A Pilot Randomized Controlled Trial of the Effects of Continuous Glucose Monitoring on Metabolic Control in Children with Type 1 Diabetes

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Graduate Department of Nursing Science
University of Toronto

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Abstract

Type 1 diabetes (T1D) is one of the most common chronic illnesses affecting children. Rigorous metabolic control helps delay long-term health complications in children with T1D. Continuous subcutaneous insulin infusion (CSII) with continuous glucose monitoring (CGM) provides information not available with self-monitoring of blood glucose (SMBG) alone. Few studies have evaluated the effectiveness of CGM on metabolic control in children using CSII. A 12-week multi-site pilot randomized controlled trial (RCT) was carried out in order to provide preliminary indicators of the effects of CGM compared to SMBG on metabolic control and fear of hypoglycemia, as well as provide an estimate of recruitment rates, assess compliance with allocated treatment, and determine participants’ satisfaction with allocated treatment. Children in the intervention group were asked to wear CGM for up to five days per week and perform three SMBG calibration checks per day. Children in the usual care group were asked to perform three SMBG checks per day.
Forty children and adolescents participated, 24 in the intervention group and 16 receiving usual care. After 12 weeks of CGM use, there was no statistically significant difference between groups in changes in mean HbA1c (CGM, -0.32 ± 0.89; SMBG, -0.05 ± 0.70; -0.27 [-0.83, -0.28], t=-0.99, p=0.33). There was a statistically significant difference between groups, favouring the intervention group, in changes in mean fear of hypoglycemia scores (CGM, -5.00 ± 6.89; SMBG, 3.13 ± 10.49; 8.13 [-13.92, -2.34], t=-2.85, p=0.007).

The findings from the pilot trial addressed several feasibility questions. Enrollment rate (48% of those eligible) and percentage of children who would participate again in a larger trial (n = 27; 71%) approached pre-set acceptability parameters, but compliance was low (only 9 participants met pre-set parameters; 39%). Currently, a larger RCT is not warranted until further studies evaluate methods to improve compliance with CGM.
Acknowledgements

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I would like to extend my sincerest gratitude to the nurses, participants, and their families for their contribution to this research project. Without you, this study never would have happened and your unwavering commitment to helping find ways to help improve the care of children living with Type 1 diabetes is astonishing. I am also especially grateful to Deborah Samuels from Medtronic Canada who provided the training and support for each of the patients and their families using Continuous Glucose Monitoring. I also received a great deal of support from a number of other sources. I would like to thank the Canadian Diabetes Association who provided funding to help run this study, Medtronic Canada, Inc. who provided the equipment and support throughout the CHILD pilot trial. In particular, I am grateful to Anne Snowdon for assisting in securing Medtronic assistance. I am also thankful to the Lawrence S. Bloomberg Faculty of Nursing for all of their financial support through the awards I received.
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Chapter 1
Introduction and Problem Statement

Type 1 diabetes (T1D) is a life-threatening autoimmune disease first appearing in childhood or adolescence. Although the exact cause of T1D is unknown, it has been suggested that there may be a viral or environmental trigger in genetically susceptible people that causes an autoimmune reaction, resulting in the loss of insulin production by the beta cells in the pancreas (Maffeis & Pinelli, 2008; Majidi & Maahs, 2012; Vehik & Dabelea, 2011). T1D is the most common endocrine disorder and one of the most common chronic illnesses affecting children (Canadian Diabetes Association [CDA], 2013). In 2013, the International Diabetes Federation (IDF) estimated that there were approximately 382 million people worldwide living with diabetes. The incidence of diabetes varies geographically, being highest in Finland (57.4 per 100 000/year) and lowest in Venezuela (0.1/100 000/year) with Canada reporting approximately 21.7/100 000 cases per year (Soltesz, Patterson & Dahlquist, 2010). In 2011, the Public Health Agency of Canada (PHAC) reported 3287 new cases of diagnosed diabetes (including both type 1 and type 2) among Canadians aged one to 19 years, with 90% of cases being T1D. The prevalence of diabetes varies across Canada with Newfoundland, Nova Scotia, and Ontario having the highest prevalence, while Nunavut, Alberta, and Quebec rank lowest. The total number of cases of diabetes in children and youth is reported to be 25 693, a prevalence rate of 0.3% (PHAC, 2011). T1D results in both short- and long-term health complications including severe episodes of hypoglycemia and diabetic ketoacidosis (DKA) as a result of hyperglycemia (Diabetes Control and Complications Trial [DCCT], 1993) and diabetes is the leading cause of long-term complications including retinopathy, nephropathy, cardiovascular disease in adults
(CDA, 2013). The PHAC (2011) also reported that although only 3.1% of all deaths in Canada in 2009 were attributed to diabetes, almost 30% of individuals who died had been diagnosed with diabetes. Diabetes is often not the primary cause of death, but many of the complications associated with the disease are associated with premature death.

In 1993, the DCCT carried out one of the most influential studies evaluating metabolic control of diabetes. The results suggested that children and adolescents with T1D should be treated with intensive insulin therapy in an effort to achieve glycosylated hemoglobin (HbA1c) levels of 8.0% or less, helping to delay and/or prevent long-term health complications. The sustained lowering of HbA1c levels by 0.4–0.8% is considered to be clinically important (Ahern, Boland, Doane, Ahern, Rose, Vincent, & Tamborlane, 2002; Sulli & Shashaj, 2006; DCCT, 1994), even when HbA1c levels are above recommended targets (DCCT, 1996; Pickup, 2011). A number of studies indicate that improvements in metabolic control may help to reduce the risk for the development and progression of retinopathy, neuropathy, and nephropathy by 35 to 76% (DCCT, 1986; DCCT, 1993; DCCT, 1994; DCCT, 1995). A reduction in HbA1c in those with an initially high level is also of clinical importance, as the relationship between absolute risk and HbA1c percentage is curved, with a much larger risk reduction in the high HbA1c range (DCCT, 1996; Pickup, 2011).

