemic targets (Silverstein, Klingensmith et al. 2005), whereas the International Society of Pediatric and Adolescent Diabetes (ISPAD) recommends a blanket target HbA$_{1c}$ of <7.5% for all youth with T1DM (Rewers, Pihoker et al. 2009).

1.3 OVERVIEW OF CURRENT MANAGEMENT

1.3.1 Insulin Analogs

Attempts to further mimic normal physiologic insulin secretion, particularly the post-prandial phase, led to development of novel synthetic insulins referred to as insulin analogs (Holleman and Hoekstra 1997). Early efforts to create rapidly absorbed analogs after subcutaneous injection were successful, but quickly re-evaluated after a dose-dependent increase in mammary carcinoma was demonstrated in mice. This was attributed to an increased affinity of the analog for the receptors of insulin-like growth factor-I, or a decreased rate of dissociation of the analog from the insulin receptor, and clinical studies were halted (De Meyts 1994). It was the structural homology of insulin with insulin-like growth factor-I that led to the development of the first analog insulin for use - insulin lispro (DiMarchi, Chance et al. 1994; Puttagunta and Toth 1998). Both lispro and then rapid-acting aspart (Heinemann, Kapitza et al. 1996) were introduced at the turn of the 21st century and arise from amino acid substitutions at position 28 (aspart) or 29 and 30 (lispro) of the beta-chain. These insulins have effect within minutes of injection, peak action at approximately thirty minutes and have a duration of action of less than four hours (Holleman and Hoekstra 1997). These characteristics have led to their widespread use in multiple daily injection regimens and in insulin pump therapy.
The observation that pre-prandial glucose values rise with short-acting analogs helped to promote the idea of increased focus on basal insulin (Holleman and Gale 2007). Intermediate and long-acting insulin analogs were then developed, with insulin glargine launched as a ‘peakless’ insulin with 24 hour duration (Lepore, Pampanelli et al. 2000). Insulin detemir was also developed, molecularly adapted by attachment of a fatty-acid tail to the beta chain of the insulin molecule, resulting in increased subcutaneous self-aggregation and buffering via increased binding to albumin (Havelund, Plum et al. 2004). Although clinical use of these analog insulins has increased exponentially, they have not displayed convincing evidence for improved glycaemic control, but have shown some advantage in reduction of nocturnal hypoglycaemia (NICE 2005).

1.3.2 Self-Monitoring of Blood Glucose (SMBG)

The goal of SMBG is to collect detailed information about blood glucose levels at many time points to enable maintenance of a more constant glucose level by more precise regimens. It can be used to aid in the adjustment of a therapeutic regimen in response to blood glucose values and to help individuals adjust their dietary intake, physical activity, and insulin doses to improve glycaemic control on a day-to-day basis (Benjamin 2002). It most commonly involves pricking a finger with a lancet device to obtain a small capillary blood sample, applying a drop of blood onto a reagent strip, and determining the glucose concentration by inserting the strip into a glucometer device for an automated reading. Test results are then recorded manually in a logbook, or stored in the glucometer’s electronic memory. With the majority of modern glucometers, later download is possible via the user’s personal computer, which can convert the data into a logbook-type format, and/or provide simple analytical focus as desired e.g. on post-prandial trends.
A wide variety of glucometers are now available, with measurement methods having advanced from original photoreflectance methods to current electrode biosensors utilising either the glucose oxidase or glucose dehydrogenase reaction to quantify glucose levels, subsequently displayed on a digital readout. Results are now available faster (5 – 15 secs) and require less sample (0.3 – 1.0 µL blood) using portable, battery-powered, handheld units, some with built-in lancet or reagent facilities (Clarke and Foster 2012). Current meters exhibit accuracy performance superior to that of previous generations, however studies demonstrate that a significant proportion of measurement still falls outside the 2006 ADA criteria of <5% deviation from reference intervals, particularly at the hypo- or hyperglycaemic extremes (Sacks, Arnold et al. 2011). Operator error also remains noteworthy and important variables such as humidity, dilution, altitude, ambient temperature and anatomic site can potentially impact upon results.

It is recommended that persons with diabetes be taught to self-monitor and use their SMBG results to correct any deviations out of a desired target range by changing their carbohydrate intake, exercising, or using more or less insulin (2014). This also enables detection of hypo- or hyperglycaemia and subsequent response to the treatment of same.

The number and regularity of SMBG should be individualised, but successful application of intensified diabetes management with MDI or CSII requires frequent SMBG (four to six times a day) and regular, frequent review of the results to identify patterns requiring adjustment to the diabetes treatment plan (Rewers, Pihoker et al. 2009). The frequency of SMBG performed is consistently associated with improved HbA1c in individuals with T1DM, both in youth using injectable regimens and those using CSII (Haller, Stalvey et al. 2004; Schutt, Kern et al. 2006; Ziegler, Heidtmann et al. 2011). However individual acceptance and performance of SMBG to an optimal
frequency remains variable, particularly among the adolescent population (O'Connell, Donath et al. 2011). Particularly for individuals using CSII, entry of ≥5 BGLs per day to the user’s pump is associated with improved glycaemic control, with an estimated 0.2% reduction in HbA1c for every BGL per day recorded (Svoren, Volkening et al. 2007; O'Connell, Donath et al. 2009; Ziegler, Heidtmann et al. 2011). One of the largest studies involving >26,000 youth aged 0-18 years with T1DM over ten years demonstrated that higher SMBG frequency was significantly associated with better metabolic control, again with a decrease in HbA1c of 0.2% for one additional SMBG per day (p < 0.001). Increasing the SMBG frequency above five per day did not result in further improvement of metabolic control in this cohort (Ziegler, Heidtmann et al. 2011).

1.3.3 Continuous Subcutaneous Insulin Infusion (CSII)

1.3.3.1 Overview of CSII

CSII consists of infusion of short-acting insulin from a reservoir within the pump into the subcutaneous tissue via a ‘giving set’ at preselected programmed rates. This delivers a continuous basal rate of small amounts of rapid-acting insulin throughout the 24 hour period, with larger user-activated ‘bolus’ doses at meal or snack times. The basal rate can be programmed to change at various intervals throughout the day, which is particularly useful in regulating overnight blood glucose levels. Bolus doses are given before meals based on the measured SMBG, carbohydrate content of the meal and anticipated exercise after the meal. Further ‘correctional’ bolus doses can be given at any time if the random blood glucose is higher than the target range and there is a need for additional insulin. All user-pump interactions are recorded in the pump device which can then be downloaded to a computer to demonstrate a log-book view of various different parameters e.g. time and values of SMBG, time and amount of carbohydrate consumed and amount of insulin delivered.
(see Figure 1-1 & Figure 1-2). This allows for critical analysis of glucose control and enables identification of areas for adjustment to improve control.

Use of CSII involves an increased level of commitment to diabetes management, with the necessity to perform generally 3-8 boluses per day, a minimum of 5 BGLs per day and changing of the line and cannula set at a minimum of every three days. Unrealistic expectations of CSII prior to commencement can be detrimental – in particular the belief that CSII reduces or eliminates responsibility for diabetes management (Grunberger, Bailey et al. 2010).

![Figure 1-1: CSII logbook download](image)
Dr. Arnold Kadish of Los Angeles, California, devised the first insulin pump in the early 1960s. Originally it was worn on the back and was roughly the size of a large backpack, but current devices are slightly larger than a pager. With refinement of this technology, CSII use in the paediatric population gained increasing popularity in the 1990s and increased ten-fold during the first decade of the 21st century (Sulmont, Lassmann-Vague et al. 2011).

1.3.3.2 CSII Outcomes

Most studies suggest that CSII does confer advantage in improvement of metabolic control parameters. The majority of studies in the paediatric population are of short duration (6-12 months) and display either equivalence or small-modest improvements in HbA1c (Weintrob, Benzaquen et al. 2003; Nuboer, Borsboom et al. 2008; Batajoo, Messina et al. 2012). Meta-analyses confirm a moderate reduction of HbA1c with CSII use of the order of -0.2 to -0.4% and are suggestive of an improvement in reduction of hypoglycaemia (Weissberg-Benchell, Antisdel-Lomaglio et al. 2003; Jeitler, Horvath...
et al. 2008; Pankowska, Blazik et al. 2009; Gane, White et al. 2010). These studies have reported no increase in adverse events with use of CSII. A Cochrane review of 976 adults and children comparing CSII with MDI in T1DM concluded that a difference in HbA1c exists, favouring CSII (weighted mean difference -0.3% (95% confidence interval -0.1 to -0.4)). There were no obvious differences between the interventions for non-severe hypoglycaemia, but severe hypoglycaemia appeared to be reduced in those using CSII (Misso, Egberts et al. 2010).

This review also examined quality of life measures and suggested that CSII offered advantage over MDI. Increased flexibility of eating and daily activities has suggested overall improvement in quality of life, but conflicting evidence exists amongst the small number of studies available, as demonstrated by meta-analysis (Barnard, Lloyd et al. 2007). Quality of life improvement post-CSII commencement has been particularly demonstrated in pre-school users and their families, attributed to reduced problems with nutrition management (Muller-Godeffroy, Treichel et al. 2009).

Achievement of glycaemic targets appears to be more likely in prepubertal children, possibly secondary to increased parental involvement in, or oversight of, daily management tasks (Nabhan, Rardin et al. 2006; Danne, Battelino et al. 2008; Hughes, McDowell et al. 2012). Commencement of CSII in younger age groups is also associated with higher rates of HbA1c target acquisition and reduced discontinuation rates (Babar, Ali et al. 2009) although no effect has been shown in terms of when CSII commencement is optimal, related to diabetes disease onset (Shalitin, Lahav-Ritte et al. 2012).

One potential disadvantage with CSII is the use therein of only rapid-acting short term insulin such as lispro or aspart. Despite concern that infusion set occlusion could result in insulin interruption and diabetic ketoacidosis, the risk of this compared with users on
injectable regimens has not been shown to be increased in large scale registry studies (Cengiz, Xing et al. 2013).

1.3.4 Continuous Glucose Monitoring Systems (CGMS) and Sensor-Augmented Pump (SAP) Therapy

1.3.4.1 Overview of CGMS

CGMS consists of two components: a sensor device which is inserted into the subcutaneous tissue and a transmitter which either records the glucose information for retrospective analysis, or relays it wirelessly to an external monitor (either a stand-alone device or directly to a user's insulin pump display screen; also known as ‘real-time’). When displayed in ‘real-time’, the sensed glucose level from the interstitium is shown in numerical and/or graphic format, averaged at intervals of between one to five minutes depending on the model. This can be accompanied by trend arrows which depict whether an individual’s BGL is increasing, decreasing or remaining stable. The rate of change of glucose concentrations can be displayed and used to generate alarms alerting the user to either actual or impending hypo- or hyperglycaemia. Stand-alone devices can be worn by the individual (e.g. using an injectable regimen), or consist solely of a monitor e.g. in a parent’s bedroom to monitor for nocturnal hypoglycaemia.

The system must be calibrated by entering a capillary blood glucose level into the person’s pump system at a minimum of twice a day (Clarke and Foster 2012). CGMS has advantages over traditional fingerprick methods in that it provides more frequent measurements (1 - 5 minute intervals), thereby showing trends in glucose and detecting excursions from the normal range which would otherwise have been missed with ‘snapshot’ BGL readings over the course of a day [see Figure 1-3 ] (Clarke and Foster 2012). The ability to download this data from either monitors or insulin pumps using
computer software allows for more in-depth retrospective analysis of patterns or trends, thereby allowing insulin rates or ratios to be adjusted accordingly.

**Figure 1-3: CGMS Vs SMBG**

Technological progress has resulted in much more user friendly devices since the first commercially available continuous glucose sensor systems. Originally microdialysis methods were used (Bolinder, Ungerstedt et al. 1992; Bolinder, Ungerstedt et al. 1993), progressing to the four subcutaneous systems currently available commercially: the Freestyle Navigator (Abbot Diabetes Care, Alameda, CA), the Guardian Real-Time (Medtronic MiniMed, Northridge, CA), the Dexcom SEVEN (Dexcom, San Diego, CA), and the GlucoDay (Menarini Diagnostics) (Hermanides, Phillip et al. 2011). All measure glucose using the glucose-oxidase reaction and all are subcutaneous needle-based systems except the GlucoDay, which is a microdialysis-type sensor not commercially available in Australia or Ireland. Glucose-oxidase acts as a catalyst which generates an electron per glucose molecule, thus generating a current proportional to the interstitial fluid glucose concentration (Klonoff 2005). Hence, the sensor continuously converts small
amounts of glucose from the subject’s interstitial fluid into an electronic signal, then translates this to a BGL value and relays it to the receiver device (Klonoff 2005).

Accuracy of measurement relative to BGL can be variable, with mean absolute relative difference (MARD) between sensed and laboratory glucose values measured between 16 – 21% (Kovatchev, Anderson et al. 2008). Newer generation sensors are becoming available, which at the time of writing are reported to have improved MARDs of 13% (Keenan, Mastrototaro et al. 2012).

1.3.4.2 Sensor-Augmented Pump (SAP) Therapy

Sensor-augmented pump therapy (SAP) is the term used to describe use of CSII combined with ‘real-time’ CGMS i.e. the ability to view interstitial glucose data transmitted from the CGMS on the pump screen, with integrated features such as alarm generation, or basal insulin suspension (see Figure 1-4). Advantages of this over SMBG include 24 hour BGL profiling, particularly revealing overnight and post-prandial glucose patterns. Devices require a variable ‘warm-up’ period ranging from 4 – 10 hours post-insertion and must be calibrated at a minimum of twice per day with a capillary SMBG level. Disadvantages include inaccuracy of BGL measurement, thereby generating ‘false’ hypo- or hyperglycaemia alarms from the system which may negatively impact upon user satisfaction and trust in the system.

Views can incorporate trend graphs of various time-frames over the past 24 hours, rate and direction of contemporary glucose change indicated by trend arrows and wireless connectivity strength. Alarms may be generated when sensed glucose levels are detected as having reached predefined ‘high’ or ‘low’ glucose levels. These levels, combined with the rate of change, can be used to calculate
predictive threshold alarms, which may be generated to give advance warning of impending hypo- or hyperglycaemia.

One model (Medtronic MiniMed Paradigm® VEO) incorporates the first algorithm allowing autonomous insulin management by the system, in the form of ‘threshold suspend’ or ‘low-glucose suspend’. This essentially allows automatic suspension of insulin delivery when a preset sensed low-glucose threshold is reached, combined with an absence of response by the user to the initial hypoglycaemia alarm. This has been used in over fifty countries but was not FDA-approved in the US until September 2013, secondary to initial concerns regarding the potential for ketosis. To date, this risk has not been shown to be increased after overnight insulin suspension (Beck, Raghinaru et al. 2014).

Figure 1-4: Sensor-augmented pump
A = insulin pump; B = cannula and line for insulin delivery; C = subcutaneous glucose sensor; D = transmitter
1.3.4.2.1 SAP Outcomes

The question of benefit to overall metabolic control with use of SAP continues to be explored. Definitive evidence exists for significant HbA$_1c$ reduction without increase in hypoglycaemia with use of SAP as compared with MDI; however it is difficult to extrapolate the amount of true benefit attributable purely to the SAP component from any potential effect of CSII over MDI in these studies (Bergenstal, Tamborlane et al. 2010; Hermanides, Norgaard et al. 2011).

The majority of studies comparing SAP to CSII with conventional self-monitoring of blood glucose comprise mostly adult populations and display mixed results to date (Hirsch, Abelseth et al. 2008; Battelino, Conget et al. 2012). The initial pilot study in a paediatric population (n=30) was encouraging, demonstrating a mean improvement in HbA$_1c$ of 0.3% after 13 weeks of SAP use, as well as an increase in time spent in the euglycaemic range from 52% to 60%. This cohort displayed excellent baseline metabolic control with a mean HbA$_1c$ of 7.1% (Buckingham, Beck et al. 2007).

Preliminary multicentre randomised controlled studies followed, led by a working group funded by the Juvenile Diabetes Research Foundation (JDRF). The first cohort of 322 adults and children (of which 114 were aged between 8-14 years old) was assessed over a 26 week period, randomised to any of three types of CGMS compatible with participants' pump systems. Primary outcome examined was the change in HbA$_1c$ from baseline to 26 weeks post-commencement. A significant reduction in HbA$_1c$ of 0.5% with SAP use was demonstrated, without increasing hypoglycaemia frequency, but only in the 98 participants aged ≥25 years old (Tamborlane, Beck et al. 2008). The use of SAP averaged six or more days per week (i.e. 86% usage) for 83% of patients 25 years of age or older, 30% of
those 15 to 24 years of age, and 50% of those 8 to 14 years of age. Further examination of the SAP subjects in this cohort confirmed that the benefit obtained with SAP was proportional to the time spent wearing the CGM component. Improved glycaemic control was shown in all age brackets when the SAP system was employed ≥80% of the time and usage during the first month of the trial was predictive of eventual usage at 26 weeks (Beck, Buckingham et al. 2009).

Other studies involving paediatric participants are suggestive of a benefit to metabolic control, but again this benefit is consistently proportional to the amount of time spent wearing the CGM device (O’Connell, Donath et al. 2009; Raccah, Sulmont et al. 2009). These studies concluded a threshold usage of ≥70%, in order to significantly reduce HbA1c by 0.5% and utilised a single type of CGMS model as compared to the JDRF study. A Cochrane systematic review of metabolic benefit conferred by SAP in both adult and paediatric populations concurs with the above findings (Langendam, Luijf et al. 2012).

Mitigation of nocturnal hypoglycaemia has been displayed in older age groups using low-glucose suspend for a three month period, without increased ketotic events or deterioration in HbA1c (Bergenstal, Welsh et al. 2013; Ly, Nicholas et al. 2013). Non-randomised paediatric clinical studies concur with this effect (Danne, Kordonouri et al. 2011).

1.3.5 Future of closed loop insulin delivery

Integration of CGMS with CSII aims to result in ‘closed-loop’ insulin delivery, i.e. a form of ‘artificial pancreas’ which minimises the requirement for a user-driven interface (Klonoff 2005; Hovorka, Nodale et al. 2013). Prototypes of this ‘closed-loop’ system aim to synthesise an insulin pump, a continuous glucose monitoring system
and a control algorithm to safely deliver insulin autonomously. Two main methods of interface are currently being explored: a subcutaneous-subcutaneous (s.c.-s.c.) system and an intravenous-intraperitoneal (i.v.-i.p.) system (Hovorka 2006). The main barrier to the s.c.-s.c. approach is time delays within the system: a ‘lag-time’ in sensed glucose measurements and delay in peak insulin absorption and action, the latter which has been partially ameliorated by application of heat at the site of insulin delivery (Raz, Weiss et al. 2009; Freckmann, Pleus et al. 2012). The system delivers appropriate insulin in the resting/overnight period, but is significantly challenged during states of rapid glucose change, such as the post-prandial period, or with exercise (Elleri, Allen et al. 2011; Phillip, Battelino et al. 2013). Hence, a hybrid approach has recently been proposed, incorporating user-driven ‘meal announcement’. The possibility of dual-hormone pumps incorporating insulin and glucagon/amylin is also being explored and algorithms are continually being revised, however participants in these trials still spent at least 30% of time outside of target glycaemic range (El-Khatib, Jiang et al. 2009; Haidar, Legault et al. 2013) (Ruiz, Sherr et al. 2012). It is unlikely that fully autonomous control will be achieved in the medium-term using the s.c.-s.c. interface.

The i.v.-i.p. system involves intravenous glucose monitoring and intraperitoneal insulin delivery via an implanted pump device, with which there is limited experience worldwide. Cost, the requirement for surgical implantation, along with potential for infection and device failure are significant deterrents to use of this system (Gin, Renard et al. 2003). Delay in insulin action also exists with intraperitoneal administration (Schaepelynck Belicar, Vague et al. 2003) and has resulted in more serious hypoglycaemia in a closed-loop comparison with the intravenous route (LeBlanc, Chauvet et al. 1986). Use of this interface is now largely limited to the intensive-care setting.
1.3.6 Progress Since DCCT/EDIC Studies

With indisputable evidence of the benefit of lower HbA$_{1c}$ levels and the subsequent paradigm shift in treatment regimens and targets that followed, initial improvement in metabolic control was achieved in the 1990s (Chase, Lockspeiser et al. 2001; Bulsara, Holman et al. 2004). However further progress in HbA$_{1c}$ reduction has not been demonstrated over the past decade in the majority of centres in the developed world, for example as demonstrated by one series of studies produced since 1995 by the Hvidoere group (Cameron, de Beaufort et al. 2014).

This group represents a research collaboration of 26 paediatric diabetes centres from 23 countries, with the aim of investigating (A) critical determinants of long-term outcomes of T1DM care and (B) which aspects of care are universally effective. In 1995, 1998 and again in 2005, three observational cross-sectional studies were undertaken across 21 international centres, with central DCCT-aligned HbA$_{1c}$ measurement (Mortensen, Robertson et al. 1998; Holl, Swift et al. 2003; de Beaufort, Swift et al. 2007).