Specifically, children with T1D are considered at high risk for developing long-term complications because of the duration of time they will live with the disease and because traditional methods for treatment often do not provide optimum metabolic control (DCCT, 1993). Intensive management of T1D involves a complex and demanding regimen with frequent insulin administration by means of: (1) multiple daily insulin injections (MDI) or (2) continuous subcutaneous insulin infusion (CSII, or insulin pump therapy) (CDA, 2013).
Intensive management also involves numerous insulin adjustments, a healthy diet, regular physical activity, and frequent blood glucose (BG) monitoring, which is considered an essential component of daily diabetes management and is required to achieve better metabolic control (CDA, 2013; DCCT, 1993, Golicki, Golicka, Groele, & Pankowska, 2008; Schutt, Kern, Krause, 2006). In addition, a strong sense of self-efficacy, in which there is a belief that one can carry out specific behaviours in specified situations (Bandura, 1997) has been shown to be an important factor related to good diabetes self-management and metabolic control (Griva, Myers, & Newman, 2000; Ott, Greening, Palardy, Holderby, & DeBell, 2000).

The development in 1978 of self-monitoring of blood glucose levels (SMBG) using blood glucose meters is purported to be one of the greatest advances in the management of diabetes in the 20th century (Bode & Sabbah, 2001). However, self-monitoring does not provide information about the direction, magnitude, duration, frequency, and causes of fluctuations in blood glucose values (Verheyen, Gios, & De Block, 2010). The recent availability of continuous glucose monitoring (CGM) may be a significant technological ally in the struggle to achieve good metabolic control (Mastrototaro, 1999; Deiss, Bolinder, Riveline, Battelino, Bosi, Tubiana-Rufi et al., 2006) as well as having the potential to yield positive psychological and behavioural effects (Kruger & Marcus, 2000).

Psychological benefits of CGM may include decreased fear and anxiety about unexpected hypoglycemia, heightened awareness of the metabolic effects of meticulous or careless self-management, enhanced diabetes self-efficacy, increased flexibility in daily living, and enhanced motivation for improved metabolic control (Diabetes Research in Children Network (DirecNet) Study Group, 2006). However, use of continuous glucose monitoring also carries the potential for adverse psychological and behavioural effects, such as feelings of being overwhelmed by the
amount of glucose data, increasing the overall burden of diabetes management, generating unrealistic expectations about its benefits, and promoting overreaction to transitory glucose fluctuations (DirecNet, 2006). Improved metabolic control is an important treatment goal for children and adolescents with T1D, and diabetes management strategies should aim to achieve good metabolic control without resulting in adverse psychological outcomes.

Electronic searches of MEDLINE, CINAHL, EMBASE, Health and Psychosocial Instruments, and Ovid Healthstar from 1950 to 2015 revealed only three published studies evaluating use of continuous subcutaneous insulin infusion with continuous glucose monitoring compared to self-monitoring alone in children with T1D. Two studies made use of a before-after design (DirecNet; 2007; Halvorson, Carpenter, Kaiserman, & Kaufman, 2007) and the remaining study was a retrospective chart review (Scaramuzza, Iafusco, Rabbone, Bonfanti, Lombardo, Schiaffini et al., 2011). Metabolic control improved in all three studies and significant reductions in HbA1c values were reported in two of the three studies.

In 2007, DirecNet first reported significant improvements in metabolic control for children with T1D using continuous subcutaneous insulin infusion with the addition of a continuous glucose monitor. They reported HbA1c values dropped significantly from 7.1% at baseline to 6.8% at the conclusion of the study (p = 0.02). Halvorson et al. (2007) reported HbA1c levels decreased from 8.1% at baseline to 7.8% at study end, but this drop was not statistically significant. Most recently, Scaramuzza et al. (2011) described that HbA1c improved significantly in both groups of children using continuous glucose monitoring (CGM) and self-monitoring groups, but the improvement was higher with those using continuous glucose monitoring. They reported children using continuous glucose monitoring experienced a decrease in HbA1c of $8.0 \pm 1.5\%$ at baseline versus $7.4 \pm 0.8\%$ at the conclusion of the study (p = 0.002)
and children using self-monitoring alone demonstrated a decrease in HbA1c of 8.0 ± 1.6% versus 7.7 ± 1.1% at study end (p = 0.006). Seventeen additional studies were identified from the initial electronic search (Chase et al., 2001; Chase et al., 2003; Deiss et al., 2006; DirecNet, 2005; DirecNet, 2012a; DirecNet, 2012b; Gandrud et al., 2007; Hathout et al., 2005; JDRF, 2008; Jeha et al., 2004; Lagarde et al., 2006; Ludvigsson & Hanas, 2003; Ludwig-Seibold et al., 2012; Rasbach et al., 2014; Schaepelynck-Belicar, 2003; Schiaffini et al., 2002; Yates et al., 2006) in which metabolic control has been evaluated in children with T1D using continuous subcutaneous insulin infusion (CSII) and/or multiple daily injections with the addition of a continuous glucose monitor compared to self-monitoring alone. Overall, metabolic control was found to significantly improve in less than half of the studies (6/17) for children using continuous glucose monitoring devices compared to self-monitoring. However, of these six studies all of the studies combined diabetes management methods in the same sample (continuous subcutaneous insulin infusion and multiple daily injections). Three of the six studies did include a randomized control group, two utilized a one-group pre-post test design, and the remaining study was a database review. Without the use of control or comparison groups, it is impossible to determine causal effects or isolate contributing factors, including the use of different and/or combined insulin treatment for diabetes management in the same study. Studies with shorter duration and those with low numbers of participants may be combined into a meta analysis, therefore, sample size is not necessarily itself a problem. The main conclusion from the systematic review is that there have been no randomized controlled trials evaluating the use of continuous subcutaneous insulin infusion used alone for diabetes management with the addition of continuous glucose monitoring compared to self-monitoring of blood glucose alone.
Problem Statement

Prior studies have provided some evidence that the use of continuous subcutaneous insulin infusion with continuous glucose monitoring may improve metabolic control in children with T1D. However the evidence is based on methodologically weak studies, and there have been no randomized controlled trials carried out. Given the importance of good metabolic control for children’s growth and development, and the potential benefits of continuous glucose monitoring, rigorous evaluation is warranted. However before an adequately-powered randomized controlled trial could be mounted, several questions needed to be answered. The aims of this pilot randomized controlled trial were 1) to provide preliminary indicators of the effects of CSII with CGM compared to SMBG on metabolic control and fear of hypoglycemia; and 2) to assess the recruitment rate, compliance with allocated treatment, and participants’ satisfaction with their allocated treatment.
Chapter 2
Review of the Literature

The literature review has been organized into four sections. First, the physiology of diabetes, including the progression of Type 1 and Type 2 diabetes is reviewed. The second section focuses on metabolic control in T1D, including measurement (HbA1c levels), as well as a discussion of short- and long-term complications. Third, the aspects of diabetes management are discussed, including methods of insulin therapy (injections and insulin infusion), aspects of diet, physical activity, and assessment of blood glucose levels, under which continuous glucose monitoring as a clinical intervention for metabolic control and fear of hypoglycemia is specifically addressed. Lastly, the concept of self-efficacy is described as a potential variable predicting adherence to advice about the requirements of diabetes management.

Physiology of Diabetes

Diabetes is a chronic metabolic disorder in which the body cannot metabolize carbohydrates, fats, and proteins because of a lack of, or ineffective use of, the hormone insulin (Ballard, 2000). Under normal physiologic conditions, the entry of glucose into beta cells triggers the secretion of insulin (Bell & Polonsky, 2001). The released insulin is carried in the blood to peripheral tissues where it binds to insulin receptors (tyrosine kinase). This initiates a cascade of trans-membrane events resulting in the uptake of glucose by cells and its metabolism into energy or storage as glycogen (Saltiel & Kahn, 2001). Glucose enters beta cells via the glucose transporter (GLUT2) and ATP (Adenosine Tyrosine Phosphate) is generated by glycolysis. This results in closure of ATP-sensitive potassium (K\(^+\)) channels, depolarization of the plasma membrane, and opening of voltage-dependent calcium (Ca\(^{++}\)) channels. The influx of calcium leads to the release of insulin, which is carried in the bloodstream to cells throughout
the body where it binds to insulin receptors. This results in autophosphorylation of insulin receptors and phosphorylation of tyrosines on the insulin receptor substrate (IRS) family and Cbl-CAP. The phosphorylated proteins provide docking sites for SH2 domains of proteins that activate different signalling pathways, resulting in translocation of the glucose transporter (GLUT 4) and uptake of glucose by the cell (Figure 1.).

Figure 1. Insulin Release and Action.

ATP – Adenosine Tyrosine Phosphate; Ca²⁺ – Calcium; GLUT2 – Glucose Transporter 2; GLUT4 – Glucose Transporter 4; Grb2 – Growth Factor Receptor-Bound Protein 2; IRS – Insulin Receptor Substrate; K⁺ – Potassium; SHP2 – Protein-Tyrosine Phosphatase 2

Defects anywhere along the beta cell-peripheral tissue pathway can result in hyperglycemia, but at the clinical level there are two major forms of diabetes: (1) Type 1 diabetes, previously known as juvenile or insulin-dependent diabetes, and (2) Type 2 diabetes, previously known as adult or non-insulin-dependent diabetes. Type 1 diabetes is caused by an absolute deficiency in the production of insulin as a result of destruction of pancreatic beta cells. Type 2 diabetes is the more common form of the disease and is the result of a double defect: inadequate or inappropriate secretion of insulin by beta cells and resistance to the action of insulin in both peripheral tissues and beta cells. Insulin resistance may be the result of a defect in any one of several genes or pathways. However, the precise defect(s) are still not known (Notkins, 2002).

**Type 1 Diabetes**

Evidence from studies investigating the presence of an inflammatory infiltrate (insulitis) in the islets, strong linkages between T1D and certain alleles of the major histocompatibility complex (MHC) and research demonstrating autoantibodies that react with islet cell autoantigens reveal that T1D is an autoimmune disease (Notkins, 2002). Specifically, T1D is characterized by the destruction of pancreatic beta cells by cytotoxic T lymphocytes (CTLs). The CTL activity triggers the release of cytokines which in turn stimulate the proliferation of activated macrophages and autoantibodies that are attracted to the site of inflammation. The autoantibodies, together with complement-mediated lysis as well as macrophage and CTL activity, are responsible for the overall destruction of pancreatic tissue. The autoimmune attack on the beta-cells, compromises the production of insulin and thereby the functions associated with insulin (Figure 2.).
Metabolic Control in Type 1 Diabetes

HbA1C

Type 1 diabetes is a lifelong condition characterized by high blood glucose variability, a tendency towards hypoglycemia, and difficulties with insulin adjustment (Golicki et al., 2008). Hemoglobin A1C (HbA1c), a test that measures the amount of glycosylated hemoglobin in the blood is used to provide an estimate of metabolic control, specifically how well diabetes is being managed over the long-term. Glycosylated hemoglobin is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose. Normal levels of glucose produce a normal amount of glycosylated hemoglobin. As the average amount of plasma glucose increases, the fraction of glycosylated hemoglobin increases in a predictable way (Peterson, Pavlovich, Goldstein, Little, England, & Peterson, 1998; Bunn, Haney, Kamin, Gabbay, & Gallop, 1976).
In the normal 120-day lifespan of the red blood cell, glucose molecules react with hemoglobin, forming glycosylated hemoglobin. In individuals with poorly controlled diabetes, the quantities of these glycosylated hemoglobins are much higher than in healthy people. Once a hemoglobin molecule is glycosylated, it remains that way. A build-up of glycosylated hemoglobin within the red cell, therefore, reflects the average level of glucose to which the cell has been exposed during its life-cycle (Peterson et al., 1998; Bunn et al., 1976; Saudek, Derr, Kalyani, 2006).