In the first study, major and significant differences were found between centres in terms of metabolic control (mean HbA$_{1c}$ levels ranging between 7.6% and 10.2%), which were not readily explainable by regimen, geography or staffing structure (Mortensen, Robertson et al. 1998). In the 3 yr period between the 1995 and 1998 studies there was a marked overall increase in insulin injection frequency, with use of MDI regimens having increased from 42 to 71% (Holl, Swift et al. 2003). The change to MDI regimens was associated with significantly increased relative mean insulin dose, a significantly increased body mass index, and an approximate doubling of the rate of severe hypoglycaemia without improved HbA$_{1c}$ values (mean of 8.9% in both the 1995 11–18 yr old and the 1998 12–18 yr old group). Relative centre ranking remained stable but
Interestingly, those centres with the lowest mean HbA1c values also had the lowest rates of severe hypoglycaemia and reported better quality of life (Hoey, Aanstoot et al. 2001).

Fourteen centres provided data on 2,093 adolescents between 1998 and 2005 (de Beaufort, Swift et al. 2007). This study again showed that despite major and continuing changes in the use of newer insulin regimens (including CSII), modes of administration, and attempts to improve service provision, glycaemic control did not improve over a decade, with overall mean HbA1c 8.6% in 1995, 8.7% in 1998 and 8.6% in 2005. The lowest mean HbA1c in this study was in the group using twice-daily freemixing of insulin (7.9% ± 0.1) but rather than suggesting superiority of this regimen, it was concluded that it was the mode of employ of that regimen by particular centres that was the significant factor. Indeed, collaborative target setting and effective communication within families were stronger determinants of metabolic control than any other clinical, team resource, ethnic, or demographic variable assessed. These findings would suggest that therapeutic strategies in and of themselves are not enough to obtain desired clinical outcomes.

Data from other large studies and national registries do not display any correlation between insulin regimen and glycaemic control (Nordly, Mortensen et al. 2005; O’Hagan and Harvey 2010; Rosenbauer, Dost et al. 2012). Despite enormous educational and financial effort towards the implementation of technology, use of insulin analogs and other pharmacotechnological innovations, progressive improvement in overall HbA1c is not being experienced, with mean HbA1c values remaining outside target (see Table 1-1) (Ziegler, Heidtmann et al. 2011; HQIP 2012; Wood, Miller et al. 2013; Redon, Beltrand et al. 2014). Currently in large unselected cohorts, mean HbA1c values are repeatedly among the lowest from Germany/Austria and this effect persists in the
prepubertal population, when compared to a similar large cohort from the USA (Maahs, Hermann et al. 2014). In addition, there was no difference demonstrated between CSII and MDI users in this DPV cohort. There has also been report of deterioration in outcomes between 2003 and 2013 despite more clinic attendance, introduction of transition and multidisciplinary clinics and increased CSII use (Johnson, Elliott et al. 2014). Hence, the premise of this work is the exploration of how this technology is being employed at an individual level and the exploration of ‘non-clinical’ barriers towards regimen success.

Table 1-1: Multinational data of metabolic outcomes

<table>
<thead>
<tr>
<th>Population</th>
<th>Age Group</th>
<th>Mean HbA1c</th>
<th>Source of Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US (2010-2012)</td>
<td>1-5</td>
<td>8.2%</td>
<td>Type 1 Diabetes Exchange Clinical Network</td>
</tr>
<tr>
<td></td>
<td>6-12</td>
<td>8.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13-19</td>
<td>8.7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-19</td>
<td>8.4%</td>
<td></td>
</tr>
<tr>
<td>England (2010-2011)</td>
<td>&lt;25</td>
<td>8.9%</td>
<td>National Paediatric Diabetes Audit Report 2012</td>
</tr>
<tr>
<td>Wales (2010-2011)</td>
<td>&lt;25</td>
<td>8.9%</td>
<td>National Paediatric Diabetes Audit Report 2012</td>
</tr>
<tr>
<td>Denmark (2006)</td>
<td>&lt;18</td>
<td>8.2%</td>
<td>National Diabetes Registry</td>
</tr>
<tr>
<td>Germany/Austria (2009)</td>
<td>&lt;20</td>
<td>8.1%</td>
<td>DPV</td>
</tr>
<tr>
<td>France (1998-2007)</td>
<td>5-19</td>
<td>8.3%</td>
<td>Aide aux Jeunes Diabetiques</td>
</tr>
</tbody>
</table>

DPV= Diabetes Patienten Verlaufs dokumentation
1.4 LINK BETWEEN SELF-CARE AND $H_{b}A_{1C}$

There has been much controversy since the late 1990s regarding the terminology surrounding diabetes self-care activities (McNabb 1997; Lutfey and Wishner 1999; Hearnshaw and Lindenmeyer 2006). Construction of a diabetes regimen is ideally achieved by individualisation of options pertinent to the person concerned, chosen in collaborative consultation with the individual’s health-care professional. Historically, this has progressed from the paternalistic notion of “compliance”, which was conceptualised as an individual patient characteristic requiring modification to fit in with the demands of the medical system (Lutfey and Wishner 1999). Furthermore, “non-compliance with medical treatment” was listed as a diagnosis in the handbook of psychiatric disorders DSM-III, further propagating the authoritative practitioner-submissive patient construct. The more patient-centred terms “adherence” and “concordance” were then substituted and whilst the former is still widely used, a redefinition has been recently suggested as “the degree to which a patient follows a predetermined set of behaviours or actions (established cooperatively) to care for diabetes on a daily basis” (McNabb 1997). Problems with an agreed definition, as well as overlap with the previous connotations of compliance, are resulting in a move towards using terms such as “self-management” and “self-care activities”, which may better reflect the fluid nature of the concept (Hearnshaw and Lindenmeyer 2006; Choufani, Shuman et al. 2010; Thomason 2012).

The complexity of daily diabetes care has also resulted in difficulties with self-care quantification, with various measures struggling to satisfactorily coalesce all elements such as insulin administration, diet, exercise, glucose testing and clinic attendance (McNabb 1997). The measures used in studies are heterogeneous and reliant on self-reporting (McNabb 1997).
Studies examining the prevalence of low self-care behaviours in diabetes converge at around 50% (Hauser, Jacobson et al. 1990; Morris, Boyle et al. 1997; Peyrot, Rubin et al. 2005), in agreement with studies on children and adolescents with other chronic illnesses (Lutfey and Wishner 1999; Kyngas 2007). Since publication of the DCCT (1993), the implicit assumption is that optimal self-care behaviours result in optimal glycaemic control and this link has been supported by demonstration of a moderate effect size on meta-analysis of 2,500 children and adolescents (Hood, Peterson et al. 2009). This effect was independent of sociodemographic or disease characteristics and pervasive in both child and adolescent age groupings.

1.4.1 Pump behaviour

The ability of CSII to deliver an improvement in achievement of target HbA$_1c$ is largely user-driven, requiring input of all carbohydrate consumed, regular SMBG and regular titration of rates and ratios according to observed blood glucose levels (BGL). User-modifiable behaviours have repeatedly been shown to directly correlate with level of glycaemic control achieved.

Registration of the correct amounts of carbohydrate consumed, in a timely fashion pre-prandially, is a critically important care component to reduce post-prandial glycaemic excursions. Insulin omission from missed bolus doses is common, particularly amongst the adolescent population (~30%), and has been associated with a negative impact on HbA$_1c$ in several studies (Danne, Battelino et al. 2008; Olinder, Kernell et al. 2009; O'Connell, Donath et al. 2011). Accuracy of carbohydrate counting is also important, with clinically significant loss of post-prandial control displayed once carbohydrate estimation is not within 10g of actual meal carbohydrate (Smart, King et al. 2012). Overestimation of the carbohydrate content of snacks and underestimation of large meals is a common occurrence (Smart,
Ross et al. 2010). Other bolusing factors, such as pre-prandial administration (Scaramuzza, Iafusco et al. 2010), type of bolus chosen and consistent utilisation of the bolus-calculator integral to most CSII models all have impact on metabolic control achieved (Shashaj, Busetto et al. 2008; Blazik and Pankowska 2012).

Frequency of pump infusion line change may also be important. One randomised crossover study showed that glycaemic control deteriorates after 48 hours without changing the infusion set line (Thethi, Rao et al. 2010), whilst another pilot study suggested an optimal frequency for infusion set change of 72 hours (Schmid, Hohberg et al. 2010). Several studies have suggested a large proportion of CSII users exhibit suboptimal line-change frequency (Johansson, Adamson et al. 2005; Hammond, Liebl et al. 2007).

Frequency of SMBG performed and entered by users into their pump device has repeatedly been shown to have strong correlation with overall HbA$_1c$ achieved, presumably via minimisation of time spent in the hyperglycaemic range. This concept was originally suggested for individuals using injectable regimes (Levine, Anderson et al. 2001; Haller, Stalvey et al. 2004), but the correlation appears to be even more linear for users of CSII. A decrease of 0.2% in HbA$_1c$ for each additional BGL per day performed has been suggested (O'Connell, Donath et al. 2011), with the effect appearing to ‘plateau’ at 5 BGLs per day entered into the user’s pump (Ziegler, Heidtmann et al. 2011).

Finally, adequate rate/ratio insulin adjustment, resulting from reflection upon glycaemic patterns in an ‘active’ management strategy appears to be beneficial to overall control (White, O'Connell et al. 2013).
1.4.2 CGMS behaviour

Evidence is now emerging of a benefit to metabolic control with SAP use compared to CSII alone, but most of these studies include children and adolescents as a subgroup along with a larger cohort of older adults (Beck, Buckingham et al. 2009; O’Connell, Donath et al. 2009; Battelino, Conget et al. 2012). Original trials assessing use of the GlucoWatch device showed no improvement in HbA$_1c$, but this device was difficult to use and caused significant skin irritation. Trials with current devices have resulted in metabolic benefit, but this is directly proportional to the duration with which the CGMS device is being worn. For achievement of a clinically significant reduction in HbA$_1c$ and improved time in the normoglycaemic range, studies have suggested a threshold usage of ≥80% [Abbott Freestyle “Navigator” CGMS system] (Diabetes Research in Children Network Study, Buckingham et al. 2007), or ≥70% usage [Medtronic Minimed Paradigm] (O’Connell, Donath et al. 2009; Raccah, Sulmont et al. 2009). This practically equates to use of RT-CGM in conjunction with CSII for 6 or 5 days per week respectively.

Paediatric tolerability for use of SAP for this duration appears to be limited, with significant reduction over time displayed in usage, particularly among the adolescent population (Weinzimer, Xing et al. 2008; Diabetes Research in Children Network Study, Weinzimer et al. 2009; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Beck et al. 2009). Issues of hyperallergenicity to the adhesive are reported in 5-10% of participants in these trials. It would seem prudent that this drop-off in usage is incorporated into future cost-effectiveness analyses where SAP/CGMS is concerned.
1.5 COST-BENEFIT ANALYSIS OF INTENSIVE THERAPY IN T1DM

An economic analysis of the DCCT estimated intensive therapy to be 2-3 times more expensive than conventional therapy (1995). The major contributor to the increased cost was the number of out-patient visits per year (12 versus 4) and the costs of self-care, comprising equipment to facilitate increased SMBG testing, insulin pumps and pump supplies. However, a subsequent economic model taking into account projections of reduced T1DM complications, improved productivity and reduced mortality displayed that intensive therapy is more cost-effective in the longer term, especially if it was possible to deliver within a framework of 4 out-patient visits per year (Herman and Eastman 1998). Similarly, a cost-effectiveness model for T2DM deduced that intensifying treatment doubles pure costs over the course of a lifetime, but that the reduction in lifetime costs of complications offsets this difference, particularly within minority groups and those with a longer duration of T2DM (Eastman, Javitt et al. 1997). Another prospective multivariate analysis of 1,694 adults with diabetes displayed 3-year costs in those with coronary heart disease and hypertension at over 300% the costs of those individuals with diabetes only (46,879 US dollars vs. 14,233 US dollars; P < 0.05) (Gilmer, O’Connor et al. 2005). Higher HbA1c predicted higher costs only for those with baseline A1c >7.5% (P = 0.015) in this study.

1.5.1 Cost-Benefit Analyses of New Technologies in T1DM

1.5.1.1 CSII

Rising health-care costs and an increased demand for, and expectation of, health-care services have raised new issues regarding the efficacy and value of health technologies and other relatively new treatment modalities. It is essential that health-care planners critically analyse the increasing costs of medical care in
order to determine rational allocation of finite resources. Recent studies analysing the effectiveness of CSII include both youth and adult populations in their mathematical analyses, both in the UK and Australia.

Utilising a modelling analysis using a validated CORE Diabetes Model, a UK group attempted to project the long-term costs and outcomes of CSII compared to MDI in the United Kingdom. This study revealed that treatment with CSII is associated with a significant improvement in mean quality adjusted life expectancy (QALE) of 0.76 ± 0.19 years compared with MDI and concluded that CSII produced an incremental cost-effectiveness ratio (ICER) of £25,648 per quality-adjusted life-years (QALY) than MDI (Roze, Valentine et al. 2005). However, it must be noted that these projections were based upon the assumption of a mean HbA$_{1c}$ improvement with CSII use of 1.2%, which may only be achievable in highly motivated individuals demonstrating poor metabolic control prior to pump initiation.

The Australian model also aimed to project long-term costs and outcomes of CSII versus MDI. This group reported a reduction in the cumulative incidence of blindness of 21% (RR = 0.79) and end-stage renal failure of 24% (RR = 0.78), as a result of the improved glycaemic control subsequent to CSII use over a 60-year simulation time-frame. Similar observations were made for other diabetes-associated complications, such as myocardial infarction (11% lower, RR = 0.89). Treatment with CSII was associated with higher mean direct lifetime costs of $41,779 in the adolescent group, but a corresponding gain of 0.56 QALYs for adolescents, as well as a higher overall life expectancy of 0.537 years. Direct costs were outweighed by these findings, generating an ICER of AUD$88,220 versus $77,851 per life-year gained for CSII compared with MDI for adult and adolescent patients respectively (Cohen, Minshall et al.}
2007). The authors showed that the sensitivity of this analysis was strongly influenced by the changed ratio in HbA$_{1c}$.

1.5.1.2 CGMS

As more data emerge about metabolic, quality of life and long-term effects of CGMS, more studies of its cost-effectiveness are required. One of the main barriers to its widespread adoption is the associated cost, which is rarely covered by insurance schemes or government subsidy (Telgener and Lowe 2008). A preliminary assessment of use of the GlucoWatch Biographer was performed and concluded that use of the Biographer, if sustained for the life of the cohort, would delay the development of the first serious diabetes complication by 4.1 yr. Treating 18 subjects would prevent one case of blindness and 1.4 cases of renal failure. The intervention cost was determined to be $91,059/years-of-life (YOL), $61,326/QALYs, and $9930/yr free of a major complication. If the biographer ceased to be effective after age 17, the cost per QALY would increase to $103,178/QALY gained (Eastman, Leptien et al. 2003).

A more recent study compared the cost-effectiveness of SAP in the current environment versus conventional SMBG in individuals with T1DM, using trial data from the original JDRF study cohort as described in section 1.3.4.2 (Tamborlane, Beck et al. 2008). The cohort was analysed in 2 groups, those in whom SAP use resulted in a HbA$_{1c}$ of <7.0% and those with HbA$_{1c}$ of ≥7.0%. In the cohort with higher HbA$_{1c}$, the long-term cost-effectiveness analysis for SAP was projected to reduce the lifetime probability of microvascular complications; the average gain in QALYs was 0.60. The incremental cost-effectiveness ratio (ICER) was $98,679/QALY (95% CI -60,000 [fourth quadrant] to -87,000 [second quadrant]). For the HbA$_{1c}$ <7.0% cohort, the average gain in QALYs was 1.11. The ICER was $78,943/QALY (15,000 [first quadrant] to -291,000 [second quadrant]). This group concluded that if the benefit of SAP had been
limited to the long-term effects of improved glucose control, the ICER would exceed $700,000/QALY. However, considerable uncertainty surrounded these estimates and even more importantly in relation to the work outlined in this thesis, individuals aged 15-24yrs were effectively excluded from the analysis, as this group did not show any HbA$_{1c}$ improvement and demonstrated the lowest SAP usage among all the age-groupings analysed in the original trial (mean usage 30% versus 50% in those aged 8-14yrs and 83% in those aged >25yrs old).

1.6 SUMMARY

In the preceding paragraphs, it has been established that:

Diabetes is a large burden on health-care systems worldwide. This burden is expected to increase exponentially given the rising incidence of the disease, which is developing in a younger cohort, thereby exposing individuals to a longer duration of disease over the course of their lifetime.

Micro- and macrovascular complications contribute overwhelmingly to the increased mortality, morbidity and reduced quality of life experienced by individuals with diabetes. The risk of these complications is substantially reduced with intensive therapy, aiming for as close to normoglycaemia as possible. HbA$_{1c}$ directly correlates with future complications risk.

Economic analyses support the cost-effectiveness of intensification of therapy and of use of diabetes technologies such as CSII and SAP, given the associated long-term reduction in complication risk. However, these models only show effectiveness when technologies are used efficiently, culminating in successful HbA$_{1c}$ reduction. Progressive improvement in HbA$_{1c}$ levels amongst youth is not being
demonstrated in the majority of centres over the last decade, despite widespread implementation of diabetes technologies.

User behaviour strongly correlates with HbA\textsubscript{1c} achieved in both CSII and SAP. Whilst intensification of treatment is definitively cost-effective, new technologies only provide acceptable effectiveness if adequately adopted by users.

1.7 OUTLINE OF RESEARCH DIRECTION

It follows from the above summary that successful selection of patients with T1DM for initiation of the more expensive treatment modalities is essential in order to ensure most rational utilisation of limited health-care resources. This is also fairer to patients, their families and health-care provider teams in terms of allocation of time, expectations, education effort and expense.

My hypothesis was that it is possible to predict usage of advanced diabetes technologies using individual characteristics to predict human behaviour.

The research strategy employed was as follows:

A) Assess whether automation of self-care behaviour can have a positive impact on glycaemic control in youth with type 1 diabetes mellitus

B) Conduct a systematic literature review to define relevant demographic, inter- and intrapersonal factors associated with HbA\textsubscript{1c} or self-care

C) Develop a questionnaire-based tool based upon the findings of the above review

D) Clinically trial the predictive capacity of this tool in youth commencing CGM

E) Clinically trial the performance of this tool in youth commencing CSII
1.8 SETTING AND METHODS COMMON TO ALL STUDIES

1.8.1 Setting

All trials as further described below were conducted at the Royal Children’s Hospital (RCH), in Melbourne, Australia between January 2010 and September 2013.

1.8.2 Structure of the RCH Diabetes Clinic

The paediatric diabetes clinic at RCH provides services to approximately 60% of children with diabetes in the state of Victoria. The area serviced by the clinic is a large, sociodemographically diverse region comprising approximately two thirds of Melbourne and its surrounds (population 4.2 million). At the end of December 2011, the clinic had approximately 1600 patients aged <18.0 years with Type 1 diabetes. The majority of patients are followed up from diagnosis of T1DM at RCH; however the clinic also offers specialist ‘outreach’ services at a number of regional Victorian centres. The service is staffed by a multi-professional team of doctors, diabetes nurse educators, social workers, dieticians and administrative staff. The team aims to review all patients every 3 months in the diabetes outpatient clinic; additional appointments with allied health staff may also be scheduled as required for those who require further education or intensification of their diabetes management. Transition of care to the adult services occurs at the age of approximately 18 years old, dependent upon employment status or completion of secondary education.

1.8.3 Self-Management Education

Young people with diabetes, their families and extended families or carers all take part in a structured education programme regarding diabetes and self-management of T1DM after initial diagnosis, or after transfer to the RCH service. This programme is rigid in its
content but flexible in its delivery, being tailored by allied healthcare staff according to the needs, educational level and adaptation to diagnosis of each family. A comprehensive programme is delivered primarily by the diabetes nurse educators (equivalent to the clinical nurse specialist role in Ireland), with the assistance of dieticians and is delivered usually over three days on a one-educator-to-one-family basis. This is in tandem with national guidelines and recommendations of the Australasian Paediatric Endocrinology Group (APEG) and covers basics such as pathogenesis of T1DM, insulin injection technique, dosing and titration, daily living with diabetes, attenuation of complication risk and health promotion surrounding complication screening, smoking, exercise, foot care and cardiovascular health. Patients post-diagnosis are also reviewed by a departmental social worker, but there is currently no psychologist available to the service.

Delivery of this education in an ambulatory manner is prioritised where possible, facilitating early discharge from hospital. Where necessary, community based nurses visit the individual’s home to assist with insulin administration until the education process is complete. Where this “Hospital in the Home” service is activated, families continue to visit the hospital itself each day for delivery of the structured T1DM education. Advice re dosage titration is sought via phone communication between community nurses and doctors from the RCH diabetes department during this process. Barriers to accessing this service include distance from the hospital, difficulties with numeracy or English language fluency, difficulty with completion of SMBG and/or treatment of hypo- or hyperglycaemia, or psychosocial concerns. Where ambulatory education delivery is not possible, the patient remains an in-patient until the programme is completed to the satisfaction of the family and health-care professionals involved. Progress of each newly-diagnosed patient is reviewed at twice weekly departmental meetings. Upon discharge, patients are supplied with standardised written information and are
followed up as necessary with close phone or e-mail contact by the educator initially involved, with a medical out-patient appointment within two weeks.