Measuring glycosylated hemoglobin assesses the effectiveness of therapy by monitoring long-term serum glucose regulation. The HbA1c level is proportional to average blood glucose concentration over the previous three months. However, this average is not representative of daily glycemic fluctuations or indicative of the effects that diet, physical activity, and insulin have on blood glucose on a daily basis. Nevertheless, HbA1c levels are widely accepted and used as the most reliable means of assessing overall metabolic control and remains to be the best indicator by which to judge the effectiveness of long-term diabetes management and metabolic control in clinical practice (ADA, 2014; Berg & Sacks, 2008; Goldstein, Little, Lorenz, Malone, Nathan, Peterson et al., 2004; Jeffcoate, 2003; Koga, 2014; Nathan, Kuenen, Borg, Zheng, Schoenfeld, & Hein, 2008; Saudek et al., 2006). In addition, HbA1c has been described as the ‘gold standard’, for target setting by professional bodies (ADA, 2001, 2002; American College of Endocrinology, 2002; CDA, 2008; 2013; International Diabetes Federation, 1999), for assessment of new therapeutic strategies and efforts to modify or reduce risk factors (Bagust, Hopkinson, Maier, & Currie, 2001; Fleming, Jhee, Coniff, Riordan, Murphy, Kurts, 1999), and has also been proposed in several countries for the diagnosis of diabetes (Jaisson, Desmons, Renard, Chevelle, Leroy, and Gillery, 2014; Sacks, Arnold, Bakris, Bruns, Horvath, Kirkman et al., 2011).
The Canadian Diabetes Association Clinical Practice Guidelines (2008) define recommended metabolic targets for children with T1D; including HbA1c levels (Table 1). As improved metabolic control reduces both the onset and progression of diabetes-related complications in children and adolescents with T1D aggressive attempts should be made to reach the recommended metabolic targets outlined below (DCCT, 1993, 1994, 1995, 1996).

Table 1.

Recommended Metabolic Targets for Children with Type 1 Diabetes

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>HbA1c (%)</th>
<th>Fasting (Preprandial) Blood Glucose Level (mmol/L)(mg/dL)</th>
<th>2-Hour Postprandial (mmol/L) (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 6</td>
<td>Less than 8.5</td>
<td>6.0 – 12.0 (108-216)</td>
<td>--</td>
</tr>
<tr>
<td>6-12</td>
<td>Less than 8.0</td>
<td>4.0 – 10.0 (72-180)</td>
<td>--</td>
</tr>
<tr>
<td>13-18</td>
<td>Less than 7.0</td>
<td>4.0 – 7.0 (72-126)</td>
<td>5.0 – 10.0 (90-180)</td>
</tr>
</tbody>
</table>


Short-Term Metabolic Control Complications

At diagnosis, acute symptoms of T1D include polyuria, polydipsia, lethargy, and loss of muscular bulk and weight loss, regular thrush, blurring of vision, unexpected cramping, and/or feeling constipated (CDA, 2013; Lowes, 2008).

Hypoglycemia. Severe episodes of hypoglycemia, the most common adverse event associated with T1D, can occur suddenly and are characterized by unpleasant physical and psychological symptoms such as shaking, sweating, drowsiness, nausea, poor motor coordination, dizziness, and fatigue, as well as irritability and mental confusion (CDA, 2013;
Wild, von Maltzahn, Brohan, Christensen, Clauson, & Gonder-Frederick, 2007). Hypoglycemia is a major concern for children with T1D and can affect their ability to achieve glycemic targets (CDA, 2013) as well as potentially interfering with day-to-day life by inducing distressing symptoms as well as through its acute effects on the brain and cognition (Jones & Davis, 2003). Further, asymptomatic hypoglycemia is important especially when it develops nocturnally, when most children do not test blood glucose levels. There are concerns that it may be a cause of central nervous system damage in the young if it is prolonged or profound (Golden, Ingersoll, Brack, Russell, Wright, & Huberty, 1989). In addition to the high frequency of asymptomatic hypoglycemia at night, most severe episodes of hypoglycemia, involving seizure and comas occur nocturnally (DCCT, 1991; Davis, Keating, Byrne, Russell, & Jones, 1998).

Studies have shown that children and adolescents experience high rates of severe hypoglycemia, as much as a three-fold increase in children who have intensified diabetes management (DCCT, 1993; DCCT, 1997). Intensive management consisted of three or more insulin injections per day or the use of an insulin pump compared to conventional therapy comprising two or more insulin injections each day. Fear of hypoglycemia is considered to play a significant role in diabetes management (Irvine, Cox, & Gonder-Frederick, 1994), particularly for children with diabetes (Green, Wysocki, & Reineck, 1990). Given the unpleasant aspects and the potentially life threatening nature of severe hypoglycemia, it is not surprising that many people with T1D have a significant fear of developing hypoglycemia. This fear is particularly prevalent in patients who have experienced severe hypoglycemic episodes previously, as the more unpleasant or traumatic the event, the more likely someone is to develop anxiety about a repeat episode (Wild et al., 2007). In order to avoid the aversive symptoms of past hypoglycemia episodes, patients who have fear of hypoglycemia may engage in “over-
compensatory” behaviours, including taking less insulin than they need or keeping elevated blood glucose concentrations in order to avoid hypoglycemia (Cox, Irvine, Gonder-Frederick, Nowacek, & Butterfield, 1987; Green, Feher, & Catalan, 2000; Wild et al., 2007). However, this type of coping response may result in poor metabolic control and increase the risk of serious short- and long-term health consequences associated with diabetes (Wild et al., 2007).

**Hyperglycemia and diabetic ketoacidosis.** Diabetic ketoacidosis (DKA), as a result of severe hyperglycemia, can result in symptoms of nausea and vomiting, shortness of breath, seizures, coma, and death (DCCT, 1993). DKA occurs in 15 to 67% of new-onset diabetes and at a frequency of 1 to 10 episodes per 100 patient years in those with established diabetes (Levy-Marchal, Patterson & Green, 2001). DKA has also been identified as the leading cause of morbidity and mortality in children with diabetes (Dahlquist & Kallen, 2005) and risk is increased in children with poor metabolic control or previous episodes of DKA (Keenan, Foster & Bratton, 2002). While most cases of DKA are corrected without incidence, 0.7 to 3.0% of pediatric cases are complicated by cerebral edema (CE) (Edge, Hawkins, & Winter, 2001). Although a relatively rare complication linked to DKA, cerebral edema is associated with significant rates of morbidity ranging from 21 to 35% of cases and mortality ranging from 21 to 24% (Rosenbloom, 1990).

**Long-Term Metabolic Control Complications**

In the long-term, poor metabolic control leads to increased risks for chronic microvascular complications including nephropathy, retinopathy, and neuropathy (CDA, 2013; DCCT 1993). Further, diabetes is the leading cause of blindness, end-stage renal failure, nontraumatic amputation and cardiovascular disease. The latter is the leading cause of death in individuals with diabetes and occurs 2- to 4-fold more often compared to people without the
disease (CDA, 2013). Although relatively rare in pre-pubertal children, other complications associated with T1D include dyslipidemia and hypertension which all increase in frequency and severity with age (CDA, 2013).

**Management of Type 1 Diabetes**

**Insulin Therapy**

Insulin therapy remains the mainstay of metabolic control in people with T1D and can be administered by syringe or pen (multiple daily insulin injections; MDI), or pump (continuous subcutaneous insulin infusion; CSII) (CDA, 2013).

**Multiple daily insulin injections (MDI).** Multiple daily insulin injections rely on the use of basal-bolus insulin regimens in which basal insulin is provided by an intermediate-acting insulin or long-acting insulin analogue once or twice daily and bolus insulin is provided by a short-acting insulin or a rapid-acting insulin analogue given at each meal (CDA, 2013). This method of insulin delivery requires the use of either a syringe, in which the insulin dose is drawn up from a vial into the syringe, or a pen, whereby the insulin cartridge is inserted into a pen-like device and the appropriate insulin dose is selected by turning a dial on the pen. The insulin is then injected into the child’s abdomen, arms, or legs, usually between two to four times each day.

**Continuous subcutaneous insulin infusion (CSII).** Continuous subcutaneous insulin requires the use of an insulin pump, which is a battery-operated device worn on the outside of the body that continuously delivers rapid-acting insulin subcutaneously through a catheter inserted into the abdomen (insulin aspart; Novorapid or insulin lispro; Humalog). The pump automatically delivers insulin at a steady basal rate that is pre-programmed into the pump by the user and is delivered continuously over 24 hours. The basal rate is set to the minimum insulin
needed to suppress gluconeogenesis and ketogenesis, while keeping blood glucose levels within
the normal range without inducing hypoglycemia (Weintrob, Shalitin, & Phillip, 2004). A top-
up of bolus or meal-time insulin can be manually programmed into the pump. The mealtime
boluses are calculated by an algorithm and depend on the caloric and nutritive composition of the
meal, the blood glucose concentration before the meal, and the anticipated level of physical
activity after the meal (Weintrob et al., 2004).

Diet

Diet and nutritional intake are important components in the management of T1D in
order to achieve optimal health outcomes (Alexander, Wilson, Howells, Waldron, Swift, Saha et
al., 2005; Maffeis & Pinelli, 2008; Mehta, Volkening, Quinn, & Laffel, 2008; Wysocki, Greco,
& Buckloh, 2003). However, the dietary regimen for T1D is complex and challenging because
children with T1D often face strict dietary requirements, including matching the insulin dose to
the grams of carbohydrate consumed (ADA, 2014), which may require increased regimentation
and scheduling with regards to eating habits. Children with T1D, like other children without
chronic disease also have transient food preferences, demonstrate food refusal, emotional
lability, and behavioural resistance, which can make it difficult to achieve a healthy and balanced
diet (Golden, Russell, Ingersoll, Gray, & Hummer, 1985; Patton, Dolan & Powers, 2007; Winter,
1982; Wysocki, Huxtable, Linscheid, & Wayne, 1989). As a result of these dietary behaviours,
numerous studies have shown problems with adherence to diet in patients with T1D (Delamater,
Smith Kurtz, & White, 1988; Mackner, McGrath, & Stark, 2001; Schmidt, Klover, Arkfen,
Delamater, & Hobson, 1992). Specifically, adherence rates of children and adolescents living
with T1D and following a well-balanced, nutritionally adequate diet ranges from 21% to 56%,
based on self-reported adherence ratings (Delamater et al., 1988).
In order to follow recommended energy and nutrient intake, a regular meal pattern with regular meal composition is necessary. Otherwise, irregularity could easily lead to insulin misuse, weight gain and/or hypoglycemia (Maffeis & Pinelli, 2008). However, many children with diabetes worry about negative peer reactions to blood glucose testing and diet limitations, including avoidance of forbidden foods that contain high concentrations of sugar (Thomas, Peterson, & Goldstein, 1997). There is evidence that children and adolescents find the constraints of a diabetes regimen difficult, including adhering to appropriate dietary behaviours.