Education pre-technology commencement is delivered in a similar standardised fashion within the department. Patients commencing CSII utilisation are educated by staff in age-matched pairs, along with their families. Individuals wear an insulin pump device filled with saline for a week prior to the commencement of CSII proper. Whilst continuing to administer their injectable regimen, this gives an opportunity to practice self-care behaviours necessary for pump usage. A structured programme is then delivered in the hospital over 2.5 days by an educator and a dietician within the department. Education is a mixture of didactic and informal sessions, with a large proportion comprising demonstration and practical use of insulin pumps. At conclusion, a formal test of knowledge acquired is completed by the individual and/or their parents/guardians where appropriate. Follow-up is maintained as required by phone and e-mail, similar to the post-diagnosis process. Patients and families are free to initiate contact whenever necessary and a 24-hour telephone support service is available, with access to departmental staff until 11pm and advice from 23:00 – 07:00 given by medical registrars on duty in-house, with the support of departmental medical staff where required.

Insulin pumps in Australia are covered by a manufacturer warranty for four years after initiation. At this point, permission is sought from the individual’s health insurer to ‘upgrade’ a user’s pump to a new version. Individuals undergoing an ‘upgrade’ process have 2-3 hours of education pertaining to the new model delivered by a diabetes nurse educator, often in conjunction with other individuals/families.
1.8.4 *HbA\textsubscript{1c} Monitoring at the RCH Diabetes Clinic*

Point of care HbA\textsubscript{1c} is measured using the Bio-Rad D-10\textsuperscript{TM} Haemoglobin Testing System (Bio-Rad Laboratories Inc., Hercules, CA, USA), which employs the principles of high performance liquid chromatography. A 5 μL capillary blood sample is required to perform the analysis. Normal (non-diabetic) reference range for HbA\textsubscript{1c} assessed using this method is quoted at 4.5-5.7% (26-39 mmol/mol). The co-efficient of variance for its use in the RCH laboratory is consistently ≤2.8%.

1.8.5 *Auxology*

Weight is measured on digital scales in light clothing with shoes removed; height is measured using a stadiometer. Puberty is assessed according to Tanner and Whitehouse and defined as breast stage 2 or more in girls and pubertal volume ≥4ml in boys (Tanner and Whitehouse 1976).

1.8.6 *Diabetes Clinic Database*

Clinical information pertaining to each patient interaction at the diabetes clinic is recorded on the diabetes clinic database following each outpatient clinic session. General information recorded on all children includes auxology data, pubertal status, other illnesses or medications. Diabetes specific information includes insulin regimen and dosing, current HbA\textsubscript{1c}, problematic hypoglycaemia, presence of lipo hypertrophy or lipo atrophy and adherence to dietary guidelines. Additional information regarding SMBG monitoring data, psychosocial wellbeing, adherence to diabetes management and recommendations for change are recorded as deemed necessary by individual physicians.

The clinic database contains information from all patients seen at the RCH diabetes clinic. The database allows clinicians the opportunity
to review clinical data from previous individual encounters. In addition, summary statistics relating to the overall clinic or subgroups (defined for example by age or insulin regimen) at a given time point can be retrieved.

1.8.7 Central RCH Computerised Record of Patient Data

The central computerised record of patient data at RCH is known as CLARA (Clinical Lookup And Result Acknowledgement). All data are stored according to a patient’s unique Unit Record (UR) number. Information recorded on CLARA includes individual patient outpatient visits, inpatient admissions and results of all investigations performed at RCH (biochemistry, other pathology, radiology etc). All data are password protected; passwords are only available to hospital staff involved in clinical care.
CHAPTER 2: Can integrated technology improve self-care behaviour in youth with type 1 diabetes?: a randomised crossover trial of automated pump function.
2.1 INTRODUCTION

As established previously, maintenance of HbA₁c within defined targets is critical to reduce the risk of developing macro- and microvascular diabetes-associated complications (1993), however a significant proportion of youth do not attain this goal, particularly during adolescence (Lernmark, Dahlqvist et al. 1996; Leonard, Jang et al. 2002; de Beaufort, Swift et al. 2007; Cameron, Cotterill et al. 2013). Whilst CSII can provide increased meal and exercise flexibility, achievement of adequate glycaemic control remains highly dependent on user behaviour (Olinder, Kernell et al. 2009; O'Connell, Donath et al. 2011; White, O'Connell et al. 2013). Achievement of target HbA₁c has repeatedly been shown to positively correlate with the number of BGLs performed per day, both in youth on injectable insulin regimens and in those utilising CSII (Levine, Anderson et al. 2001; Haller, Stalvey et al. 2004; Wood, Moreland et al. 2006; Shalitin, Gil et al. 2010; O'Connell, Donath et al. 2011). Studies of this correlation have mainly relied upon BGL data obtained from self-report or logbook, with a few studies using objective BGL data extracted directly from glucometers (Driscoll, Johnson et al. 2011; Helgeson, Honcharuk et al. 2011; Ziegler, Heidtmann et al. 2011). For BGLs to positively impact on glycaemia with use of CSII, they need to be performed and also entered into the user’s pump, to enable correction insulin delivery when required. Until recently, this has required the user to manually input BGLs into their pump device; adherence to this process is variable in children and adolescents. Adjunct glucometers have recently been developed which allow an individual’s capillary BGL to be automatically delivered to their pump using wireless technology, thus removing the necessity of this manual step.
2.2 AIMS AND OBJECTIVES

The objective of this study was to assess whether use of an automated integrated blood glucose measurement and insulin pump device, as compared with standard insulin pump device with manual BGL input, resulted in higher mean daily frequency of blood glucose measurements recorded in a user’s pump after 6 months of use. We also aimed to assess whether use of the automated system impacted on frequency of other pump interactions, user satisfaction and glycaemic control (as assessed by HbA₁c) after six months of use.

2.2.1 Trial Registration

This trial was registered pre-commencement at the Australian New Zealand Clinical Trial Registry (ACTRN12611000142932).

2.3 METHODS

Participants were recruited for this randomised crossover trial from the out-patient population of The Royal Children’s Hospital (RCH), Melbourne. Study phases consisted of an ‘automated’ arm during which participants used the study device incorporating wireless BGL transfer and a ‘manual’ arm where participants utilised their own pump, with conventional manual input of BGLs to the pump. Each study phase was of six months duration. Ethics approval was obtained from the institutional Human and Research Ethics Committee (HREC) and written informed consent was obtained from all participants ≥18 years old, with additional consent from a parent/guardian where a participant was aged <18 years old.

2.3.1 Inclusion/Exclusion criteria

Inclusion criteria for participation were: diagnosis of T1DM, age <20 years old, established use of an insulin pump with manual BGL entry for >1 year and a user’s current pump remaining within warranty for
the trial duration. No HbA$_{1c}$ or baseline BGL monitoring criteria were applied. Individuals with a history of previous significant skin reaction to pump consumables, or lack of English language comprehension were excluded.

2.3.2 Recruitment, Randomisation & Design

2.3.2.1 Recruitment

Insulin pumps are considered out-of-warranty after four years of use, after which users are automatically entitled to a new device, or an upgraded model where one exists. Our recruitment strategy initially targeted this population, as one which may be interested in trial of an alternative pump, before concluding upon a pump for usage for the next four years. This was also representative of a cross-section of our CSII population within the entire RCH clinic who started using CSII across one year. Hence, postal invitations to participate were sent to all eligible CSII users within our patient population whose current pump warranty was due to expire between 13-24 months from trial commencement (n=78). Active recruitment was also undertaken in the out-patient department by myself.

2.3.2.2 Study Device

The automated pump system studied was the Accu-Chek® Spirit Combo, [Roche™, Basel, Switzerland], which was the only system available in Australia at the time of recruitment which incorporated automated wireless BGL delivery. Remote control functionality from a hand held unit that includes the glucometer component of the system is included in this device (see Figure 2-1). This allows delivery of meal boluses with integrated bolus-dose calculation and other pump adjustment, without the necessity for pump exposure. Bolus and correction insulin calculation (“bolus wizard”) is also integrated in this handset device. In contrast to other insulin pump devices in use in our clinic, the “bolus wizard” is not accessible via the pump directly,
although manual boluses can be delivered via the pump. As it was felt that removal of the handset and education regarding self-calculation of insulin dose would insert a large confounder to final analyses, participants used their own insulin pump during the manual phase of this study. All users were instructed to only utilise the bolus wizard function of the device (i.e. the handset) for insulin dose calculation during the automated phase. It is important to clarify that this functionality merely constitutes automated delivery of a user’s BGL to the pump, but does not involve any other increased automation, such as autonomous insulin delivery. For example, in the event that a user’s BGL was higher than target range, the system would recommend bolus insulin delivery, but completion of same would be user-activated via the handset.

![Handset and Insulin pump](image)

**Figure 2-1: Study device – Accu-Chek® ‘Spirit’ Combo [Roche]**

Similar wireless functionality has since been incorporated into other insulin pump systems, delivered by Medtronic (Bayer® meter), Animas (One Touch® Ping® meter-remote) and has been intrinsic to
the Omnipod® system, although the latter remains unavailable in Australia.

2.3.2.3 Randomisation & Study Design

Participants were randomised to stay on their own manual BGL entry pump device or to commence use of the automated version, using a computer-derived randomised block randomisation schedule to maintain balance between treatment arms and achieve allocation concealment. Sealed blank envelopes were selected sequentially by the principal investigator (myself) as participants were recruited.

Participants used the device to which they were randomised for the first six months, then crossed over to use the alternative system for the next six month period (second phase).

At commencement of their six-month automated system phase, all participants had a 3 hour standardised instructive session covering its use. Further support was provided as necessary via participant-initiated contact with hospital diabetes nurse specialists. All CSII users at our centre are encouraged to regularly 'download' their pump information to diabetes nurse specialists in between out-patient appointments, to assist with regular insulin titration according to BGL levels. Out-patient appointments are scheduled regularly at three-monthly intervals with the participant’s treating physician, from where data for this trial were collected as set out below. Where a participant failed to attend a scheduled appointment with their physician, they were reviewed separately within 2 weeks by the principal investigator and data recorded.

2.3.3 Outcomes

Primary outcome examined was between group difference in the mean number of blood glucose measurements per day recorded by
each pump, over the course of each 6 month period of use. Secondary outcomes were metabolic control, auxology, participant satisfaction and other pump download parameters as detailed below. For our primary outcome, the total number of BGLs as a mean from weeks 7-26 of each phase was documented and the means of the pooled automated system were compared with the means of the pooled standard manual system. The first six weeks of data from each phase were excluded from analysis in order to reduce the chances of ‘novelty effect’ or in the second phase, ‘carryover effect’. During each study phase, BGLs recorded in the pump were obtained from pump download at baseline, 3 months post-commencement, and 6 months post-commencement. To evaluate the discrepancy between number of BGLs performed and number actually entered into a user’s pump during the phase of pump and manual glucometer use, data from all glucometers used by participants were also downloaded, or manually extracted by investigators where electronic download was not possible. This step was not necessary during the phase of automated system use. Height and weight were recorded at trial commencement, each outpatient appointment and at trial completion. HbA$_{1c}$ was measured as described in Section 1.8.4.

As an objective measure of device satisfaction, participants independently completed the fully validated Insulin Delivery System Rating Questionnaire (IDSRQ) (Peyrot and Rubin 2005) at the end of each six-month study phase. The IDSRQ is a Likert-graded questionnaire composed of six subscales assessing: patient perceptions of treatment satisfaction, impact on daily activities, treatment system efficacy, diabetes-related worries and treatment burden, psychological well-being and overall treatment system preference (see sample in Appendix A). Responses were reverse-coded where necessary and means for each subscale were calculated, as per the original descriptive paper (Peyrot and Rubin 2005).
Other pump download information was also assessed at three-monthly intervals, namely: total daily dose (TDD) per kilogram bodyweight (units/kg/day), number of boluses per day, number of carbohydrate entries, and percentage of insulin delivered as basal versus bolus. Other than the scheduled investigations as outlined above, no additional contact above that of standard diabetes outpatient care was initiated by investigators.

2.3.4 Sample Size Estimation and Statistical Analyses

Audit of a sample of our patient population 2 years previously revealed a mean of 3.2±1.7 BGLs per day being recorded in the pump in those using a CSII regimen (O'Connell, Donath et al. 2011). A smaller sample of our CSII population 1 year previously revealed a mean of 4.4±2.2 BGLs/day, again assessed by pump download without contemporaneous glucometer data. Since studies have consistently documented that a clinically significant improvement in diabetes control is achieved when users perform ≥5 blood glucose measurements per day (Anderson, Ho et al. 1997; Levine, Anderson et al. 2001; Moreland, Tovar et al. 2004; Shalitin, Gil et al. 2010); we calculated a sample size of 24 would give 80% power to detect a meaningful difference (i.e. detection of increase of 1.0-1.8 BGLs/day based on the 2 previous audits) in our population, using a crossover trial design. A p-value of <0.05 was set as level of significance. Allowing for potential study withdrawal, as well as considering manufacturer device support, we planned to recruit up to a maximum of forty participants.

Data were recorded and described in accordance with published CONSORT guidelines for randomised trials. All analyses of outcome variables were performed using planned intention to treat analyses. Data were entered into Microsoft Excel and Epidata, then exported to STATA® (Statacorp, TX, USA, Version 11) for analysis. Paired t-tests
were used to evaluate the difference in mean values of primary and secondary outcome parameters between the study groups. Post-hoc subgroup analyses were also performed using paired student's t-test between groups.

2.3.5 Study Funding

All equipment for the automated study phase was supplied by Roche but this company did not have any input into the study design, analysis, or reporting of findings. No other external funding was sought or used in this study.
2.4 RESULTS

Between June 2011 and February 2012, a total of 35 participants were recruited; 29 as a result of the original mail out and 6 directly from the out-patient clinic. At recruitment, 6 participants were using Animas OneTouch® Ping® insulin pumps and the other 29 were using Medtronic MiniMed Paradigm® devices. Following randomisation, a total of 9 participants withdrew from the trial (See Figure 2-2 for flowchart). Baseline data at trial commencement are shown in Table 2-1.

Table 2-1: Baseline data of participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (Started with manual pump)</th>
<th>Group B (Started with automated pump)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%female)</td>
<td>18 (50%)</td>
<td>17 (58%)</td>
<td>35 (54%)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>12.5 ± 2.3</td>
<td>13.8 ± 3.4</td>
<td>13.1 ± 2.9</td>
</tr>
<tr>
<td>Diabetes Duration (yrs)</td>
<td>5.5 ± 2.0</td>
<td>6.0 ± 2.25</td>
<td>5.8 ± 2.1</td>
</tr>
<tr>
<td>Duration pump use (yrs)</td>
<td>2.5 ± 0.5</td>
<td>2.5 ± 0.75</td>
<td>2.5 ± 0.6</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>1.0 ± 1.0</td>
<td>0.83 ± 0.63</td>
<td>0.92 ± 0.85</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.6 ± 0.76</td>
<td>8.0 ± 1.1</td>
<td>7.8 ± 0.96</td>
</tr>
<tr>
<td>BGLs/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recorded in pump</td>
<td>5.3 ± 1.4</td>
<td>5.5 ± 1.9</td>
<td>5.4 ± 1.6</td>
</tr>
<tr>
<td>Daily insulin dose (U/kg)</td>
<td>0.88 ± 0.3</td>
<td>0.88 ± 0.2</td>
<td>0.88 ± 0.3</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation.
(BMI-SDS = Body Mass Index-Standard Deviation Score.)
Figure 2-2: CONSORT Participant Flow Diagram

Note: Overall RCH clinic population = 1,600; approx overall active CSII population = 450; initial mailout to 78 patients whose pump due to expire between 13-24 months of trial commencement
2.4.1 Primary Outcome: Recorded Blood Glucose Measurements in Pump

Use of the automated insulin pump and meter resulted in a higher number of blood glucose levels per day entered into the pump after six months of use when compared to use of the manual glucometer/pump device (5.8 ± 1.7 BGLs per day versus 5.0 ± 1.9 BGLs per day; p = 0.02). This difference was more marked at the three month time point (6.0 ± 1.9 versus 4.8 ± 1.6; p = 0.003) as shown in Figure 2-3. This analysis was conducted in 27 individuals for whom data were available at 6 months in the automated phase and 31 who similarly completed the manual phase; hence the paired t-test considered 27 individuals in total. Paired data were available for 30 participants at the three month time point.

Download of all glucometers used by participants during the manual phase demonstrated a significant difference between the number of BGLs performed per day and the number that were successfully manually entered into the user’s pump over 6 months [5.7±2.4 per day in glucometer vs. 4.8±1.8 per day entered into pump; p = 0.02].

Ability to perform intention to treat analysis was limited by the absence of final BGL outcome data in the 9 participants who withdrew during the trial. Methods of data modelling were felt to be inappropriate given that participants reverted to using the comparator pump system and that only 3 of the 9 withdrawals persisted with the automated pump for >3 months. However, intention to treat analysis was performed using participants’ final HbA1c data (see secondary outcomes, section 2.4.2.1).
Figure 2-3: Graph of mean & confidence intervals of no. of BGLs per day at each trial time point.
Automated pump group represented by circles, manual glucometer/pump by diamonds.
*=p<0.05 between pump groups.

2.4.2 Secondary Outcomes

2.4.2.1 Glycaemic Control

No difference in overall glycaemic control was demonstrated between groups at any point in the study period. Mean HbA$_1c$ after 6 months of automated pump use was 8.0% ± 1.3 (64 mmol/mol) vs. 7.7% ± 0.9 (61 mmol/mol) after six months of manual glucometer/pump use, [p = 0.86]. Despite increased frequency of entered BGL values at 3 months, HbA$_1c$ at this time point did not differ either [7.7% (61 mol/mol) automated Vs 7.6% (60 mol/mol) manual; p = 0.38].

As specified above, intention to treat analysis was also performed, inclusive of participants who withdrew from participation during the trial. This showed no difference between groups either [7.8% ± 1.3
(62 mmol/mol) automated pump Vs 7.7% ± 1.0 (61 mmol/mol) manual pump; p = 0.58].

On subgroup analysis, participants at trial commencement who were entering a suboptimal number (<5) of BGLs per day into their pump (n=13) experienced significantly improved glycaemic control after 6 months of automated pump use [mean ΔHbA₁c: -0.9% (<5 BGLs/day) vs. +0.5% (≥5 BGLs/day at baseline); p=0.003], see Figure 2-4. Similar analysis of the same subgroups of users during the phase of manual glucometer/pump use showed no significant difference in ΔHbA₁c [-0.4% (<5 BGLs) vs. +0.12 (≥5 BGLs); p=0.17]. The group entering <5 BGLs per day at baseline were older [15.2±1.9 years Vs 11.9±2.8 years; p<0.001], but did not otherwise differ in duration of diabetes, duration of pump use, gender, or HbA₁c at baseline.

Figure 2-4: Box plot of change in HbA1c by baseline BGL/day
2.4.2.2 Regression of BGLs versus HbA\textsubscript{1c}

Regression analysis performed on data gathered at baseline, showed that number of BGLs performed per day negatively correlated with metabolic control achieved and predicted 25% of variance in HbA\textsubscript{1c} (Figure 2-5). Each increase in one BGL/day was associated with a decrease of 0.3% in HbA\textsubscript{1c}.

![Figure 2-5: Regression of BGL/day with HbA1c](image)

2.4.2.3 Insulin Dose, Bolus Behaviour and BMI

The TDD (units/kg/day) was similar for the two groups at the start of the study. During automated pump system use, TDD was higher compared to the manual pump system phase [0.93 ± 0.2 automated pump versus 0.87 ± 0.1 manual glucometer/pump; p=0.04]. No difference was noted between groups in percentage of total daily dose given as basal insulin [42.9% ± 8 automated pump versus 43.9% ± 5 manual pump; p = 0.43].

There was also no difference in the number of boluses per day performed by users in either study group [6.5 ± 0.5 automated pump...
Randomised Trial of Automated Pump

versus 6.9 ± 0.5 manual pump; \( p = 0.36 \), or in BMI-SDS values at any time point.

2.4.2.4 User Satisfaction

Contacts with diabetes nurse specialists were similar between the two groups during each phase of pump use [4 contacts (IQR 3-5.5) during automated phase Vs 3.5 contacts [IQR 1 – 6] during manual phase; \( p = 0.63 \)]. There was no difference in quantification of satisfaction on the IDSRQ on overall satisfaction \( (p = 0.67) \), or on any of the 6 satisfaction-specific subscales. However, other IDSRQ subscales revealed that users of the automated pump were less likely to recommend it to other pump users \( (p = 0.007) \) and also comparatively preferred use of their own (manual) pump \( (p = 0.005) \).

2.4.3 Withdrawals and Adverse Events

In total, 9 out of the 35 participants withdrew from the trial (6 female, 3 male), 7 during the phase of automated pump use and 2 from the manual phase, just prior to crossover to use of the automated system. Documented reasons for withdrawal are as per Figure 2-2, with 89\% (8 out of 9) reporting or anticipating difficulty adjusting to the automated ‘new’ pump. Participants who withdrew from the trial protocol had a shorter duration of diabetes [54 months duration Vs 75 months; \( p = 0.035 \)], but not of pump usage. There was no difference between subjects who withdrew and those who completed the protocol in baseline HbA\(_1c\), order of pump system randomisation, or any download parameters (BGL or boluses per day/total daily dose/percentage delivered as basal).

No severe hypoglycaemic events or episodes of diabetic ketoacidosis were recorded. No minor adverse events were noted in either study group. During the course of the study, one participant reverted to using an injectable insulin regimen during the automated
pump phase. This resulted from long-term self-care concerns and followed collaborative consultation between participant and their treating physician.