Delamater et al., (1988) measured dietary skills of diabetic children to assess dietary adherence in specific situations. Thirty-four children and adolescents with T1D (mean age 14.0 ± 2.4 years) completed an interview in which they were asked about their dietary adherence in different situations. Reported adherence problems occurred most frequently during the following situations: 24% of children reporting rarely adhering to their afternoon snack, 18% reported rarely adhering to their diet while at school, 12% reported rarely adhering while dining at restaurants, and 12% reported rarely adhering while with friends. Correlational analyses showed that HbA1c levels were directly correlated with poor adherence at school (r=0.36; p < 0.04) and while with friends (r = 0.46; p < 0.005), i.e. was associated with worse metabolic control, represented by higher HbA1c levels. More recently, Mehta et al. (2008) conducted a larger cross-sectional analyses of 119 children aged 9 -14 years (mean 12.1 ± 1.6 years) with T1D to evaluate dietary adherence and metabolic control using the six-item diet subscale of the Diabetes Self-Management Profile (DSMP). The diet subscale scores are self-reported and can range from 0 to 17 points, with higher scores reflecting greater dietary adherence, meaning how well children adhere to their prescribed diet plan. They found that the mean child diet score was 11.3 ± 3.3 (range 4-17), indicating that children adhered to their diets approximately 66% of the time.
Physical Activity

Both the Canadian and American Diabetes Associations suggest that all patients with diabetes should be given the opportunity to participate in physical activity. Those with diabetes should be informed that regular physical activity is a key part of their diabetes management and treatment plan (ADA, 2014; CDA, 2013). However, children living with T1D may experience a number of limitations in terms of physical functioning, including reduced participation in sports and other physical activities.

Regular physical activity or sports participation is associated with numerous beneficial effects for children with T1D. These include improved metabolic control, lipid profiles, body weight, blood pressure levels, self-concept, peer group interaction and quality of life, as well as decreased cardiovascular risk factors and mortality (ADA, 2014; Ekeland, Heian, Hagen, Abbott, & Nordheim, 2006; Fox, 1999; Franco, de Laet, Peeters, Jonker, Mackenbach, & Nusselder, 2005; Kujala, Kaprio, Sarna, & Koskenvuo, 1998; Laaksonen, Atalay, & Miskanen, 2000; Massin, Lebrethon, & Rocour, 2005; National Institute for Clinical Excellence [NICE], 2004; Valerio, Spagnuolo, Lombardi, Spadaro, Siano, & Franzese, 2007). However, a cross-sectional case control study of 138 children and adolescents with T1D compared to 269 healthy controls revealed that only 25% of young diabetic patients met the guidelines for healthy physical activity. Further, less than 50% of these children spend time playing sports (Valerio et al., 2007).

Blood Glucose Monitoring in Type 1 Diabetes

In combination with insulin therapy, diet, and physical activity, the accurate determination of blood glucose concentrations is an important factor for intensified diabetes management. Monitoring blood glucose levels is important in an effort to achieve improved
metabolic control. Recommended targets for HbA1c are levels less than 8.0% for children between the ages of 6 and 12 and less than 7.0% for adolescents between the ages of 13 and 18 (CDA, 2008). In 2013, the CDA modified these targets in an effort to further improve metabolic control with recommended HbA1c levels less than 7.5% for children between the ages of 6 and 12 and targets for adolescents remaining at less than 7.0%. Studies have demonstrated a strong association between adherence to blood glucose monitoring and metabolic control (Anderson, Ho, Brackett, Finkelstein, & Laffel, 1997; Hood, Butler, Volkening, Anderson, & Laffel, 2004; Ziegler, Heidtmann, Hilgard, Hofer, Rosenbauer, and Holl, 2011). Specifically, Anderson et al. (1997) used a cross-sectional design to investigate child and parent behaviours that relate to adherence and metabolic control in 89 children, aged 10 to 15 years with T1D. The current insulin and blood glucose monitoring routines were ascertained from an interview developed by the authors to assess in detail the division of responsibility within families during a typical day for two tasks: insulin injections and blood glucose monitoring. Together the families completed the Blood Glucose Monitoring (BGM) score, in which higher scores indicated greater parental involvement in ensuring that the diabetes management tasks were carried out. Although more younger (10-12 years) than older patients (13-15 years) monitored their blood glucose levels four or more times per day, the majority of patients in both age groups (59% in the younger group, 77% in the older group) checked their blood glucose levels two or three times daily. Parental involvement in blood glucose monitoring was correlated with adherence to blood glucose monitoring ($r = 0.25; p < 0.02$), indicating that the children of parents more involved in blood glucose monitoring checked their blood glucose levels more frequently. After controlling for other variables, Anderson et al. (1997) found that adherence to blood glucose monitoring remained the consistent predictor of overall metabolic control ($R^2 = 0.19, p < 0.02$).
Specifically, metabolic control improved significantly as the frequency of blood glucose monitoring increased, from an HbA1c value of 9.9% ± 0.44% (SE) when the blood glucose level was checked zero or one time per day, to 8.3% ± 0.22% when the blood glucose level was checked four or more times daily. Due to a relatively small sample size, the lack of a control group, and the cross-sectional nature of the study it is difficult to generalize these findings. However, this study lends further support to the growing body of literature demonstrating that increased blood glucose monitoring is associated with better metabolic control, as indicated by lower HbA1c levels.

A longitudinal study of 300 children and adolescents between the ages of 7 to 16 years with T1D was carried out to evaluate the predictors of metabolic control and to assess how metabolic control affects the incidence of short-term adverse outcomes in a pediatric sample with T1D (Levine, Anderson, Butler, Brackett, & Laffel, 2001). Patients were followed prospectively for one year and at each medical visit, a health history and physical examination was performed. Insulin dose, frequency of insulin injections, and frequency of blood glucose monitoring were recorded by clinicians in participant’s charts. HbA1c levels were taken at each visit and the occurrence of clinically significant events (hospitalizations, emergency department visits, and hypoglycemic episodes) was ascertained by questionnaires administered to the children and their families at each visit.

In a multiple linear regression model controlling for duration of diabetes, pubertal stage, and gender, Levine et al. (2001) found that blood glucose monitoring frequency significantly predicted HbA1c value in an inverse manner. Specifically, metabolic control improved significantly as the frequency of blood glucose monitoring increased, from an HbA1c value of 9.1% ± 0.34% (mean + SE) when blood glucose monitoring was performed at most once per day,
to 8.9% ± 0.16% when blood glucose monitoring was performed three times per day, to 8.0% ± 0.31% when blood glucose monitoring was performed five or more times per day ($R^2 = 0.12$, $p < 0.0001$). These findings support the hypothesis that frequent blood glucose monitoring improves overall metabolic control; however, this cannot be stated for certain using this type of study design.

Until recently, measurement of blood glucose could only be achieved by attaining multiple capillary finger-sticks each day using a blood glucose meter using self-monitoring of blood glucose (Burge, Mitchell, Sawyer, & Schade, 2008). Self-monitoring of blood glucose levels is an essential part of diabetes management (Nordly, Mortensen, Andreasen, Hermann, & Jorgensen, 2005). However, it has been identified as a practice that is cumbersome, inconvenient, expensive, and is often a deterrent to achieving target blood glucose goals (Burge, et al., 2008). Even when applied consistently, self-monitoring provides only a glimpse into blood glucose concentration without providing any information about the direction or rate of blood glucose change. As a result, many patients are unable to achieve blood glucose targets even though they test their blood glucose multiple times each day (Burge, et al., 2008).

Continuous glucose monitoring provides a) real-time information about current interstitial fluid glucose concentrations, b) short-term feedback about the effectiveness of diabetes interventions (such as insulin administration), and c) warnings when glucose concentrations become dangerously high or low. Further, continuous glucose monitors display glucose trend information graphically, allowing patients to anticipate hypo- and hyperglycemic events, thereby potentially avoiding anxiety related to experiencing such episodes (Raccah, Sulmont, Reznik, Guerci, Renard, Hanaire, et al., 2009). However, the potential main advantage of continuous glucose monitoring may be that it can help identify fluctuations and trends in
glucose levels that would otherwise go unnoticed with standard HbA1c tests and intermittent self-monitoring of blood glucose (Edelman & Bailey, 2009; Klonoff, 2005; 2005). Recognition of fluctuations in glucose trends has been shown to provide maximal information about shifting glucose levels in order to make improved treatment decisions (Klonoff, 2005; 2005).

Despite the potential benefits, continuous glucose monitoring may result in information-overload, and children with T1D may experience adverse psychological and behavioural effects. These may include increased treatment burden, anxiety, and unrealistic expectations about the benefits of increased access to blood glucose information (DirecNet, 2006). In light of these potential negative effects, a randomized controlled trial of 200 children with T1D between the ages of 7-18 years evaluated the psychological impact of use of continuous glucose monitoring. The study demonstrated neither beneficial nor adverse effects on either parents or children after using continuous glucose monitoring. Specifically, there were no significant changes in scores on the Diabetes Self-Management Profile (DSMP), an indicator of diabetes adherence, the Pediatric Quality of Life Scale (PedsQL), representative of favourable or unfavourable quality of life, and lastly, the Diabetes Worry Scale (DWS), which indicates diabetes-related anxiety following the use of continuous glucose monitoring (DirecNet, 2005; DirecNet, 2006). The use of a large sample size and a control group are strengths of this study. However, the participants demonstrated favourable status at baseline in terms of metabolic control (mean HbA1c = 8.0%), treatment adherence (mean DSMP score = 63), and quality of life (mean PedsQL = 30). Thus, the study participants tended to be in better metabolic control and to report better adherence and diabetes-related-quality of life than might be true of a randomly selected sample of diabetes clinic patients. Given this, it is possible that use of the continuous glucose monitor could not drastically improve these outcomes in this particular sample (DirecNet, 2006). Enrolment of a
more broadly representative sample of patients could provide a more sensitive evaluation of the metabolic and psychological effects of continuous glucose monitoring use.

**Self-monitoring of blood glucose levels.** Self-monitoring of blood glucose requires that patients perform a number of finger pricks with a lancet to obtain a small blood sample, applying a drop of blood onto a reagent strip, and determining the glucose concentration by inserting the strip into a blood glucose meter providing an automated reading. Test results are then recorded in a logbook and/or stored in the glucose meter’s electronic memory (Benjamin, 2002). The 2008 Canadian Diabetes Association Clinical Practice Guidelines recommends that patients with T1D perform at least three self-monitoring tests per day, including both pre- and postprandial measurements, as well as nocturnal blood glucose measurements, to provide some information regarding the effects of food eaten, insulin administered, and physical activity engaged in. Postprandial monitoring is rarely done in children under the age of 12, except for those on pump therapy for whom targets are not available. In 2013, the CDA adjusted their recommendations for self-monitoring and suggested that at least four self-monitoring tests are completed per day for children and adolescents.