At trial conclusion, participants were offered the option of continuing to use the automated pump on an ongoing basis. Nine (25.7% of overall) participants (6 female, 3 male) chose this option. This group were more likely to be adolescent, with longer duration of diabetes [87 months versus 63 months; \( p = 0.01 \)], but similar duration of pump usage.

### 2.5 DISCUSSION

This randomised crossover study demonstrates that automation can result in increased numbers of BGLs recorded in users’ pumps; however no extra boluses and no overall change in HbA\(_1c\) occurred as a result. Akin to other work (Driscoll, Johnson et al. 2011; Helgeson, Honcharuk et al. 2011), this study is one of the few to utilise objective BGL data extracted directly from users’ glucometer(s) and insulin pump systems, but extends this further by a) randomization of participants to the order of manual versus automated and inclusion of a crossover phase ; b) inclusion of user satisfaction survey; c) data collected at multiple time-points.

Analysis of available data from this cohort during the phase of manual glucometer/pump use revealed that on average, users were neglecting to enter one blood glucose value per day into their pump. Previous research has established glycaemic benefits with entering \( \geq 5 \) BGLs / day (Anderson, Ho et al. 1997; Haller, Stalvey et al. 2004; Svoren, Volkening et al. 2007). The lack of appreciable impact of the increased BGL data on overall HbA\(_1c\) in this cohort may relate to the fact that participants were already entering a mean of 5.4 BGLs per day at baseline. It is possible that recruitment was biased by a more motivated cohort volunteering to partake in this study, which in turn
may have been more likely to display higher levels of diabetes self-care.

Given this unexpected baseline finding, it was felt appropriate to perform subgroup analyses of this cohort, by those who were and were not recording an optimal number (≥5) of BGLs per day at baseline. Of note, these analyses were post hoc and unplanned at the study’s outset. The subgroup of older adolescents who were not routinely performing this recommended number of BGLs per day at baseline demonstrated a marked improvement in glycaemic control during the phase of automated pump use. Akin to other studies documenting a Hawthorne effect on HbA$_1$c, this group exhibited a 0.4% improvement whilst using their own pump (DeVries, Snoek et al. 2003; Gale, Beattie et al. 2007), but experienced a further mean improvement of 0.5% in addition to this whilst using the automated system. Whereas the overall group recorded an increased number of BGLs during the automated pump phase, these data indicate the automated system may be especially advantageous for individuals who are having difficulty manually transferring more than five BGLs per day into their pump. It is interesting that this subgroup did not record an increased number of boluses per day, an increase in their total daily dose, or percentage dose derived from basal insulin. It may be that improved consistency of pre-prandial bolusing behaviour could have contributed to their HbA$_1$c reduction, although this cannot be substantiated from download data available.

Nine participants did not complete the study protocol, the majority dropping out during the phase of automated pump use, or just prior. This may represent a limitation of the crossover study design in this instance, as participants had a comparator with which they were already very familiar. However, the required number of participants as estimated in our original sample size calculation still completed the study, so the power of this trial was not adversely affected.
Although the majority of participants were less likely to change to the automated system at the end of the study, nine individuals chose to remain using the automated pump after trial completion. That this group was older may represent an increased comfort level with technology operation amongst adolescents, in comparison to older adults, who are more likely to assume responsibility for daily pump operation on behalf of younger children.

This study was also limited by the inability to reliably document the regularity and appropriateness of insulin basal rate or bolus ratio titration by users in response to identified glycaemic patterns. Passivity regarding setting adjustment to achieve target BGLs has recently been recognised as a significant barrier to control (White, O’Connell et al. 2013) and may also explain why glycaemic control did not improve overall, despite increased BGL data with automated system use. It is also interesting that users increased their TDD during the automated pump phase, but neither an increase in number of boluses per day, nor change to their bolus:basal ratios were observed. It may be that increased interaction with a novel technology resulted in users augmenting their basal insulin delivery rates themselves, while the increased number of BGL data resulted in an increase in the proportion of bolus insulin delivered as a ‘correction’, as has been noticed previously with the bolus calculation algorithm used by this automated device (Zisser, Wagner et al. 2010); unfortunately, this is not possible to elucidate from pump download data.

It remains the case that despite increased allied health support and continued enhancement of diabetes technologies, the majority of youth with type 1 diabetes still do not achieve target HbA1c (Cameron, Cotterill et al. 2013). This is the primary incentive driving closed-loop technology development but until this is a clinical reality, personalised barriers to target HbA1c achievement must be identified. Recent studies have demonstrated the benefit of a goal-oriented
consultation process towards target glycaemic control accomplishment (Swift, Skinner et al. 2010; Boot, Volkening et al. 2013).

This study shows that, amongst an adolescent group in particular, focusing on ensuring all BGLs are entered into the pump can assist continued improvement of glycaemic control. However even when successful increment of raw BGL number was obtained, this did not result in increased numbers of insulin boluses or HbA1c improvement overall. That removal of one self-care barrier does not translate into positive contagion i.e. improvement of other related behaviours - suggests that the problem of low self-care may not be simply solved by technology innovation.

The above findings guided future research strategy towards a goal of stratification of additional obstacles to glycaemic target realisation. Following on from this, I proceeded to classify these obstacles according to certain demographic, intrapersonal and interpersonal characteristics. Findings derived from this next step would form the foundation of a predictive prospective tool.
CHAPTER 3 : Demographic and Personal Factors Associated with Metabolic Control and Self-Care in Youth with Type 1 Diabetes
3.1 INTRODUCTION

Optimal self care behaviour impacts positively on glycaemic control, independent of age, sociodemographic or disease characteristics (Hood, Peterson et al. 2009). Nonetheless, the prevalence of low self-care behaviours in type 1 diabetes during childhood and adolescence is approximately 50% (Hauser, Jacobson et al. 1990; Morris, Boyle et al. 1997); thus is similar to rates of self-care in other chronic paediatric illness (Adams, Pill et al. 1997; Lutfey and Wishner 1999; Kyngas 2007).

In recent years, advances in insulin types and administration systems, coupled with improved dose titration using ‘real-time’ glucose monitoring devices have enabled more physiologically-similar insulin delivery. “Intensification” of therapy has been the goal of diabetes care in the post-DCCT period, but the primary focus so far has been via pharmaco-technological methods with a lesser emphasis upon psychosocial aspects of care (Cameron, Northam et al. 2007; Skinner and Cameron 2010). Despite greater reliance on increasingly complicated insulin delivery regimens and glucose sensing technologies, national databases and multinational studies indicate that HbA$_{1c}$ levels of children and particularly adolescents are still suboptimal. As discussed, the Hvidoere Study Group showed that in spite of intensification of therapy from 1998-2005 in 21 centres encompassing over 2,000 children, there was minimal improvement in mean HbA$_{1c}$ between centres over this timeframe, with the lowest mean HbA$_{1c}$ recorded in those on twice-daily regimens (de Beaufort, Swift et al. 2007).

Insulin regimen intensification involves increased time and effort on the part of the individuals, their families and their healthcare-providers, particularly for those commencing CSII, or insulin pump therapy (Kaufman, Halvorson et al. 1999; Colquitt, Green et al. 2004). Selection criteria for intensive regimens such as CSII differ
across centres. Some centres advocate restriction of pump therapy only to motivated youth and their families (Williams, Storch et al. 2005; Fisher 2006; Lassmann-Vague, Clavel et al. 2010), while other groups have shown improved metabolic control in individuals with previously high HbA$_{1c}$ levels, and advocate a relaxation of selection criteria (Lombardo, Iafusco et al. 2007; Phillip, Battelino et al. 2007). CSII discontinuation rates are estimated at 4 to 26% (Schifferdecker, Schmidt et al. 1994; Ronsin, Jannot-Lamotte et al. 2005; Hofer, Heidtmann et al. 2010) with most common reported reasons being low/unsafe pump usage, individual choice, and cutaneous complications.

As described above, clinical trials of new diabetes technologies have been limited by relatively low participant usage overall, particularly in the adolescent age group (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Tamborlane et al. 2008; O'Connell, Donath et al. 2009). However, subanalyses of these studies have shown that when patients use the technology as prescribed, metabolic benefits ensue (Beck, Buckingham et al. 2009). The issue then is not the technology itself but the uptake and incorporation of that technology into overall self-management.

Various measures of assessing self-management and related psychosocial variables in type 1 diabetes have been described and reviewed (McNabb 1997; Hearnshaw and Lindenmeyer 2006; Iannotti, Schneider et al. 2006). To date however, literature reviews have not addressed the issue of behaviour with regards to new and emerging diabetes technologies (Hamilton and Daneman 2002; Schwartz, Cline et al. 2010). The purpose of this review then is to explore the interface between unique individual characteristics and diabetes self care that may impact on an individual’s ability to optimally integrate advanced technologies into their daily diabetes care regimen.
3.2 AIMS/OBJECTIVES OF THIS REVIEW

This systematic review aimed to identify studies where demographic, inter- or intrapersonal characteristics of participants were examined as predictors of, or strongly associated with, self-care and/or metabolic control. The objective was to then qualitatively synthesise this body of literature and identify consistent factors robustly linked with diabetes health-related outcomes, with an additional focus on diabetes technologies. Finally, aspects where there is paucity of data were identified and recommendations made for direction of future research efforts.

3.3 METHOD

A systematic search of Ovid Medline, PsycINFO, Embase and Cinahl was performed on 03/12/2010 using the following search strategy:

1. ((insulin dependent diabetes or IDDM or type 1 diabetes) not type 2).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
2. limit 1 to (english language and yr="1993 -Current")
3. (compliance or adheren$ or factor$ or self care or self-care or predictor$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
4. 2 and 3
5. (metabolic control or outcome or self care or glucose or behaviour$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
6. 4 and 5
7. limit 6 to ("all child (0 to 18 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)" or "young adult (19 to 24 years)"

Studies published since 1993 were targeted for this review, as it is reasonable to assume there was a shift in therapeutic goals following
the original DCCT publication in that year (1993). Titles and abstracts were scanned for relevance and then full papers were screened for inclusion by one researcher [ON - myself]. Studies were included if they examined one or more inter-/intra-personal or demographic factor for correlation with metabolic control or self-care as an outcome, were written in English and had a cohort of more than 50 participants. Studies were excluded if they included >20% of participants with type 2 diabetes in their assessment, or if they did not have an identifiable cohort of children/adolescents. The references of the most recent reviews/studies in each domain were searched for studies of relevance, yielding five further studies (Hanson, De Guire et al. 1996; Kaufman, Halvorson et al. 1999; Davis, Delamater et al. 2001; Haller, Stalvey et al. 2004; McVean, Eickhoff et al. 2007). Uncertainty about inclusion/exclusion of a study was resolved by discussion with other researchers [TS or FC].

Articles were managed in a library generated with EndNote software (X4) and data were extracted and entered into a database. Finally quality criteria were applied, with papers assessed for appropriate representativeness, rigour, transferability, clarification and justification (Kitto, Chesters et al. 2008). Due to the disparate range of measures, concepts, samples and contexts of the studies, a quantitative analysis was not statistically feasible, hence, a qualitative synthesis was performed, with results presented in the narrative and grouped by domain.

3.4 RESULTS

A breakdown of the search process is represented in Figure 3-1. Seventy studies that met all criteria were identified in the demographic, inter- and intrapersonal domains, representing 11,686 children and adolescents with diabetes. These are designated ‘empiric’ studies in the rest of the following chapter text. The majority of studies excluded were not designed to empirically examine a
specific predictor. Increasing interest in this area is demonstrated as per Figure 3-2.

Figure 3-1: Study Selection Process. CINAHL = Cumulative Index to Nursing and Allied Health Literature

Fifteen studies employed a longitudinal design, the remainder were cross-sectional (see Table 3-1). All used HbA$_1c$ as a measure of metabolic control. Adolescents represented the largest group studied (54.3%), with other studies also examining children only (7.1%) and both groups together (38.6%).
Figure 3-2: Number of studies returned by year
### Table 3.1: Empiric selected studies

<table>
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<tr>
<th>Demographic</th>
<th>INTERpersonal</th>
<th>INTRApersonal</th>
<th>Author</th>
<th>Year</th>
<th>Cohort</th>
<th>Age range</th>
<th>Study type</th>
<th>Duration</th>
<th>Self-care measure</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1997</td>
<td>89</td>
<td>8-17y</td>
<td>cross-sectional</td>
<td>0.5-6</td>
<td>SMBG</td>
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<td>Stress, Resources</td>
<td>Auslander</td>
<td>1993</td>
<td>53</td>
<td>2.2-18y</td>
<td>cross-sectional</td>
<td>NS</td>
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SMBG=self-monitoring blood glucose; NS=not-specified(in paper or for cohort as a whole); Duration=duration of diabetes; IDDMQ-R=insulin dependent diabetes mellitus questionnaire-revised; SCI=self-care inventory; SDSCA=summary of diabetes self-care activities; DSMP=diabetes self-management profile; DMS=diabetes management scale; DCQ=diabetes compliance questionnaire; SCQ=self-care questionnaire; SCB=self-care behaviour; NCPRq=health care provider rating questionnaire; SSCA=summary of self-care activities; SRQA=self-report questionnaire on adherence; DSCA=diabetes self-care activities measure; ADTRQ=adherence to diabetes treatment regimen questionnaire.
3.4.1 Demographic Characteristics

3.4.1.1 Gender

Associations between diabetes outcome parameters and gender were described in the majority of papers, however three empiric studies were found which directly addressed the influence of gender as the main focus of the study (Naar-King, Idalski et al. 2006; Korbel, Wiebe et al. 2007; Hochhauser, Rapaport et al. 2008). As was the case with earlier studies in the literature, the results were equivocal, but showed a trend towards higher HbA$_{1c}$ in adolescent girls. One paper emphasised the mediating role of depression, showing evidence that depression rates rise in girls as age increases and self-care decreases (Korbel, Wiebe et al. 2007).

Interestingly, in one cohort of urban youth with higher HbA$_{1c}$ levels, boys exhibited lower self-care than girls; however no gender differences were demonstrated in overall metabolic control (Naar-King, Idalski et al. 2006). In this cohort, boys’ externalising symptoms inversely correlated with self-care and girls showed more anxiety symptoms. Overall these studies indicated that gender may be confounded by mental health variables which in turn mediated the relationship between gender and diabetes outcome.

**Summary**: currently, there is no obvious relationship between gender and self-care or HbA$_{1c}$.

3.4.1.2 Age and puberty

Both metabolic control and self-management deteriorate during adolescence (Leonard, Jang et al. 2002; Ingerski, Anderson et al. 2010). Various theories have been put forward to explain this pervasive decline. Changes in peer-parental influences at a time of increasing autonomy for self-management have been shown to result in decreased self-care behaviour (Hamilton and Daneman 2002). The incidence of psychopathology and family conflict at this age is
also higher than at any other time in childhood (Kovacs, Mukerji et al. 1996).

In addition, pubertal development may be even more influential than age per se on HbA\textsubscript{1c} (Hochhauser, Rapaport et al. 2008). Previous cross-sectional reports consistently show that pubertal development is associated with a 25–30% reduction in insulin sensitivity, with the peak reduction occurring at mid-puberty, followed by increased sensitivity by late puberty (Amiel, Sherwin et al. 1986; Travers, Jeffers et al. 1995; Moran, Jacobs et al. 1999).

\textit{Summary:} Adolescence is associated with decreased self-care and deterioration in metabolic control and puberty itself is a period of marked insulin resistance, further contributing to this effect.

3.4.1.3 Socioeconomic Status

Papers which directly examined socioeconomic status (SES) revealed that low SES grouping is persistently and significantly associated with poorer glycaemic control, as quantified by HbA\textsubscript{1c} (Gallegos-Macias, Macias et al. 2003; Carter, Cutfield et al. 2008; Pereira, Berg-Cross et al. 2008). A study from New Zealand showed that, after controlling for ethnicity, belonging to a low SES household was associated with a modest increase in HbA\textsubscript{1c} of 0.43% (Carter, Cutfield et al. 2008). Again, the mediating effects of mental health in this circumstance appeared to be important. In a cohort of youth with diabetes from lower SES groups, depression was twice as prevalent in those with higher HbA\textsubscript{1c} than in those whose HbA\textsubscript{1c} was closer to target (Hassan, Loar et al. 2006). The roles of parental employment and education were not as robustly associated with outcomes, with paternal (Cameron, Skinner et al. 2008) or maternal (Florian and Elad 1998) employment or paternal education level (Faulkner and Chang 2007) showing varying correlations with HbA\textsubscript{1c}.

\textit{Summary:} Lower SES grouping is associated with and predictive of lower self-care and higher HbA\textsubscript{1c}.
3.4.1.4 Race/Ethnicity

The variables of race and ethnicity are often confounded by ethnic minority status, socioeconomic deprivation, and language and cultural impediments to accessing health care resources. Belonging to an ethnic minority or immigrant population is a strong predictor of both suboptimal glycaemic control and low self-management; this link has been replicated across the US, Europe and Australasia (Auslander, Thompson et al. 1997; Delamater, Shaw et al. 1999; Gallegos-Macias, Macias et al. 2003; Povlsen, Olsen et al. 2005; Frey, Templin et al. 2007; Carter, Cutfield et al. 2008; Ashraf, Li et al. 2009). The disparity between African-American and Caucasian youths with diabetes is well-described, with a difference of 1.5-1.9% in HbA1c attributed to a higher prevalence of single parenting, higher proportion of people from lower SES, and lower levels of self-care (Auslander, Thompson et al. 1997; Faulkner and Chang 2007; Ashraf, Li et al. 2009; Kamps, Hempe et al. 2010). This difference remained significant after statistical adjustments for the effects of insulin dose, diabetes duration and SES (Delamater, Shaw et al. 1999). One longitudinal study showed that differences in glycaemic control began shortly after diagnosis and continued to accelerate well beyond the point of diagnosis (Frey, Templin et al. 2007). Hispanic youth, as the fastest increasing minority population in the US, have been shown to have HbA1c levels 0.45% higher than their white non-Hispanic counterparts (Gallegos-Macias, Macias et al. 2003). Maori and Pacific islanders are disproportionately represented in disadvantaged areas in New Zealand, but in multiple regression models, ethnicity explained more of the variance in HbA1c level than deprivation index (Carter, Cutfield et al. 2008). This was also reflected in the short and long-term consequences of poor diabetes control, with minority youth having higher rates of diabetic ketoacidosis, severe hypoglycaemia, retinopathy and nephropathy (Heckler 1985). Other factors linked to racial identity such as higher
stress levels and higher bereavement may also potentially exert an influence on diabetes outcomes, but further research is required in this area, before attributing findings to race or ethnicity per se.

Summary: Belonging to an ethnic minority group is associated with, and predictive of, higher HbA\(_{1c}\).

3.4.1.5 Family Structure

Family structure is defined as the composition and membership of the family and the organisation and patterning of relationships among family members (http://medical-dictionary.thefreedictionary.com/family+structure). At 24 months post diabetes diagnosis, metabolic control in ethnic minority youth from single-parent families deteriorated almost three times as fast as youth of similar ethnicity from two-parent families (Frey, Templin et al. 2007). This correlation was not confined to minority populations however. A convenience sample of 155 children in a large university-affiliated hospital showed that children from a single-parent family structure had a mean HbA\(_{1c}\) 1.25% higher than children from two-parent families (Thompson, Auslander et al. 2001). When this was explored further, predictors of higher HbA\(_{1c}\) within the single-parent family structure were children of older age and those who missed clinic appointments, reflecting a link with decreased self-management. Family factors also differed, with single-parent families reporting higher family stress and lower resources, cohesion and esteem.

When family factors were assessed in 2062 adolescents across 19 different countries, biological parents living separately again emerged as having a strong association with higher HbA\(_{1c}\), along with paternal unemployment (Cameron, Skinner et al. 2008). Where parents were together, more frequent blood glucose testing was observed in their child/adolescent with diabetes (Urbach, LaFranchi et al. 2005),
implicating self monitoring of blood glucose as a possible self-care mediator of metabolic control.

*Summary*: having a single-parent family structure has a disadvantageous effect on self-care and HbA$_{1c}$, particularly in adolescence.

### 3.4.2 Interpersonal Characteristics

#### 3.4.2.1 Family

#### 3.4.2.1.1 Family Functioning and Support

Since the early 1990s there has been increasing recognition of the impact of family functioning on metabolic control and self-care behaviours. Family functioning is often measured by the sum of seven constituents based on the McMaster model from 1978 (Epstein 1978). These constituents assess general functioning and six other dimensions encompassing problem solving skills, communication, family roles, interpersonal responsiveness and involvement, and behaviour control. Understandably, the child/adolescent’s perceptions of family functioning often had more influence on diabetes outcomes than measured family functioning itself (Leonard, Jang et al. 2005; Duke, Geffken et al. 2008).

The most popular model is that of less cohesive functioning negatively impacting on self-care behaviours, with negative repercussions for metabolic control. This is strongly supported by one U.S. study, where less cohesive functioning accounted for 49% of the variance in metabolic control (Lewin, Heidgerken et al. 2006). When functioning was examined in an economically disadvantaged cohort, higher family warmth and cohesion correlated with improved self-care and glycaemic control, although interestingly, child behaviour problems mediated HbA$_{1c}$ in their model rather than self-care (Cohen, Lumley et al. 2004). High cohesiveness has been
strongly associated with lower HbA$_{1c}$ in other studies (Jacobson, Hauser et al. 1994; Fiese and Everhart 2006).

Alternative hypotheses suggest direct effects of less cohesive functioning on glycaemic control via neuroendocrine pathways; a reverse model where the psychosocial ramifications of dealing with poor diabetes control results in suboptimal family functioning has also been proposed (Cohen, Lumley et al. 2004). None of the empiric papers found addressed these theories directly.

Higher family support positively correlates with improved diabetes responsibility and self-care. This relationship may be age-related, with the effect of parental guidance on HbA$_{1c}$ being weaker in adolescents than in younger children. A positive correlation between family support and self-care was demonstrated in four studies (Wysocki 1993; Lewandowski and Drotar 2007; Pereira, Berg-Cross et al. 2008; Hsin, La Greca et al. 2010), with one showing no association (Pendley, Kasmen et al. 2002); this difference may relate to age and was a phase one study report.

Summary: lower levels of family functioning, in particular cohesiveness, are associated with lower levels of self-care and higher HbA$_{1c}$.

3.4.2.1.2 Parenting Style

Parenting style has been analysed in three empiric published studies (Davis, Delamater et al. 2001; Shorer, David et al. 2011; Monaghan 2012). Categories of style are still based around Baumrind’s model, with parenting described as authoritarian, authoritative, or permissive (Baumrind 1967). Both the first and second styles involve the establishment of clear rules for behaviour, with exponents of the authoritative style displaying disciplinary methods that are more supportive and explanatory rather than punitive. The permissive
parenting style is associated with a lack of clear boundaries and avoidance of confrontation.

Sufficient guidance delivered in a non-coercive manner was positively correlated with improved outcomes in a study of youth aged 8-18 years (Lewin, Heidgerken et al. 2006). A small study of pre-adolescent (aged 4-10 years old) children demonstrated that parental warmth was associated with better adherence ratings, explaining 27% of the variance in ratings (Davis, Delamater et al. 2001). In contrast, a restrictive/authoritarian parental style was associated with higher HbA₁c levels and when compounded by the presence of youth externalising behaviours (i.e. aggressiveness, a tendency to act out, disruptiveness), was been shown to be particularly detrimental to control, mediated by decreased self-care [youth aged 8.25-18.75] (Duke, Geffken et al. 2008). Increased authoritativeness resulted in improved child responsibility, but did not translate into improved glycaemic control in another cohort aged 8-11 years old (Monaghan 2012). One study (Miller-Johnson, Emery et al. 1994) showed no relationship between parenting and outcomes, in an 8-18 year old age group.

Summary: an authoritative “loving, but firm” approach which minimises diabetes-associated stress and results in a more appropriate distribution of responsibility for disease management appears to be optimal. However, further research into this area, particularly in the vulnerable pre-adolescent period is warranted, as this group is experiencing an increasing diabetes incidence, is most dependent on their parents and will experience a longer disease duration in the course of their lives.

3.4.2.1.3 Conflict

All studies used the Diabetes Family Conflict Scale (DFCS) for conflict quantification (Anderson, Vangsness et al. 2002; Dashiff, Bartolucci et al. 2005; Lewin, Heidgerken et al. 2006; Lewandowski
and Drotar 2007; Pereira, Berg-Cross et al. 2008; Williams, Laffel et al. 2009), bar one which used the Parent-Child Scale (PCS) (Miller-Johnson, Emery et al. 1994). Higher levels of conflict were correlated with lower self-care and metabolic control in all but one study, which showed no effect (Dashiff, Bartolucci et al. 2005).

Prospective assessment of a cohort of individuals over a two year period found that a strong parent-youth team reduced conflict and improved adherence to SMBG, predicting improvement in glycaemic control overall (Anderson, Vangsness et al. 2002). Families with higher conflict scores at diagnosis had higher HbA1c levels when reviewed 6 months later (Ingerski, Anderson et al. 2010). When parent-child relationships were examined, conflict was a consistent correlate of both self-care and metabolic control and explained unique variance in diabetes outcomes independent of other aspects of the parent-child relationship (Miller-Johnson, Emery et al. 1994). When conflict was analysed in the context of psychological distress, more acrimony was reported when the child’s HbA1c was higher and when the parent experienced higher levels of anxiety (Williams, Laffel et al. 2009). It remains to be established whether a higher HbA1c results from hormonal responses to stress resulting from conflict, or if conflict arises from disagreement about lower self-care behaviours which themselves are resulting in suboptimal glycaemic control.

Where diabetes-specific behavioural family intervention was examined in a controlled trial setting, significant improvement in HbA1c was demonstrated in the intervention group both immediately post-intervention and again after 18 months (8.8% at 6 & 18 months Vs 9.6% at baseline) (Wysocki, Harris et al. 2006; Wysocki, Harris et al. 2007). Whilst this was associated with improved conflict scores at 6 months, the beneficial effect on conflict scores did not persist at 18 months. However, benefits in family communication and problem-solving skills, which are direct mediators of conflict, continued to be seen.
Summary: Whatever the source, high levels of intra-familial conflict are associated with a detrimental effect on both diabetes self-care and HbA$_1c$. This has been reflected in short to medium-term benefits when active interventions were aimed at improvement of conflict-resolution skills.

3.4.2.1.4 Diabetes Responsibility

Maintenance of parental involvement in diabetes management tasks is consistently associated with more favourable diabetes-related health outcomes (Skinner, John et al. 2000; Cameron, Skinner et al. 2008; Helgeson, Reynolds et al. 2008; Wysocki, Nansel et al. 2009; Hsin, La Greca et al. 2010; Ingerski, Anderson et al. 2010; Shorer, David et al. 2011). In adolescents, one caveat to this rule is their agreement with the level of parental involvement. Outcomes have been negatively impacted where there is either disagreement between parties as to whether the teen or their parents are primarily responsible for diabetes management, or where the teen perceived parental over-involvement (Cameron, Skinner et al. 2008). This may be the basis behind one study where only a model of shared teen-parent responsibility had beneficial effects (Helgeson, Reynolds et al. 2008). A number of studies examined parental monitoring as a proxy of responsibility and all concluded that high levels of parental supervision correlated with improved self-care and metabolic control in adolescents (Anderson, Ho et al. 1997; Ellis, Podolski et al. 2007; Berg, Butler et al. 2008; Horton, Berg et al. 2009). A caring family environment alone may not be enough to produce benefit without adequate parental monitoring (Ellis, Podolski et al. 2007). In one study both mothers and fathers had positive impact on metabolic control through reduction of externalising behaviours, but only high levels of paternal monitoring were associated with a lower HbA$_1c$ mediated through higher self-care (Horton, Berg et al. 2009). Control can also be improved where caregivers were assessed as collaborating well together (Wysocki, Nansel et al. 2009). Increased
maternal empowerment also has been shown to contribute positively towards healthy self-care behaviours in children (Florian and Elad 1998). Of note, several interventional studies which resulted in enhanced parental involvement in adolescent diabetes care have all resulted in improved metabolic control in the intervention groups (Anderson,Brackett et al. 1999; Grey, Davidson et al. 2001; Murphy 2007).

Summary: Lower parental responsibility for, and involvement in, diabetes-focused daily tasks has been shown to be associated with lower self-care and higher HbA$_{1c}$.

3.4.2.2 Extra-familial Networks

3.4.2.2.1 Peers and School

Peer influence on behaviour is larger in adolescence than childhood, given the increasing autonomy and independence from parents with increasing age (Berndt 1979). Extreme peer orientation is the tendency to ignore parental advice and self care to fit in with friends. In a moderately large cohort of 252 participants, adolescents who displayed higher peer orientation exhibited lower self-care ($r = -0.28$) and higher HbA$_{1c}$ ($r = 0.23$) (Drew, Berg et al. 2010). When addressing peer orientation as a mediator between parental relationships and diabetes health outcomes, this analysis demonstrated an indirect path, or partial mediation. No differential was found for age or gender.

One model has shown that when adolescents make negative attributions of friend reactions, (e.g. apprehension about disapproving responses from friends to their adherence behaviours) this resulted in difficulty with self-care in social situations and increased feelings of stress; the latter was associated with higher HbA$_{1c}$ (Hains, Berlin et al. 2006). While questionnaires for assessing
friend social support are being developed, early work shows that positive support has a beneficial impact on blood glucose testing (Bearman 2002). In a study of 167 youth, self-care tasks - particularly in relation to diet and blood glucose testing - were negatively impacted where individuals were experiencing bullying (Storch, Heidgerken et al. 2006). In this study, this was partially mediated by depression and victimised youth also exhibited higher HbA1c levels.

Direct or indirect victimisation of youth with diabetes, not only by peers but also by teachers, has been revealed (Peters, Storch et al. 2008). This again has a negative effect on self-management and on metabolic control, but only significantly so in a younger age grouping (8 – 11 years old).

Summary: High peer orientation was associated with higher HbA1c and lower self-care, especially where it was felt that friends would have a negative view of self-care behaviours, or where bullying was associated.

3.4.2.2.2 Health Professionals

No empiric studies were identified that addressed relationships with health care providers as a predictor. One study of various factors from Finland identified physician support as being the second most powerful predictor of higher self-care in 300 adolescents with diabetes (odds ratio 6.69), after threat to mental wellbeing. Nursing support was also significantly associated with improved self-care (odds ratio 6.28). (Kyngas 2007)

3.4.3 Intrapersonal Characteristics

3.4.3.1 Personality

Research into personality in diabetic youth is increasing, particularly as the ‘Big Five’ taxonomy of personality has been accepted as a gold standard measurement of paediatric personality domains.
(McCrae and Costa 1987). These five factors are traits thought to capture the essence of individual differences in personality and are listed as conscientiousness, extraversion, agreeableness, openness to experience and emotional stability. Prior to this, most research work was carried out into child temperament, a similar but narrower construct (Rovet and Ehrlich 1988; Garrison, Biggs et al. 1990; Weissberg-Benchell and Glasgow 1997).

Longitudinal assessment of both child and parental personality in 64 families concluded that children with higher agreeableness, conscientiousness and emotional stability had lower HbA1c levels (Vollrath, Landolt et al. 2007). Mothers’ personality traits had more significance than fathers’ in this study, with high maternal agreeableness correlating with improved child metabolic control. This study had a two year duration from diabetes diagnosis and associations were unchanged when controlled for age, assessing youth from 6 to 16 years of age.

Psychology mediation models were hypothesised and tested on 358 participants to explore the interaction between personality and self-care (Skinner, Hampson et al. 2002). The domains of conscientiousness and emotional stability were investigated based on their particular relevance to health behaviours, in a group aged 12-30 years. The most significant model in this study indicated that the effects of personality on self-care were mediated by patients’ illness beliefs, which were in turn specific to each personality trait. More specifically - for conscientiousness, associations with self-care were mediated by beliefs about the effectiveness of the diabetes regimen, not beliefs about the threat of consequences of diabetes. For persons where emotional stability was a predominant factor, perceived consequences of uncontrolled diabetes mediated self-management.

**Summary**: Low conscientiousness and low emotional stability in particular were associated with higher HbA1c levels. How personality
factors exert their influence on metabolic control has appeared to result from behaviours determined by illness beliefs, each specific to the individual’s dominant personality traits.

3.4.3.2 Beliefs, Cognitions and Attitudes

How people respond to a situation is primarily determined by how they perceive it, rather than the actual situation itself (Kendall 1992). Where thinking processes were shown to be negative or maladaptive, youths reported more general and diabetes-related stress. The latter had detrimental effects on glycaemic control, whilst the former was indirectly associated with HbA1c through its effect on self-management behaviours (Farrell, Hains et al. 2004).

The assessment of beliefs has been confounded by heterogeneous populations and measurement tools. When health beliefs in minority youth were assessed, the perception of risk of short-term complications was associated with metabolic control (Patino, Sanchez et al. 2005). In this study, risk of both long and short term complications was optimistically perceived to be greater to others rather than to one’s self; a similar finding has also been reported elsewhere (Frey, Guthrie et al. 1997).

Compensatory beliefs (CBs) are convictions that negative effect of less healthy behaviours can be compensated for by engaging in another behaviour (Rabiau 2006) e.g. “I do not need to test my blood sugar because I will not eat any sweets”. Where CBs concerning glucose testing were endorsed by adolescents, there was a correlation with deterioration of metabolic control, even after controlling for diabetes knowledge (Rabiau, Knauper et al. 2009). In a prospective study of adolescents, beliefs in the effectiveness of the treatment regimen were predictive of better dietary self-care (Skinner and Hampson 1998).
Summary: Maladaptive or compensatory beliefs were shown to have an association with lower metabolic control.

3.4.3.3 Psychiatric Comorbidity

Youth with type 1 diabetes are at higher risk of psychiatric disorder in the range of twice to thrice that of the general population (Northam, Matthews et al. 2005), with higher rates in girls and with increasing diabetes duration. Whilst early pre-1993 studies linking psychiatric disorder and outcomes were conflicting (Simonds 1977; Close, Davies et al. 1986; Blanz, Rensch-Riemann et al. 1993), subsequent publications demonstrate small-to-moderate associations with metabolic control (Kovacs, Mukerji et al. 1996; Stewart, Wang et al. 2009). General psychopathology had a more robust association with metabolic control than depression itself in each of these longitudinal studies, with mean follow-up periods of 5 and 9 years respectively. Youths’ self-reported symptoms correlated significantly with metabolic control and risk of subsequent hospitalisation, whereas their parents’ reporting of their symptoms did not (Stewart, Wang et al. 2009). Depression affecting parents themselves also showed significant negative associations with youths’ metabolic control through decreased parental monitoring (Eckshtain, Ellis et al. 2010).

With so much focus on diet in the management of diabetes, it has generally been believed that individuals with diabetes are at an increased risk of developing eating disorders. However the literature to support this has been inconsistent: some reports have demonstrated no increased risk (Striegel-Moore, Nicholson et al. 1992; Meltzer, Prine et al. 2001) while others have concluded an increased risk exists (Rodin, Johnson et al. 1986; Engstrom, Kroon et al. 1999; Neumark-Sztainer, Patterson et al. 2002). What has been definitively established though, is that when either subclinical disordered eating or overt anorexia/bulimia nervosa co-exists with diabetes, it is associated with higher HbA1c (Rodin, Johnson et al.)
1986; Meltzer, Prine et al. 2001; Neumark-Sztainer, Patterson et al. 2002). In a study of insulin omission in 341 females aged 13-60 years, 31% reported intentional medication omission (Polonsky, Anderson et al. 1994). Approximately half this number attributed fear of weight gain as the main reason for their insulin omission. This group had significantly higher diabetes-distress, lower self-care and higher HbA1c levels.

Summary: Psychiatric comorbidity, in particular disordered eating, has shown associations with lower self-care and higher HbA1c.

3.4.3.4 Knowledge, Self-Efficacy & Skills

Self-management of diabetes involves multiple daily decisions around food, timing of glucose testing, response to results and insulin administration. It may be logical then to expect that better decision-making competence should be associated with improved self-care behaviours; this has been confirmed in the context of positive-parent communication (Miller and Drotar 2007). Similarly, a high level of executive functioning (e.g. planning, organisation and working memory) correlated with lower HbA1c, mediated by self-care, in a prospective study of children with diabetes (McNally, Rohan et al. 2010).

There has been a lot of interest in self-efficacy as defined by Bandura’s concept of confidence in one’s own ability to take actions to achieve a specific goal (Bandura 1997). Most studies found self-efficacy to positively correlate with self-care and (where assessed) metabolic control (Ott, Greening et al. 2000; Iannotti, Schneider et al. 2006; Chih, Jan et al. 2010); however this was not confirmed in a Turkish population (Pinar, Arslanoglu et al. 2003). Measures of self-efficacy were heterogeneous, but cohorts with higher levels were up to 1.63 times more likely to achieve target glucose control (Chih, Jan et al. 2010). There was a trend towards higher self-efficacy levels in boys (Iannotti, Schneider et al. 2006; Chih, Jan et al. 2010), except in
the Turkish study (Pinar, Arslanoglu et al. 2003), which the authors discussed was unexpected given the male-oriented nature of their society. Glycaemic control has been demonstrated to be poorest when higher expectations of positive outcomes were associated with lower self-efficacy, possibly reflecting a disengagement from diabetes when youth lack confidence in their own management competence (Iannotti, Schneider et al. 2006).

Intervention studies have shown that self-care and self-efficacy can be increased by support programmes using modern technologies such as text-messaging and the internet; nonetheless, this has not translated into improved metabolic control (Franklin, Waller et al. 2006; Wangberg 2008).

*Summary*: Higher self-efficacy and executive functioning are associated with higher levels of self-care and lower HbA$_1c$.

### 3.4.3.5 Coping, Stress & Behaviour

A significant relationship has been demonstrated between coping and glycaemic control, with all studies undertaken in adolescents. Various measures of coping have been studied, with each study attempting to distinguish between functional and dysfunctional coping mechanisms in response to general and diabetes-related stressors (Nakamura and Kanematsu 1994; Luyckx, Seiffge-Krenke et al. 2010; Skocic, Rudan et al. 2010). An active or problem-focused coping style was associated with more optimal levels of metabolic control, as opposed to an emotion-focused avoidant style, which resulted in wishful thinking or ventilation of feelings (Nakamura and Kanematsu 1994). Clinically meaningful pathways relating coping, psychological symptomatology and glycaemic control have been elucidated (see Figure 3-3) (Luyckx, Seiffge-Krenke et al. 2010). Higher HbA$_1c$ levels and higher symptoms predicted avoidance coping across time; this cycle appeared to potentiate itself. No strong gender trend was shown in any of the studies.
Behaviour and coping are closely intertwined, with life stressors resulting in behaviour reactions generated by an individual’s coping style. Externalising behaviours tended to be higher in boys and associated with higher HbA1c (Kovacs, Charron-Prochownik et al. 1995; Cohen, Lumley et al. 2004; Duke, Geffken et al. 2008; Skocic, Rudan et al. 2010). Internalising behaviours (i.e. withdrawal, lack of activity) tended to be more common in girls and correlation with HbA1c was variable (Cohen, Lumley et al. 2004; Luyckx, Seiffge-Krenke et al. 2010; Skocic, Rudan et al. 2010).

In a randomised study comparing the impact of coping skills training in a group of intensively treated adolescents with diabetes, logistic regression revealed that training was significantly associated with achievement of a target HbA1c of ≤7.2% (Grey, Davidson et al. 2001). Another intensive 5-day in-patient skills programme showed benefit in reduction of severe hypoglycaemic events, but no effect on HbA1c (Bott, Bott et al. 2000).

**Summary**: An avoidant, emotion-focused coping style is associated with higher HbA1c levels.

### 3.4.4 Technology-Specific Factors

Literature on technology-specific predictive factors is increasing, with the majority of studies addressing predictors of self-care on insulin pump (CSII) therapy. Cohorts ranged from 93 to 421 participants, published from 2006 to 2010. All studies were cross-sectional or retrospective and all concluded that initiation of CSII at a younger age was associated with better metabolic control (<12 years old in the largest study) (Nabhan, Rardin et al. 2006; McVean, Eickhoff et al. 2007; Shalitin, Gil et al. 2010). A shorter duration of diabetes and a lower HbA1c pre-initiation of CSII were also robust predictors of later glycaemic control (McVean, Eickhoff et al. 2007; Shalitin, Gil et al. 2010). Links between metabolic control and self-care were implied
with better control associated with increased SMBG (Shalitin, Gil et al. 2010), number of basal rates (Nabhan, Rardin et al. 2006) and frequency of cannula changes (McVean, Eickhoff et al. 2007). Achievement of glucose targets was obtained in 35-40% of cohorts, and discontinuation rates were reported as being 15-25%. Regarding the latter, retrospective attempts to predict discontinuation resulted in significance attributed to: female gender, higher HbA1c at pump initiation and adolescent age grouping (de Vries 2011). Psychosocial factors as correlates of metabolic control and/or self-management remain relatively unexplored, although one comparison of adolescents on CSII (n=95) versus MDI (n=47) showed the CSII group had less negative feelings around performing SMBG and displayed more shared diabetes responsibility. This was associated with a higher frequency of 1 SMBG per day being performed in the CSII cohort, who had improved metabolic control compared with adolescents on an MDI regimen (HbA1c 8.4% Vs 9.2%). No differences were demonstrated in the areas of family conflict, self-efficacy, or depressive symptoms (Cortina, Repaske et al. 2010).

Data pertaining to personal factors / characteristics associated with improved use of continuous glucose monitoring systems are limited. A large prospective randomised trial found that both self report of more frequent daily blood glucose measurements and age >25 years at baseline were predictive of higher subsequent CGM use (Beck, Buckingham et al. 2009).

### 3.5 CONCLUSIONS

There are robust predictors that are reproducibly associated with self-care and metabolic control. The factors predictive of lower self-care are presented (see Table 3-2) as stratified by the original organisational model. From this literature review, the domains of ethnicity, socioeconomic status, family structure and family conflict
are the most reproducible factors associated with self-care and metabolic control.

**Table 3-2: Predictors of lower self-care/metabolic control**

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<td>Part of ethnic minority grouping</td>
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<td>Single-parent family structure</td>
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<td>Higher family conflict</td>
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<td>Lower parental responsibility/monitoring</td>
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<td>Extreme peer orientation</td>
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<td>Avoidant emotion-focused coping style</td>
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<td>Presence of psychiatric disorder/disordered eating</td>
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<td>Lower executive functioning</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Technology-specific</strong></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Lower number of SMBG per day</td>
<td></td>
</tr>
<tr>
<td>Adolescence</td>
<td></td>
</tr>
</tbody>
</table>

A theoretical model is proposed of the dynamics between these factors and the pathways by which they mediate their effects (see Figure 3-3). Pathways were chosen which have been shown to be significant in the papers as examined for this review. These pathways have generally been elucidated by testing of hypothetical models, with the most statistically supported option chosen.
Figure 3-3: Theoretical model of interacting pathways between factors. Factors associated with both self-care and HbA1c indicated with asterisk. Red arrows indicate persistently negative effect. Double-headed arrows indicate factors with dual effect i.e. can effect each other in either direction.

There are many areas with a paucity of studies exploring the effect of personal factors on self-care and/or metabolic control and this review has highlighted the following in particular (see Table 3-3).

- Behaviour types and the way in which these mediate an individual’s coping style
- Parenting style, particularly in the pre-adolescent age group where this appears to have an increased influence
- Peer orientation
- Influence of health professional groups and clinic structure
- Personality and family factors specifically in CSII/CGMS

<table>
<thead>
<tr>
<th>Areas worthwhile targeting for future research efforts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interpersonal and intrapersonal factors, specifically in the CSII/CGMS populations</td>
</tr>
<tr>
<td>Behaviour types and the way in which they mediate an individual’s coping style</td>
</tr>
<tr>
<td>Peer orientation, including type of peer group</td>
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<tr>
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</tr>
<tr>
<td>Influence of health professional groups and clinic structure</td>
</tr>
<tr>
<td>Links between stress and self-care, investigating mediators such as family functioning</td>
</tr>
</tbody>
</table>

### 3.6 DISCUSSION

Health care resources are limited and clinicians must be judicious in their allocation. This responsibility must be counterbalanced with patient advocacy and facilitating access to healthcare options. Newer diabetes-related technologies offer the opportunity for lowering HbA1c in some patients, but these systems are expensive. Where technologies are utilized to their full potential, their initial monetary cost should be far outweighed by gains from eventual reduction in treatment of diabetes complications (Herman, Dasbach et al. 1997; Giannini, Mohn et al. 2009). However without appropriate user-interface operation, this premise becomes less tenable.

Until a user-independent closed-loop insulin delivery system becomes available, human behaviour will remain the limiting variable of clinical utility of any insulin delivery or glucose sensing system.
There is currently no consensus regarding selection criteria for application of diabetes technology in patient groups. The evidence appraised in this review indicates that individual psychosocial factors and demographic characteristics could be taken into consideration when advising youth about the potential benefits of various diabetes technologies. From the above analysis, there are 13 robust demographic, interpersonal and intrapersonal predictors of lower self-care behaviours and higher HbA₁₋₀ levels.

The ability to reliably predict self-care and those who will appropriately utilise advanced technology is useful when advising an individual regarding their therapy regimen. A pro-active approach of identification of self-care ability and tailored therapy may minimize expensive crisis-based interventions resulting from inappropriate treatment regimens. Cost savings from avoiding clinical crises may free-up resources for other aspects of care such as psychosocial support. Psychosocial support in turn may optimise an individual’s inter- and intrapersonal characteristics and allow them then to engage in more intensive and clinically effective therapies- a virtuous cycle of support.

Whilst this is the first review to examine and weave demographic, interpersonal and intrapersonal factors into a predictive model, it is limited by the heterogeneity of studies and statistical analysis was not possible. It must also be acknowledged that the designation of headings is somewhat arbitrary and there is overlap in some areas, particularly where the effects of one factor significantly mediate or confound another.

In conclusion, this review re-emphasises that there is no “one size fits all” solution in the management of type 1 diabetes. Further research efforts may be best directed towards evaluation of personalised interventional strategies to assist individuals. Of particular value may be more prospective studies attempting to
disentangle the links between stress, family conflict and less cohesive family functioning. There is also a knowledge hiatus regarding the links between stress and self-care in adolescence and in the area of parenting style, particularly in the crucial pre-adolescent period. The latter may provide another target for positive intervention. Whilst some work has been done to assess the impact of demographic variables on optimal employment of CSII/CGMS, relevant inter- and intrapersonal factors remain relatively unexplored. Given that these groups may display higher motivation by their selection for CSII/CGMS, exploring their personality factors in more depth than has previously been done may be very interesting. Whilst interventions in some domains such as coping and self-efficacy have shown some worthwhile psychosocial effect benefits, interventions targeting family conflict and division of diabetes responsibility appear to have more of an impact on HbA$_{1c}$.

With the relevant factors identified, the next step of creation of a predictive tool was undertaken.
CHAPTER 4: Design of the Predictive Tool
4.1 INTRODUCTION

To date, a reliable tool has not been devised to predict which patients adapt positively to their diagnosis of diabetes according to intra-/inter-personal and demographic factors. My aim therefore was to both construct such a tool and assess its potential predictive value in clinical settings. To construct the tool, I coalesced the thirteen personal factors identified as robustly associated with diabetes-related outcomes from the systematic review into six domains, comprising:

1. Self-Efficacy
2. Responsibility
3. Conflict
4. Behaviour
5. Coping
6. Demographic data

These items were then amalgamated to construct a novel questionnaire or tool to be administered in the subsequent clinical trial of individuals commencing utilisation of CSII or SAP (see Figure 4-1).

The six domains were chosen based on pre-existing available questionnaires, each validated to assess one of the particular factors shown to display robust association with self-care or glycaemic control, as per the previous chapter. Although the source questionnaires were validated in their entirety and not in composite parts, my aim was not to establish the validity of the new composite tool – rather to test the hypothesis that prediction of an individual’s future technology engagement was possible in a pilot study.
4.2 SCALES

The first five domains were assessed and incorporated into the novel tool using questionnaire items selected from five pre-existing validated questionnaires, each specifically designed to assess one of the five particular domains as follows:

1. To assess self-efficacy, I extracted 8 items from the Self-Efficacy Scale (Grossman, Brink et al. 1987);
2. To assess diabetes-related responsibility, I selected 4 items from the Diabetes Family Responsibility Questionnaire (Anderson,Auslander et al. 1990);
3. For the assessment of conflict, I extracted 4 items from the Diabetes Family Conflict Scale (revised) (Hood, Butler et al. 2007);
4. To assess behaviour, I selected 13 items from the Diabetes Family Behaviour Checklist (Lewin, Geffken et al. 2005);
5. To assess coping, I extracted 8 items from the Adolescent Coping Scale (Frydenberg and Lewis 1996).

These five previously validated questionnaires have been widely used to assess diabetes-related psychosocial outcomes in young people and reproducibly display robust internal and external validity scores. Please see Appendix B for these questionnaires in full. Full scales were not utilised as this would have made the tool prohibitively lengthy for use in this age group, as well as impractical to administer in a clinical setting. Instead, items were selected from the pre-existing scales either by weighted factor analysis where indicated in the published papers (Frydenberg and Lewis 1996; Lewin, Geffken et al. 2005; Hood, Butler et al. 2007), or where unavailable, after discussion amongst the research team.

The Adolescent Coping Scale was not validated in a population younger than 12 years old, hence both a child and an adolescent questionnaire were developed, with alternative questionnaire items selected to ensure age-appropriateness from the KidCope scale (Spirito, Stark et al. 1988).

The sixth domain of my tool consisted of items assessing generic demographic data, specifically: gender, age, ethnicity, family structure and postcode. The latter was assigned a grading indicative of socio-economic status according to the index of relative socio-economic advantage and disadvantage from the Socio-Economic Indexes For Areas (SEIFA index) (2008).
4.2.1 Tool Age Brackets

The adolescent tool was designed for and administered to trial participants aged 12 to 20 years old. The child version of the tool was designed for and administered to participants aged 8 to 11.99 years.

4.2.2 Method of Completion

Questionnaires were confidentially self-completed by the person with diabetes, with younger participants offered assistance to complete the questionnaire by the principal investigator or parents as required and as directed by the young person themselves. The questionnaire generally took 15-20 minutes to complete.
4.2.3 Adolescent Questionnaire Sample

Many thanks for taking the time to fill out this research questionnaire. It should take 15-20 minutes to fill out. Try not to think too long about any one question, just pick the answer which best fits with yourself and your experience of having diabetes. All questionnaires are confidential and answers will not be seen by anyone but the research team.

Please read the instructions at the beginning of each section on how to best answer the questions. There are six sections.

Study ID number: ______________

SECTION 1.

After each question, please circle the appropriate answer to show how much you believe you can or cannot do what is asked now.

1. **Keep track of my own blood sugar levels**
   - Very sure I can’t
   - Sure I can’t
   - Probably I can’t
   - Sure I can
   - Very sure I can

2. **Tell a friend I have diabetes**
   - Very sure I can’t
   - Sure I can’t
   - Probably I can’t
   - Sure I can
   - Very sure I can

3. **Take responsibility for getting my homework and chores done**
   - Very sure I can’t
   - Sure I can’t
   - Probably I can’t
   - Sure I can
   - Very sure I can

4. **Follow my doctor’s orders for taking care of my diabetes**
   - Very sure I can’t
   - Sure I can’t
   - Probably I can’t
   - Sure I can
   - Very sure I can
SECTION 2

For each of the following parts of your diabetes care, tick the box for the answer that best describes the way you handle things at home. If you take responsibility or remind your parents to do things almost all the time, tick the YOU box. If you and your parent(s) share responsibility, tick the EQUAL box. If your parent(s) reminds you to do things, tick the PARENT box.

9. Telling teachers about diabetes

10. Deciding what to eat at meals or snacks

11. Remembering when blood sugar should be tested

12. Adjusting insulin according to sugar test results
SECTION 3.

During the PAST MONTH, I have argued with my parent(s) about...........

(tick box)

<table>
<thead>
<tr>
<th></th>
<th>Almost never</th>
<th>Sometimes</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>14. Remembering to check blood sugars</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Giving shots or boluses (pump)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Rotating sites/infusion sets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. Logging blood sugar results</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SECTION 4.

For each item, please **tick the box** for Not True, Somewhat true, or Certainly True...

<table>
<thead>
<tr>
<th></th>
<th>Not true</th>
<th>Somewhat true</th>
<th>Certainly true</th>
</tr>
</thead>
<tbody>
<tr>
<td>18. My parent(s) understand how I feel about having diabetes.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. My parent(s) congratulate me for sticking to my diabetes plan.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. My family plan activities to fit in with my diabetes.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. I try to be nice to other people. I care about their feelings.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22. I am restless, I cannot stay still for long.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23. Other people my age generally like me.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>24. I get very angry and often lose my temper.</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>25. I am often unhappy, depressed, or tearful.</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>26. I usually do as I am told.</td>
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<td></td>
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<tr>
<td>27. I worry a lot.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>28. I have one good friend or more.</td>
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</tr>
<tr>
<td>29. Other children pick on me or bully me.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30. I often volunteer to help others (parents, teachers/co-workers, children..)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SECTION 5

Please indicate by marking the appropriate box, the things you do to deal with your concerns or worries. Mark 1, 2, 3, 4, or 5 as you come to each statement, as in the following example:

<table>
<thead>
<tr>
<th>Doesn’t apply or don’t do it</th>
<th>Used very little</th>
<th>Used sometimes</th>
<th>Used often</th>
<th>Used a great deal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

31. Spend more time with friends

32. Pray to God to look after me

33. Consciously ‘block out’ the problem

34. Hope that the problem will sort itself out

35. Organise a group to look at the issue

36. Daydream about how things will turn out well

37. Get support from others such as parents or friends

38. Go out and have a good time and forget about my troubles
SECTION 6

About yourself...

(Please tick the correct box)

39. I am a: Boy [ ] Girl [ ]

40. My age is: [ ] years old

41. Ethnic origin
   [ ] White/Caucasian
   [ ] Aboriginal/Islander
   [ ] Asian
   [ ] African
   [ ] Other

42. At home
   [ ] Live with both my parents at home
   [ ] Live with one parent at home
   [ ] Live with another family member (e.g. grandparent)
   [ ] Live with foster parents
   [ ] Other

43. My Postcode: _______________

Thank you very much for filling out this questionnaire. Please hand it to the research team or post it in the envelope provided.
4.2.4 Child Questionnaire Sample

Many thanks for taking the time to fill out this research questionnaire. It should take 15-20 minutes to fill out. Try not to think too long about any one question, just pick the answer which best fits with yourself and your experience of having diabetes. All questionnaires are confidential and answers will not be seen by anyone but the research team. Your parent(s) can help you to fill it out if you like.

Please read the instructions at the beginning of each section on how to best answer the questions. There are six sections.

Study ID number: _____________________
SECTION 1

After each question, please **circle the appropriate answer** to show how much you believe you can or cannot do what is asked now.

1. Keep track of my own blood sugar levels
   - Very sure I can’t
   - Sure I can’t
   - Probably I can’t
   - Sure I can
   - Very sure I can

2. Tell a friend I have diabetes
   - Very sure I can’t
   - Sure I can’t
   - Probably I can’t
   - Sure I can
   - Very sure I can

3. Take responsibility for getting my homework and chores done
   - Very sure I can’t
   - Sure I can’t
   - Probably I can’t
   - Sure I can
   - Very sure I can

4. Follow my doctor’s orders for taking care of my diabetes
   - Very sure I can’t
   - Sure I can’t
   - Probably I can’t
   - Sure I can
   - Very sure I can

5. Figure out how much insulin to give myself when I am sick in bed
   - Very sure I can’t
   - Sure I can’t
   - Probably I can’t
   - Sure I can
   - Very sure I can

6. Feel able to stop a low reaction (a hypo) when I am having one
   - Very sure I can’t
   - Sure I can’t
   - Probably I can’t
   - Sure I can
   - Very sure I can
7. **Believe that I have the ability to have control over my diabetes**
   - Very sure I can’t
   - Sure I can’t
   - Probably I can’t
   - Sure I can
   - Very sure I can

8. **Prevent blindness and other complications from my diabetes**
   - Very sure I can’t
   - Sure I can’t
   - Probably I can’t
   - Sure I can
   - Very sure I can

**SECTION 2**

For each of the following parts of your diabetes care, **tick the box** for the answer that best describes the way you handle things at home. If you take **responsibility** or remind your parents to do things almost all the time, tick the **YOU** box. If you and your parent(s) **share responsibility**, tick the **EQUAL** box. If your parent(s) reminds you to do things, tick the **PARENT** box.

13. Telling teachers about diabetes

14. Deciding what to eat at meals or snacks

15. Remembering when blood sugar should be tested

16. Adjusting insulin according to sugar test results
SECTION 3

During the PAST MONTH, I have argued with my parent(s) about...........
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SECTION 4

For each item, please **tick the box** for Not True, Somewhat true, or Certainly True...

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<td>I often volunteer to help others (parents, teachers/co-workers, children..)</td>
<td></td>
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</tbody>
</table>
SECTION 5

Please circle whether you use any of the following ways to deal with a difficult situation, for example, when you were diagnosed with diabetes.

<p>| | | |</p>
<table>
<thead>
<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>31. I did something like watched TV or played a game to forget it</td>
<td>Always</td>
<td>Sometimes</td>
</tr>
<tr>
<td>32. I stayed by myself</td>
<td>Always</td>
<td>Sometimes</td>
</tr>
<tr>
<td>33. I tried to see the good side of things</td>
<td>Always</td>
<td>Sometimes</td>
</tr>
<tr>
<td>34. I blamed myself or someone else for causing the problem</td>
<td>Always</td>
<td>Sometimes</td>
</tr>
<tr>
<td>35. I tried to fix the problem by doing something or talking to someone</td>
<td>Always</td>
<td>Sometimes</td>
</tr>
<tr>
<td>36. I yelled, screamed, or got mad</td>
<td>Always</td>
<td>Sometimes</td>
</tr>
<tr>
<td>37. I wished the problem had never happened</td>
<td>Always</td>
<td>Sometimes</td>
</tr>
<tr>
<td>38. I tried to feel better by spending time with others like my family or friends</td>
<td>Always</td>
<td>Sometimes</td>
</tr>
</tbody>
</table>
SECTION 6

About yourself...
(Please tick the correct box)

39. I am a: Boy [ ] Girl [ ]

40. My age is: [ ] years old

41. Ethnic origin
   [ ] White/Caucasian
   [ ] Aboriginal/Islander
   [ ] Asian
   [ ] African
   [ ] Other, please tell us: _______________________

42. At home
   [ ] Live with both my parents at home
   [ ] Live with one parent at home
   [ ] Live with another family member (e.g. grandparent)
   [ ] Live with foster parents
   [ ] Other, please tell us: _______________________

43. My Postcode is: _______________________

Thank you very much for filling out this questionnaire.
Please hand it to the research team or post it in the envelope provided.
CHAPTER 5: Prospective Clinical Trial of Tool in Technology Population
5.1 INTRODUCTION

Whether CSII or SAP therapy benefit all youth with diabetes, or just a select well-motivated supported subset, remains a highly controversial point (Williams, Storch et al. 2005; Lombardo, Iafusco et al. 2007; Lassmann-Vague, Clavel et al. 2010). There are currently very few criteria to guide which individuals would benefit most from starting an insulin pump program, or augmentation of established CSII with CGMS (Kaufman, Halvorson et al. 2001). Both CSII and CGMS have established moderate benefit both in terms of metabolic control and reduction of nocturnal hypoglycaemia in the paediatric population (Weissberg-Benchell, Antisdel-Lomaglio et al. 2003; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, Tamborlane et al. 2008; Misso, Egberts et al. 2010). However, attainment of these benefits is dependent upon considerable user effort, with the metabolic advantage obtained correlating in an almost linear fashion with the amount of interaction at the user-technology interface.

Specifically in the CSII population, HbA$_1c$ has been demonstrated to reduce by 0.2% for each extra BGL per day performed and entered into the user’s pump (O’Connell, Donath et al. 2011), with an apparent plateau effect at ~6 BGLs per day (Ziegler, Heidtmann et al. 2011). The number of carbohydrate and correction boluses completed per day also correlates significantly with HbA$_1c$ attained (Danne, Battelino et al. 2008; Olinder, Kernell et al. 2009). In the SAP population, usage of CGMS for $\geq$70% of the week ($\geq$5 days per week) has been shown to correlate with a clinically significant reduction in mean HbA$_1c$ of 0.5% (Beck, Buckingham et al. 2009; O’Connell, Donath et al. 2009). Until user-independent systems become available, human behaviour will remain a significant factor limiting the impact of these technologies on target HbA$_1c$ achievement, particularly in the adolescent population (Liberman, Buckingham et al. 2011).
Commencement of CSII or CGMS is expensive both in terms of monetary cost and in educational time on the part of users, their carers and the health-care professionals involved. Cost-benefit analyses have demonstrated that this preliminary outlay is worthwhile, via subsequent reduction of the future considerable cost of treating micro- and macrovascular complications (Roze, Valentine et al. 2005; Cohen, Minshall et al. 2007). However, this is contingent upon delivery of a significant improvement in metabolic control with technology usage.

The ability to reliably predict higher usage of technology would therefore be helpful when advising an individual regarding their insulin regimen and diabetes management strategies. This would allow stratification of youth by psychosocial preparedness prior to introduction or intensification of technology, rather than with rescue measures when an individual is already experiencing difficulty with their regime, or when low self-care behaviour has become entrenched.

A questionnaire-based tool (referred to hereafter as ‘the questionnaire’) was designed as described in CHAPTER 4, incorporating the thirteen factors identified from the systematic review as described in CHAPTER 3.

5.2 OBJECTIVE

The objective of this study was to assess the ability of this questionnaire to predict future technology usage in youth commencing CSII and ‘real-time’ CGMS/SAP. A cohort commencing use of CSII were chosen as an example of a technology-naïve population, whereas those commencing SAP therapy were intensifying their use of established technology.
5.3 RESEARCH DESIGN AND METHODS

A prospective study was carried out at RCH Melbourne, assessing the performance of the predictive tool in two groups: (A) 50 youth commencing augmentation of established CSII with ‘real-time’ CGMS and (B) 47 youth switching from an injectable insulin regimen to CSII, with regular self-monitoring of capillary blood glucose.

Inclusion criteria common to both groups were: confirmed diagnosis of type 1 diabetes, age between 8 and 20 years old, English language fluency and home access to the Internet. Informed consent was signed prior to study commencement by participants, or by their parents/guardians where aged <18 years old. Ethics approval was obtained from the institutional Human Research Ethics Committee and the trial was conducted in accordance with the Declaration of Helsinki.

5.3.1 Trial registration

This trial was registered prior to commencement at the Australian New Zealand Clinical Trial Registry (ANZCTR) and given registration number ACTRN12611001043921.

5.3.2 Trial Funding

No external source of funding was sought or used in this trial. All CGMS equipment (Minilink™ transmitters and Enlite™ sensors) was supplied by Medtronic (Northridge, CA, USA) for use in this study. This company did not have any further input into study design, analysis, or reporting of findings.

5.3.3 Definitions of Usage

High usage of technology was defined as the usage previously demonstrated to correlate with a clinically significant improvement in
HbA\textsubscript{1c} of 0.5\%, at a timepoint where usage has been shown to be predictive of future usage in a paediatric population. This is the usage recommended to individuals at technology commencement at RCH.

5.3.3.1 CGMS Usage

In the CGMS group, high usage was defined as ≥70\% usage (i.e. percentage of time sensor was worn) per week, assessed at three months from CGMS commencement (Beck, Buckingham et al. 2009; Diabetes Research in Children Network Study, Weinzimer et al. 2009; O'Connell, Donath et al. 2009). CGMS usage was calculated from pump download data at one, two, and three months post-commencement and averaged over each month.

The primary outcome assessed was the accuracy of the questionnaire in prediction of CGMS usage at 3 months post-commencement. Secondary outcomes were usage during the 1\textsuperscript{st} and 2\textsuperscript{nd} month, HbA\textsubscript{1c}, and other pump parameters recorded monthly, namely: bolus frequency, number of BGLs recorded per day, TDD and percentage of TDD administered as basal insulin.

5.3.3.2 CSII Usage

In the CSII group, high usage was defined as ≥5 BGLs per day recorded in the pump device, assessed at six months post-commencement (Levine, Anderson et al. 2001; O'Connell, Donath et al. 2011; Ziegler, Heidtmann et al. 2011). This was also extrapolated from pump download data and assessed at baseline, three months and six months, averaged over the preceding fortnight.

The primary outcome analysed was the questionnaire’s accuracy in prediction of CSII usage (BGLs recorded per day) at 6 months post-commencement. Secondary outcomes assessed were: height,
weight, HbA$_{1c}$, $\Delta$HbA$_{1c}$, number of boluses per day, line change frequency, TDD, basal:bolus ratio at baseline, 3, 6 and 12 months. Data collection was extended to 12 months in order to investigate the ongoing relationship of usage with time. See Figure 5-1 for graphic representation of study design.

![Figure 5-1: Study Design](image)

5.3.4 Participants and Recruitment

5.3.4.1 CGMS participants

At the time of recruitment, the only available pump system compatible with CGMS at our institution was the Medtronic MiniMed Paradigm® (Northridge, CA, USA). All active eligible patients in our hospital database were sent a postal invitation to participate in group A (CGMS group). In addition to the common criteria outlined above, youth recruited had been using CSII for a minimum of six months, were CGMS-naïve and were without another medical condition which could interfere with daily wearing of a sensor. Participants completed the novel questionnaire (as described in Chapter 4) just prior to
delivery of a 3 hour standardised CGM-instruction session. This session covered the basics of SAP use, practicalities such as calibration, interpretation of data and extra features available such as low-glucose suspend. Initial settings and alarms were individualised and no algorithm was provided for use with the CGMS as it was felt that this could have added a possible confounder to subsequent analysis. Participants were then supplied with transmitters and sensors to enable 3 months continuous home use and ‘uploaded’ their pump monthly to the research team via the Carelink™ internet software program. Pump setting changes were not made by myself but participants were encouraged to liaise with their diabetes nurse educator for assistance with appropriate adjustment.

5.3.4.2 CSII participants

Participants in group B (CSII group) had already decided in a study-independent collaborative decision with their physician to switch insulin regimen to use of CSII. The RCH diabetes department applies some baseline criteria pre-consideration for CSII: the ability to count carbohydrates, demonstration of a minimum of 4 BGLs/day on glucometer download and basic understanding of CSII utilisation.

All eligible youth due to commence CSII in our institution between Jan 2012 and March 2013 were approached to partake in this study prior to their scheduled pump training week, with 96% agreeing to complete the questionnaire. Data were collected from participants' subsequent scheduled out-patient appointments, at 3-monthly intervals.

HbA1c was recorded at each appointment as previously described in Section 1.8.4.
5.3.5 Statistical Analysis

Due to the pilot nature of this study, a power calculation was difficult due to a paucity of similar published data. Previous studies of CGMS usage in the paediatric population had sample sizes of 30 and 45 respectively and established persistent high usage after 3 months in 46-57% of participants (Diabetes Research in Children Network Study, Buckingham et al. 2007; 2010). Given the published 6-10% drop-out rate we aimed to recruit 50 patients to each study cohort, the most important factor being an adequate cross-section of individuals, with variable metabolic control.

Data were recorded and described in accordance with published STROBE guidelines for cross-sectional studies. Parametric data were described using mean, SD and analysed using paired t-test. Non-parametric data were described using median, IQ range and assessed using Wilcoxon’s rank-sum test, with chi-squared analysis used for categorical data. A p value of <0.05 was considered statistically significant. Data were entered into Microsoft Excel and Epidata and exported to SPSS (Chicago, IL, USA, Version 22.0), which was then used to generate a model using logistic regression with forward stepwise conditional. Usage was defined as the dependent variable and split into binary high/low outcomes. Bivariate relationships were explored between usage and each independent variable (raw questionnaire scores). Forward stepwise conditional was used to select variables in the order in which they maximised the statistically significant contribution to the model, with demographic variables entered first, along with baseline HbA1c followed by the questionnaire items. We used the same method for each cohort, with a view to identifying consistent predictors of technology usage.
5.4 RESULTS

5.4.1 CGMS (Group A)

Baseline data regarding the 50 CGMS participants by usage group are presented in Table 5-1. Participants were 44% male, 96% Caucasian, 96% in a two-parent family structure, with an overall mean age of 13.1 ± 3 years and mean duration of diabetes of 6.5 ± 2.9 years. Baseline HbA₁c overall ranged from 6.4 – 11% (46 – 97 mmol/mol); mean 7.8 ± 0.9% (62 mmol/mol).

Five participants withdrew from the study and returned the equipment prior to completing the three months (1=adhesive hypersensitivity; 1=worsened anxiety; 2=disliked wearing sensor; 1=general diabetes disengagement). These participants were assigned a low usage outcome. A further seven were not using the CGMS at all by the third month, all of whom demonstrated usage in the lowest quartile from the first 4 weeks.

At the 3 month primary endpoint 12 out of 50 individuals met the criteria for high usage, with 38 exhibiting low or zero usage (see Table 5-2). Neither age, gender, ethnicity, family composition or socio economic status were associated with high usage. However, high users had lower HbA₁c at baseline (7.2 ± 0.4 vs. 7.9 ± 0.9; p = 0.01) self monitored more frequently at baseline (7.0 ± 1.6 vs. 5.5 ± 1.6; p = 0.006) and gave more boluses at baseline (10.1 ± 3.3 vs. 7.6 ± 2.4, p = 0.006).
Table 5-1: Baseline characteristics CGMS group

<table>
<thead>
<tr>
<th></th>
<th>Low Usage n=38 (76%)</th>
<th>High Usage n=12 (24%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M=15</td>
<td>M=7</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>F=23</td>
<td>F=5</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>12.7±2.9</td>
<td>14.3±2.8</td>
<td>0.11</td>
</tr>
<tr>
<td>Duration diabetes</td>
<td>6.4±2.6</td>
<td>6.9±3.6</td>
<td>0.59</td>
</tr>
<tr>
<td>Duration pump use</td>
<td>3.1±1.8</td>
<td>2.7±2.2</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Baseline HbA1c (%)</strong></td>
<td><strong>7.9±0.9</strong></td>
<td><strong>7.2±0.5</strong></td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>(mmol/mol)</td>
<td>63</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Baseline BGL/day</td>
<td>5.4±1.6</td>
<td>7.0±1.6</td>
<td>0.006</td>
</tr>
<tr>
<td>Baseline boluses/day</td>
<td>7.6±2.4</td>
<td>10.1±3.3</td>
<td>0.006</td>
</tr>
</tbody>
</table>

All data presented as mean±SD, with inferential analysis by paired t-test except * = chi-squared

Table 5-2: Outcomes 3 months post-CGMS

<table>
<thead>
<tr>
<th></th>
<th>Low Usage n=38 (76%)</th>
<th>High Usage n=12 (24%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%) (mmol/mol)</td>
<td>7.8±0.8</td>
<td>7.3±0.5</td>
<td>0.06</td>
</tr>
<tr>
<td>∆HbA1c (%)</td>
<td>-0.2±0.7</td>
<td>+0.1±0.4</td>
<td>0.17</td>
</tr>
<tr>
<td>BGL/day</td>
<td>6.0±1.5</td>
<td>6.9±1.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Boluses/day</td>
<td>8.2±2.5</td>
<td>9.5±3.1</td>
<td>0.13</td>
</tr>
<tr>
<td>Total daily dose (U/kg/day)</td>
<td>0.89±0.2</td>
<td>0.82±0.2</td>
<td>0.24</td>
</tr>
<tr>
<td>% TDD as basal insulin</td>
<td>44±5</td>
<td>41±5</td>
<td>0.17</td>
</tr>
</tbody>
</table>

All data presented as mean±SD, with inferential analysis by paired t-test
5.4.1.1 User-pump interaction

Overall user-pump interaction declined as the three month period progressed (see Table 5-3). After the initial increase in usage during the 1st month, values then regressed towards baseline until the 3 month endpoint, at which timepoint no significant difference was seen between the recorded mean baseline and 3-month values for BGLs/day (p = 0.09) or boluses/day (p = 0.35). Overall, mean total daily insulin dose remained static over the trial period at 0.87 U/kg/day, although the percentage derived from basal insulin increased from 41% to 43% (p = 0.008).

<table>
<thead>
<tr>
<th>Table 5-3</th>
<th>User-pump interaction frequency by month - CGMS group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline</td>
</tr>
<tr>
<td>CGMS Usage (%)</td>
<td>66.3±22</td>
</tr>
<tr>
<td>BGLs/day</td>
<td>5.8±1.8</td>
</tr>
<tr>
<td>Boluses/day</td>
<td>8.2±2.8</td>
</tr>
</tbody>
</table>

Data presented as mean±standard deviation; BGLs = blood glucose levels; p-value month1 Vs month3, student’s paired t-test, except ‡ = Wilcoxon signed rank test

5.4.1.2 Logistic Regression Analysis CGMS

Multiple logistic regression analysis (see Table 5-4, Figure 5-2 and Figure 5-3) incorporating gender, baseline Hba1c and two questionnaire items resulted in 92% of participants being allocated to the correct high/low usage groups. Both items that were found to be predictive were from the conflict domain and related to blood glucose testing – participants in high usage groups reporting less conflict with carers regarding (1) “remembering to check blood sugars” and (2) “logging/recording blood sugars”. The resulting Receiver Operating Characteristic (ROC) curve, see Figure 5-4, has an area under the curve of 0.95. Errors in the model derive from one participant being
predicted to have high usage, who had an actual 3 month usage of 53%, and 3 participants predicted to have low usage, with actual usage data of 72%, 70% and 88%.

### Table 5-4: Logistic regression analysis CGMS group

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>-3.629</td>
<td>1.476</td>
<td>6.047</td>
<td>1</td>
<td>.014</td>
</tr>
<tr>
<td>Baseline HbA1c</td>
<td>-3.645</td>
<td>1.358</td>
<td>7.201</td>
<td>1</td>
<td>.007</td>
</tr>
<tr>
<td>conf14</td>
<td>-3.973</td>
<td>1.706</td>
<td>5.425</td>
<td>1</td>
<td>.020</td>
</tr>
<tr>
<td>conf17</td>
<td>2.858</td>
<td>1.445</td>
<td>3.911</td>
<td>1</td>
<td>.048</td>
</tr>
<tr>
<td>Constant</td>
<td>33.782</td>
<td>12.186</td>
<td>7.686</td>
<td>1</td>
<td>.006</td>
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</tbody>
</table>

conf14 and conf17 represent questionnaire items.

### Figure 5-2: CGMS classification table

![Classification Table](image-url)
### Variables in the Equation

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Variables</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>gender39</td>
<td>-2.785</td>
<td>1.263</td>
<td>4.859</td>
<td>1</td>
<td>.027</td>
<td>.062</td>
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<tr>
<td></td>
<td>a1cpre</td>
<td>-2.968</td>
<td>1.131</td>
<td>6.877</td>
<td>1</td>
<td>.009</td>
<td>.052</td>
</tr>
<tr>
<td></td>
<td>conf14</td>
<td>-1.669</td>
<td>.756</td>
<td>4.965</td>
<td>1</td>
<td>.026</td>
<td>.186</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>27.963</td>
<td>10.269</td>
<td>7.416</td>
<td>1</td>
<td>.006</td>
<td>139.3415678973</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2</th>
<th>Variables</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>gender39</td>
<td>-3.629</td>
<td>1.476</td>
<td>8.047</td>
<td>1</td>
<td>.014</td>
<td>.027</td>
</tr>
<tr>
<td></td>
<td>a1cpre</td>
<td>-3.645</td>
<td>1.358</td>
<td>7.201</td>
<td>1</td>
<td>.007</td>
<td>.026</td>
</tr>
<tr>
<td></td>
<td>conf14</td>
<td>-3.973</td>
<td>1.706</td>
<td>5.425</td>
<td>1</td>
<td>.020</td>
<td>.019</td>
</tr>
<tr>
<td></td>
<td>conf17</td>
<td>2.858</td>
<td>1.445</td>
<td>3.911</td>
<td>1</td>
<td>.048</td>
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<td>Constant</td>
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<td>12.188</td>
<td>7.066</td>
<td>1</td>
<td>.005</td>
<td>4659076913411</td>
</tr>
</tbody>
</table>

*Variable(s) entered on step 1: conf14.*

*Variable(s) entered on step 2: conf17.*

---

**Figure 5-3: CGMS Regression - variables per step**

![ROC Curve](image)

**Figure 5-4: ROC curve CGMS analysis**

Diagonal segments are produced by ties.
5.4.2 CSII (Group B)

Forty-seven participants were recruited to the CSII study group, of whom 38% were male, 96% Caucasian, 81% in a two-parent family structure, with an overall mean age of 12.8 ± 2.5 years and median duration of diabetes of 2.8 years (IQ range 1.9 – 5.4 yrs). Baseline data by usage group are presented in Table 5-5, with those in the high usage group more likely to be younger and utilising a BD/twice daily insulin regimen prior to transition to pump therapy. Baseline HbA1c overall ranged from 5.9 – 11% (41 – 97 mmol/mol); mean 8.0 ± 0.9% (64 mmol/mol). At the primary end-point of 6 months, one participant had discontinued CSII use and was allocated a ‘low usage’ outcome.

Table 5-5: Baseline characteristics CSII group

<table>
<thead>
<tr>
<th></th>
<th>Low Usage n=15 (32%)</th>
<th>High Usage n=32 (68%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M=3</td>
<td>M=15</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>F=12</td>
<td>F=17</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>14.1±2.0</td>
<td>12.2±2.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Duration diabetes (yrs, median)</td>
<td>2.7</td>
<td>2.8</td>
<td>0.82†</td>
</tr>
<tr>
<td>Pre-pump regimen</td>
<td>BD=1</td>
<td>BD=12</td>
<td>0.03†</td>
</tr>
<tr>
<td></td>
<td>MDI=14</td>
<td>MDI=20</td>
<td></td>
</tr>
<tr>
<td>Baseline HbA1c (%) (mmol/mol)</td>
<td>7.8±0.8</td>
<td>8.0±1.0</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>62</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Baseline BGL/day</td>
<td>4.5±0.6</td>
<td>5.4±2.1</td>
<td>0.12</td>
</tr>
</tbody>
</table>

All data presented as mean±SD unless otherwise indicated. Inferential analyses performed using paired t-tests except *=chi-squared †=Wilcoxon ranksum
5.4.2.1 Logistic Regression Analysis CSII

At the 6 month primary endpoint, 15 out of 47 participants met the criterion for low usage, with the other 32 participants meeting the criterion for high usage (see Table 5-6). Multiple regression analysis (see Table 5-7, Figure 5-5 and Figure 5-6) using gender plus four of the questionnaire items predicted high/low usage of CSII with 95% accuracy. This analysis was performed using data from 41 participants due to missing questionnaire item answers in six cases. Errors in the model resulted from 2 participants predicted as having high testing frequency, which was actually low, being a mean of 3.9 and 4.3 BGL tests per day at 6 months. The accompanying ROC curve, see Figure 5-7, had an area under the curve of 0.96.

Three of the significant items were from the coping domain and although separate coping scales were used for the adolescent and child questionnaires, relevant coping items all differentiated an avoidant from an active coping style in both. Items from the Child Version were as follows: “I did something like watched TV or played a game to forget it [a difficult situation]”, “I wished the problem had never happened” and “I blamed myself or someone else for causing the problem”. The corresponding coping items from the Adolescent Version were [when dealing with concerns or worries]: “Spend more time with friends”, “Hope that the problem will sort itself out” and “Get support from others such as parents and friends”. The fourth item was from the behaviour domain, “my parents understand how I feel about having diabetes”.
Table 5-6: Outcomes 6 months post-CSII

<table>
<thead>
<tr>
<th>At 6 months (post CSII)</th>
<th>Low Usage n=15 (32%)</th>
<th>High Usage n=32 (68%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>7.7±0.9</td>
<td>7.7±0.8</td>
<td>0.88</td>
</tr>
<tr>
<td>∆HbA1c (%)</td>
<td>-0.1±1.1</td>
<td>-0.4±1.1</td>
<td>0.43</td>
</tr>
<tr>
<td>BGL/day</td>
<td>3.9±0.7</td>
<td>7.3±1.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Boluses/day</td>
<td>7.3±3.1</td>
<td>9.7±2.6</td>
<td>0.008</td>
</tr>
<tr>
<td>Total daily dose (U/kg/day)</td>
<td>0.80±0.2</td>
<td>0.79±0.2</td>
<td>0.89</td>
</tr>
<tr>
<td>% TDD as basal insulin</td>
<td>41±11</td>
<td>39±5</td>
<td>0.56</td>
</tr>
</tbody>
</table>

All data presented as mean±SD unless otherwise indicated

Table 5-7: Logistic regression analysis CSII group

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>gender39</td>
<td>-2.643</td>
<td>1.784</td>
<td>2.196</td>
<td>1</td>
<td>.138</td>
</tr>
<tr>
<td>behav18</td>
<td>3.588</td>
<td>1.788</td>
<td>4.025</td>
<td>1</td>
<td>.045</td>
</tr>
<tr>
<td>cope31</td>
<td>-1.641</td>
<td>.751</td>
<td>4.773</td>
<td>1</td>
<td>.029</td>
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<td>cope34</td>
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<td>1.077</td>
<td>3.673</td>
<td>1</td>
<td>.055</td>
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<td>1.000</td>
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<td>.991</td>
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</tbody>
</table>

behav18, cope 31, 34, & 37 refer to questionnaire items
### Figure 5-5: CSII classification table

<table>
<thead>
<tr>
<th>Step</th>
<th>BGL6mth5</th>
<th>B</th>
<th>E</th>
<th>Wald</th>
<th>df</th>
<th>Sig</th>
<th>Exp(B)</th>
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<tbody>
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<td></td>
<td>1.00</td>
<td>-1.501</td>
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<td>8.517</td>
<td>1</td>
<td>0.004</td>
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</tr>
<tr>
<td></td>
<td>Overall</td>
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<td>8.329</td>
<td>1</td>
<td>0.004</td>
<td>1806.657</td>
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<tr>
<td>Step 2</td>
<td>0.00</td>
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<td>0.538</td>
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<td>0.243</td>
</tr>
<tr>
<td></td>
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<td>-0.754</td>
<td>0.377</td>
<td>4.445</td>
<td>1</td>
<td>0.035</td>
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</tr>
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<td></td>
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<td>0.352</td>
<td>0.380</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>2.500</td>
<td>1.357</td>
<td>3.392</td>
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<td>12.182</td>
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<td></td>
<td>0.00</td>
<td>-1.447</td>
<td>0.560</td>
<td>6.667</td>
<td>1</td>
<td>0.010</td>
<td>0.235</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>-1.201</td>
<td>0.573</td>
<td>4.394</td>
<td>1</td>
<td>0.036</td>
<td>0.301</td>
</tr>
<tr>
<td>Step 4</td>
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<td>4.394</td>
<td>3.837</td>
<td>1.311</td>
<td>1</td>
<td>0.252</td>
<td>80.938</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>-2.643</td>
<td>1.784</td>
<td>2.196</td>
<td>1</td>
<td>0.138</td>
<td>0.071</td>
</tr>
<tr>
<td></td>
<td>0.00</td>
<td>3.588</td>
<td>1.788</td>
<td>4.025</td>
<td>1</td>
<td>0.045</td>
<td>36.146</td>
</tr>
<tr>
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<td>0.751</td>
<td>4.773</td>
<td>1</td>
<td>0.029</td>
<td>0.194</td>
</tr>
<tr>
<td>Step 5</td>
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<td>3.588</td>
<td>1.788</td>
<td>4.025</td>
<td>1</td>
<td>0.045</td>
<td>36.146</td>
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<td></td>
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<td>-1.430</td>
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<td>4.678</td>
<td>1</td>
<td>0.031</td>
<td>0.239</td>
</tr>
<tr>
<td>Step 6</td>
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<td>0.606</td>
<td>0.000</td>
<td>1</td>
<td>0.991</td>
<td>1.070</td>
</tr>
</tbody>
</table>

a. Variable(s) entered on step 1: cope31.
b. Variable(s) entered on step 2: cope37.
c. Variable(s) entered on step 3: behav18.
d. Variable(s) entered on step 4: cope34.

### Figure 5-6: CSII Regression - variables per step
Figure 5-7: ROC curve CSII analysis

When the same variables were used as yielded from the CGMS regression analysis (as above), these yielded a 70% accuracy in predicting usage in the CSII cohort.

5.4.2.2 CSII usage

One-year post-CSII commencement data were also available from 37 original participants, of whom three had reverted to injectable insulin therapy, with one individual lost to follow-up secondary to relocation. As demonstrated in the CGMS group, self-care behaviours tended to decline as time progressed, although displayed stability from the 6 to the 12 month mark in all parameters except bolus frequency (see Table 5-8). There was no difference between overall participant mean HbA$_1c$ at 6 and 12 months. Overall mean BGLs per day also remained similar at 6 and 12 months, but users were performing more boluses per day at 6 months compared to the 12 month
timepoint (8.6 ± 2.9 Vs 7.5 ± 2.7; p=0.004). This was supported by an increasing proportion of the total daily insulin dose delivered as basal insulin, although interestingly line change frequency improved over the time period.

**Table 5-8: Usage behaviours across time in CSII group (n=37)**

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>3 mths</th>
<th>6 mths</th>
<th>12 mths</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BGL frequency</td>
<td>5.1±1.8</td>
<td>6.6±1.8</td>
<td>6.3±2.0</td>
<td>5.9±1.8</td>
<td>0.25</td>
</tr>
<tr>
<td>Bolus frequency</td>
<td>9.6±2.8</td>
<td>9.0±2.9</td>
<td>7.5±2.7</td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>TDD (U/kg/day)</td>
<td>0.95±0.3</td>
<td>0.82±0.3</td>
<td>0.80±0.2</td>
<td>0.76±0.2</td>
<td>0.19</td>
</tr>
<tr>
<td>%TDD as basal</td>
<td>N/R</td>
<td>N/R</td>
<td>40±7</td>
<td>44±10</td>
<td>0.06</td>
</tr>
<tr>
<td>Line change</td>
<td>N/R</td>
<td>50%</td>
<td>61%</td>
<td>&lt;0.001²</td>
<td></td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>8.0±1.0</td>
<td>7.48±0.8</td>
<td>7.7±0.8</td>
<td>7.6±1.0</td>
<td>0.46</td>
</tr>
</tbody>
</table>

BGL = blood glucose level; TDD = total daily dose; Line change representing proportion completing recommended frequency (minimum every 3 days); p-value 6 mths Vs 12 mths; all using student t-test except ² = chi-squared analysis; N/R = not recorded

5.5 DISCUSSION

This questionnaire-based tool is the first instrument described which has been shown to successfully predict a prospective CSII or CGMS candidate’s subsequent device usage. The tool was easy to administer and widely accepted, with a 96% participation rate amongst the CSII cohort which were sequentially approached to partake over a 14-month time period.
In this pilot study, the tool correctly assigned 92% of the CGMS group and 95% of the CSII group to high or low usage outcomes. Cohorts in both groups exhibited a wide range of metabolic control at baseline. Risk models are becoming more widely used to guide clinical care (Hippisley-Cox, Coupland et al. 2009; Schwartz, Axelrad et al. 2014) and stratification of an individual’s future engagement with technology prior to commencement would be especially useful in an economically-constrained, waiting-list driven environment. Individuals identified with potential for ‘low usage’ could have barriers to their diabetes-related self-care identified and targeted for intervention prior to the CGMS/CSII intensive education process, creating a cycle of support that may serve to enhance service delivery and long-term regimen success. Recent commentary has concluded that the successful prediction of insulin pump outcomes is “impossible” (Jankovec, Cesak et al. 2014), however we would suggest that the clinical variables explored to date (e.g. baseline HbA1c, total insulin dose, age, body mass index) have been too narrow. We have shown that considering “non-clinical” demographic, inter- and intrapersonal predictors is effective.

Whilst psychosocial variables were predictive of technology usage, the variables’ utility varied with the specific nature of the technological tool in question. Although this might initially seem counterintuitive it is in fact not surprising. The CGMS cohort was older, had a longer diabetes duration (and thereby potential for diabetes fatigue) and exhibited a lower proportion of high usage (24%) compared to the younger CSII cohort at 68%. Younger age at initiation has been shown repeatedly to be one of the most robust factors predicting successful technology uptake and likely represents greater parental involvement with diabetes care (Nabhan, Rardin et al. 2006; McVean, Eickhoff et al. 2007; Shalitin, Gil et al. 2010; Jankovec, Cesak et al. 2014).
Conflict-focused questionnaire items predicted CGMS usage whereas CSII usage was more related to coping and behaviour domains. By its nature, CGMS is more BGL-focused and levels of self-monitored blood glucose have been shown to directly mediate the effect of conflict on HbA1c (Anderson, Vangsness et al. 2002). It is also possible the CGMS was viewed as more of an ‘optional extra’ by participants, in contrast to CSII with which interaction is more obligatory as the route of insulin delivery. This may explain the persistence of reducing usage over time displayed in the SAP cohort as the novelty of the new technology diminished, as has been previously described (Beck, Buckingham et al. 2009). The cohorts also differed in that the CGMS group volunteered their participation, whereas the CSII group represented a more opportunistically obtained cross-section of our pump population.

Studies attempting to predict diabetes-related outcomes have largely been conducted in cohorts using injectable insulin regimens (Neylon, O'Connell et al. 2013). To our knowledge, there exist no studies as yet exploring associations of intra- or interpersonal characteristics with CSII- or CGMS-specific outcomes. Individuals commencing these technologies may represent the more engaged end of the spectrum regarding self-care. Hence it is possible that characteristics other than those already described may be associated with self-care in CGMS/CSII populations.

Similar to other studies usage declined as time continued, however usage did not translate into a differential in HbA1c in either group in this study. This may have been because the period of time between technology commencement and outcome assessment was too short, although no difference was shown when CSII outcomes between 6 and 12 months were examined except for number of boluses administered per day. It is also possible that a degree of ‘passivity’ or lack of engagement /confidence to pro-actively change pump settings and adjust insulin according to identified trends existed, preventing
effective utilisation of the information gained, as recently described (White, O’Connell et al. 2013).

5.5.1 Study Limitations
The weaknesses of this study include its relatively small sample size and relatively homogenous ethnicity. Individuals at RCH commencing pump therapy all have private health insurance, somewhat limiting the predictive contribution of socioeconomic status as a variable. Daily BGL estimates in the CSII group were averaged from the fortnight preceding an out-patient visit and this raw number has been shown to be more likely to increase in anticipation of the impending appointment. However this is more likely in individuals with higher adherence levels, which should negate the effect somewhat for this study’s purposes (Driscoll, Johnson et al. 2011).

5.6 CONCLUSIONS
This study shows that it is possible to predict users’ engagement with advanced diabetes technologies, which should be particularly useful in an adolescent population. It is possible that behaviours and/or personal characteristics which translate into successful use of SAP differ significantly from those utilised to produce successful CSII outcomes. Further evaluation is required to assess whether this usage translates into the prediction of metabolic control achieved in the longer term. Future work is necessary to evaluate performance with larger numbers in more sociodemographically diverse populations.
CHAPTER 6: Summary of Results and Implications of this work
6.1 BACKGROUND TO THIS WORK

Despite widespread adoption of CSII in centres across the world, significant proportions of youth are still not attaining HbA$_1c$ targets (Cameron, Cotterill et al. 2013; Wood, Miller et al. 2013). Extrapolation of data from the DCCT and EDIC studies would infer that these individuals have a higher risk of acquisition of diabetes-related complications, at a younger age, than their peers with target HbA$_1c$ levels. In particular given the increasing diagnosis of T1DM in younger children, both greater lifetime exposure to hyperglycaemic excursions and loss of any ‘metabolic memory’ effect may compound this disadvantage. As CSII represents the most physiologically similar method of insulin delivery currently available, it may be inferred that the interface between human behaviour and technology remains a major modifiable factor towards the acquisition of desired metabolic control.

Likewise, the advent of CGMS has offered users a ‘real-time’ window into glucose concentrations and trends which is rarely, if ever, obtained with conventional glucose monitoring. Utilisation of this extra information requires time and a commitment to diabetes management that may exceed the capacity of a busy individual or family (Diabetes Research in Children Network Study 2006). The same study comprises the limit of psychosocial research in children using CGMS to date. Whilst it established that the technology has neither adverse nor beneficial effects with regard to anxiety or quality of life, no studies have yet been conducted from a prospective point-of-view. The ‘low-glucose suspend’ feature enabled by sensor-augmented pump therapy has displayed encouraging benefits, but more autonomous systems are at present challenged by delays in both insulin action and interstitial glucose measurement. It is likely that some degree of user interaction with closed-loop systems will be necessary for the foreseeable future, e.g. in terms of meal or
exercise announcement (Kumareswaran, Evans et al. 2012). As such, it is not likely that user interaction at the technology interface will be superseded in the medium term by technology or algorithm innovation, emphasising the continued relevance of this work.

In this era of increasing health-care costs and finite health budgets, it would seem reasonable to prioritise access to those potential CSII or CGMS candidates who are most likely to benefit from it. Attempts to predict success or failure of technology have so far resulted in a few narrow criteria such as age, gender, level of SMBG and baseline HbA1c, but these were not universally replicated across studies (Beck, Buckingham et al. 2009; Shalitin, Gil et al. 2010; de Vries 2011). Since the initiation of my research in this topic, one further paediatric psychosocial risk index has been developed, but this explores prediction of poor glycaemic control between one and four years post-diagnosis and is not technology-specific (Schwartz, Axelrad et al. 2014). Given the likelihood of increasing cost accompanying increasing innovation, I felt that there was a need to focus predictive efforts on the technology aspect in the management of type 1 diabetes.

6.2 OVERVIEW OF WORK UNDERTAKEN

The overarching aim of this work was the development of a screening tool to predict engagement with diabetes technologies, via exploration of the human-technology interface and the impact of user behaviour on diabetes-related outcomes.

The initial study was designed to explore whether or not simple technology innovation could in itself lead to improved self-care parameters. As levels of self-monitored blood glucose correlate with
HbA\textsubscript{1c} achieved and are considered a robust marker of self-care behaviour in CSII users, this was chosen as the primary outcome, with other indicators such as bolusing behaviour examined as secondary outcomes. This randomised crossover trial allocated participants to using CSII with conventional manual pump entry of self-monitored blood glucose levels, or to CSII incorporating wireless delivery of self-monitored blood glucose levels directly to the pump. Participants were assessed after six months in each trial arm in order to negate any initial novelty effect, particularly pronounced over the first six weeks in trials of new technology prototypes.

The second essential component of this work was a systematic literature review which aimed to identify personalised predictors of self-care or metabolic control. Studies published since 1993 were explored, acknowledging the paradigm shift in care emphasis generated from that year onward following on from publication of the DCCT. This was organised into three domains – examining demographic, intrapersonal and interpersonal factors that were reproducibly predictive of, or strongly associated, with the above two outcomes. This involved assessment of seventy studies containing data from over 11,000 youth with type 1 diabetes. It was then intended to synthesise these studies to identify the most consistent factors therein and amalgamate these factors to construct a questionnaire-based tool. I postulated that this tool would have utility in achievement of the ultimate goal of this research – prediction of users’ future engagement with diabetes technology. It was also intended to identify areas of hiatus within the published literature in this area and make constructive recommendations regarding future research direction.

The final step in this work involved development of the questionnaire-based tool and clinical trial of its ability to predict high or low usage of CGMS or CSII among participants. This prospective cross-sectional study involved commencement of almost 100 children/adolescents
who were naïve to either CGMS or CSII, with assessment of their usage at three and six months respectively post-technology commencement.

6.3 SUMMARY OF PRINCIPAL FINDINGS

6.3.1 Randomised Crossover Trial of Automated Technology

This study showed that incorporation of wireless SMBG delivery to a user’s pump can result in an increase in the number of SMBG recorded per day. Even in a cohort performing adequate monitoring at baseline, an increase of one SMBG per day was demonstrated during the phase of use of the automated system, when compared to the manual pump system phase. Hence it is possible that the effect of this technology may be even more pronounced in a less engaged population, as was observed in a post-hoc analysis of those users who were not performing the required number of SMBG at baseline. This subgroup, who significantly increased SMBG/day with use of the automated pump system, displayed an associated significant improvement in metabolic control with a mean HbA1c decrement of 0.9%.

Overall however, although users of the automated pump system increased levels of glucose monitoring, this did not impact significantly on metabolic control, or on other pump self-care behaviour such as insulin bolusing rates. Another recent study of similar wireless technology explored the effect on bolus frequency of utilisation of an integrated bolus calculator with automated SMBG delivery (Ramotowska and Szypowska 2014). Whilst this work also demonstrated successful influence upon the behaviour under examination, this study did not translate into a positive impact upon HbA1c either. Mean HbA1c at baseline among participants in this trial
was 7.3 ± 1.2% (56.3±13.44 mmol/mol), with a similar mean SMBG/day to our cohort at baseline among the three trial arms (between 5.2 and 5.9 per day). Although usage of the bolus calculator was successfully demonstrated and had a positive impact in terms of reduction of hypoglycaemia, positive contagion to other self-care behaviour was not seen in this study either i.e. participants did not increase their SMBG/day.

Hence, I hypothesised that a trial effect exists, whereby participants will demonstrate improvement of whatever particular self-care behaviour is under exploration, but that overall improvement of engagement with diabetes care involves changing/exploration of behaviours more intrinsic to the individual. Moreover, it has been demonstrated that participants in clinical trials are more likely to score higher in assessments of competence, achievement striving and self-discipline (Almeida, Falcão et al. 2008). These personality traits may result in an increased desire to ‘please’ the research team and improve the facet of care being examined.

This study represents the first published randomised trial of the effect of wireless BGL transmission to a user’s pump in a paediatric population. The remainder of this body of work explored the hypothesis generated from the conclusions of this study: Can intrinsic individual factors be identified and used to predict diabetes-related engagement with technologies?

6.3.2 Systematic Review of Relevant Personal Predictors

In the second study I conducted a systematic review of the literature with the objective of identifying robust reproducible factors predictive of, or strongly associated with, metabolic control or self-care. Due to the heterogeneous nature of these trials this took the form of a
qualitative synthesis of relevant studies, included once applied quality criteria were met.

Studies of demographic characteristics displayed good concordance and generalisability, with similar conclusions returned from cohorts examined in countries across the world. Lower self-care and metabolic control were associated with adolescence, belonging to an ethnic minority grouping, lower socio-economic grouping, and having a single-parent family structure. Interpersonal influences on youth with T1DM often exerted an impact according to the individual's age group e.g. the effect of parenting style being more pronounced in the preschool age category, with the effect of victimisation/bullying more influential in school-age children. Other family factors were identified as having importance, namely lower family cohesiveness, higher conflict and lower diabetes-related responsibility all exhibiting negative associations with diabetes-related outcomes. Older age categories were more affected by extra-familial networks, in particular extreme peer orientation showing negative association with self-care and metabolic control. Finally, intrapersonal factors also displayed usefulness, with lower conscientiousness, emotional stability, self-efficacy, executive functioning and avoidant coping style showing particular negative associations with the outcomes of interest.

Studies pertaining to technology-specific cohorts were limited by low participant numbers, varying outcomes and short study periods, with exploration of inter- or intrapersonal factors essentially non-existent apart from one study (Cortina, Repaske et al. 2010). All studies concluded that age at technology initiation was a robust predictor of future technology success, with 12 years old identified in several studies as the cut-off above which success becomes less likely. Other factors demonstrated varying associations among studies e.g. baseline HbA1c or SMBG at technology commencement, number of basal rates, number of line changes performed and duration of
diabetes, the latter presumably also overlapping with the influence of age. Presence of the partial remission phase was probably discounted, given that the mean duration of diabetes in these studies generally exceeded three years.

These factors were then weaved into a theoretical model of interacting pathways, based upon routes identified from the studies reviewed, with the most statistically supported options selected. Also selected from the studies were the most appropriate assessment questionnaire-based tools for each domain or factor. These were then used to generate the tool for the final part of this body of work.

Many areas were identified which remain relatively unexplored, including parenting style, influence of health-care professionals, coping and behaviour and peer orientation, the latter especially important in the larger proportion of the adolescent population not achieving target HbA$_{1c}$.

### 6.3.3 Clinical Trial of Predictive Tool

The final interventional study involved generation of the questionnaire-based tool and trial in the clinical setting of its predictive ability. This approach is unique to diabetes technology in a paediatric population, although risk assessment and generation of risk indices have been employed in other fields such as type 2 diabetes and cardiovascular event probability (Hippisley-Cox, Coupland et al. 2009; Lloyd-Jones 2010).

The tool was acceptable to participants, clinically-viable and accurately predicted usage in 92% of the CGMS cohort and 95% of the CSII cohort studied. Novelty effect was demonstrated as expected and usage of each technology declined with time in both cohorts, with regression towards the pre-technology mean seen for
most self-care behaviours. This novelty effect appeared to persist somewhat at 3 months in the CSII group, again lending credence to the design of the first intervention trial (of automated wireless systems), in which each study phase had been extended to six months in order to minimise this effect upon primary outcome assessment.

At study inception, I theorised that regression analysis would produce a formulaic model which would be both predictive of usage and common to both technologies studied. The latter aspect of this was not borne out however, with factor items predicting CGMS usage only translating to predicting 70% of the CSII cohort accurately. This finding can be explained by differences between the cohorts, but also conveys a salient message – that the behaviours and personal attributes necessary for successful employ of ‘real-time’ CGMS/SAP are likely different from those which contribute to CSII success. This again emphasises the importance of further study of inter- and intrapersonal characteristics among users of these diabetes management tools.

However, this is the first study in a paediatric population to demonstrate some success in answering the elusive question regarding the likelihood of an individual’s future level of usage of CSII or SAP. It is also useful in that a large proportion of the cohorts were composed of adolescents (44% CGMS; 49% CSII), who are more likely to display lower usage and deterioration in metabolic control.

6.4 CLINICAL IMPLICATIONS OF THIS WORK AND FUTURE RESEARCH DIRECTION

All of the studies outlined above impart clinical messages valuable in the daily management of children and adolescents with T1DM. Taken
together, this work begins to answer the frequently posed question as to who will benefit from initiation of CSII or intensification with SAP.

It is evident from the literature that in centres across the world a large discrepancy exists between what is taught and what is actually practised in relation to diabetes technology management, particularly amongst adolescents. The multifaceted nature of behaviours necessary to achieve target metabolic control can translate into an insurmountable burden, given suboptimal patient characteristics or circumstances (Ritholz 2008).

Whilst technology can be provided to patients, followed by education therein, the only major component of care that cannot be directly assisted with by the health-care team is the daily usage (line changes/self-monitoring of blood glucose/bolusing for all carbohydrate ingested) necessary for that technology to exert a positive effect on metabolic control. Once usage is completed by the individual, health-care staff can then again provide a supporting role; ensuring titration of insulin to carbohydrate ratios/sensitivity factors via reflection on glucose patterns, advising on insulin adjustment on ‘sick days’, or prospective planning for impending events. Achievement of target metabolic control in a paediatric population is often a duet of the information contributed from participant usage of technology, complemented by health-care professional advice/coaching in an active management approach (Schilling, Grey et al. 2002). Hence the identification of personal features indicative of less-favourable technology usage is of great clinical utility in assisting with indirect modification of the sole factor purely under the users’ control on a daily basis. It is also helpful that psychosocial behaviour modification programmes are displaying promising results, particularly in the areas of coping and family conflict resolution (Grey, Davidson et al. 2001; Wysocki, Harris et al. 2006; Wysocki, Harris et al. 2007). The systematic review carried out is the first to synthesise
these factors and provides a reference for the majority of clinicians who care for children and adolescents with T1DM without the support of a psychologist.

Whilst innovation such as wireless automation of insulin pumps can enhance certain self-care behaviours, the randomised crossover trial as described above displays that this does not extend to augmentation of other markers of diabetes-related engagement. Nevertheless, such advances may serve to assist improvement of control in individuals struggling with transfer of an appropriate number of SMBG per day to their pump. This study also continues to emphasise the importance of support for SMBG and the critical benefit of transferring 5 or more glucose levels per day to the users’ pump.

Significant novelty effect was demonstrated, with initial behaviour amelioration beginning to regress towards pre-initiation levels at about three months post-commencement. This could possibly be countered by a restructured educational programme of continued motivation, beginning at three months post-technology initiation and used to refresh initial knowledge imparted, with addition of more ‘advanced’ technological features such as dual-wave bolusing, temporary basal rates, or basal rate pattern utilisation.

With continued emphasis placed on prevention of illness in standards of medical care, psychological screening at diagnosis of T1DM has become part of international recommendations (Silverstein, Klingensmith et al. 2005). Unfortunately multidisciplinary team resources such as psychologists are often limited (Nicholson, Taylor et al. 2009; Hawkes and Murphy 2014). As such, further development of our questionnaire should allow it to serve as a screening tool to assist guidance of potential technology candidates into a binary pathway: either progression directly to technology commencement, or targeted problem-focused intervention to
optimise the likelihood of successful engagement with technology with the aim of culmination in technology commencement, if still desired. As outlined previously, this should have positive repercussions for prioritisation of resources, as well as an additional role in prevention of low self-care behaviour before it becomes established.

Overall these data represent an advancement of our knowledge regarding personal characteristics predictive of human interaction with technology. Until true closed-loop control eventuates and allows autonomy of insulin delivery, usage at the interface is a critical modifiable factor affecting the future success of any technology employed, attendant reduction of future complication risk and improvement of overall quality of life.

In this era of personalised medicine, this approach reverts to that of William Osler, the original ‘Father of Modern Medicine’ to whom the following is attributed:

“It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has.”
CHAPTER 7: Bibliography


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