In a large cohort study of 267,232 children between the ages of 0 and 18 years (mean age 12.7 ± 4.1 years), Ziegler et al. (2011) investigated whether the frequency of self-monitoring was related to long-term metabolic control, as measured by HbA1c levels. Data from the years 1995 to 2006 were prospectively collected and analyzed using the DPV-Wiss-database. This database is a standardized, prospective, computer-based documentation of diabetes care and clinical outcomes used in Germany and Austria. They found that more frequent self-monitoring was significantly associated with better metabolic control. Specifically, a mean decrease in HbA1c (+ SE) of 0.20% (+ 0.007) for one additional self-monitoring check per day (p < 0.001) was
observed. Further, the positive effect of a higher self-monitoring frequency was most pronounced in those using continuous subcutaneous insulin infusion, underlined by a HbA1c reduction of 0.27% (± 0.017, p < 0.001) for one additional self-monitoring check per day. This was compared with those using insulin injections, where children had an HbA1c reduction of 0.09% (± 0.016, p < 0.001) for one additional self-monitoring check per day. Despite the large sample used in this study, the observational nature does not permit a clear identification of whether increased self-monitoring causes a decrease in HbA1c, only that these two variables are related in some way to one another. Regardless of this potential concern, the problem still remains that most children and adolescents with T1D only measure pre-meal blood glucose levels during the day and rarely measure blood glucose levels during the night, the time of greatest vulnerability to hypoglycemia (Porter, Keating, Byrne, & Jones, 1997). Thus, marked glycemic excursions are potentially missed by the brief glimpses into the 24 hour blood glucose profiles provided by self-monitoring of blood glucose (Boland, Monsod, Delucia, Brandt, Fernando, & Tamborlane, 2001). More frequent testing is often advised in order to provide the information needed to reduce hypoglycemia risk, adjust treatment and make appropriate lifestyle choices (CDA, 2013).

**Continuous glucose monitoring.** Continuous glucose monitoring devices record glucose levels throughout the day and night. Two methods of continuous glucose monitoring are currently available. The first is a blinded CGM, also called “professional” CGM, which captures, but does not display, the glucose readings, which are then downloaded onto a computer for viewing and retrospective analysis by the healthcare provider (CDA, 2013). The only device currently available in Canada is the iPro2 Professional CGM (Medtronic MiniMed Inc., Northridge, CA). The second method uses real-time presentation of glycemia values, also called
“personal” CGM, which the wearer can utilize to make health care decisions. Currently in Canada, these include: the MiniMed Veo™ system (MiniMed® Veo™ insulin pump with CGM [Enlite™ glucose sensor and MiniLink™ transmitter] (Medtronic MiniMed, Inc., Northridge, CA). The DexCom G4 CGM (Animas) and the Vibe with CGM (Animas) are both indicated for use in adults age 18 and older. However, with a letter of medical necessity for off-label use, children and adolescents under the age of 18 can use these devices. These devices have electrodes covered with glucose oxidase inserted into the subcutaneous tissue and measure the change in current flow caused by the enzyme-catalyzed production of hydrogen peroxide, which is proportional to the amount of glucose at the site of insertion (Hanaire, 2006). These continuous glucose monitoring devices can provide up to 288 glucose measurements every 24 hours in real-time and are used to measure an average blood glucose level every 1 to 5 minutes for 3-7 days, depending on the device. A tiny glucose-sensor is inserted just beneath the skin of the abdomen and measures the level of glucose in the tissue every 10 seconds and sends the information wirelessly to the monitor attached to a belt or the waistline of the patient’s pants. Results of two to four finger-stick blood glucose readings taken with a standard blood glucose meter and taken at different times each day are entered into the monitor for calibration and depend on the device used.

**Predicting Adherence to Advice about Diabetes Management**

In the elementary school years, children between the ages of 6 and 12 expand their skills across a broad range of areas, including athletic, artistic, scholastic, and self-control, contributing to a new sense of personal competence. During this time, children with T1D begin to expand their skills and gradually participate in diabetes self-management (Anderson & Laffel, 1997). In line with Erikson’s fourth stage of development (Industry versus Inferiority), which occurs
within this same age range, a healthy child develops a sense of industry at school and home. For children with chronic illness, specifically T1D, it is usually during these years of middle childhood that parents begin to transfer some responsibility for diabetes management to the child. Children with diabetes typically are ready to assume some self-care behaviours during this stage of development (Anderson & Laffel, 1997; Wysocki & Wayne, 1992) (Table 2). Specifically, school-age children can accomplish a number of diabetes management tasks which may include: state insulin types and numbers of injections daily, administer injection to self, rotate injection sites, draw dose with one insulin type, state the common symptoms of hyperglycemia, describe appropriate actions in response to hyperglycemia, perform blood glucose test, categorize food into food groups, and state the role of diet in diabetes treatment (Wysocki, Meinhold, Cox, & Cox, 1990). Helping children with T1D to care for themselves and make as many decisions as possible is important for maintaining adequate diabetes care. Parents are encouraged to gradually transfer responsibilities for diabetes care to their child (Pond, Peters, Pannell, & Rogers, 1995).

Adolescence is a period of rapid biological change accompanied by increasing physical, cognitive, and emotional maturity. Adolescents, who are between 12 and 18 years of age, are struggling to find their own identity that is separate from their families (Silverstein, Klingensmith, Copeland, Polotnick, Kaufman, Laffel, et al., 2005). Accordingly, Erikson’s fifth stage (Identity versus Confusion) is a time when adolescents need to develop a sense of self and personal identity. During adolescence, children are exploring their independence and developing a sense of self. Erikson suggests, that if the parents allow the child to explore, they will conclude their own identity. However, if the parents continually push him/her to conform to their views, the teen will face identity and role confusion. Unfortunately, several of the diabetes-related tasks
can interfere with the adolescents need for independence and acceptance from their peers and social groups. There is a struggle for independence from parents that is often manifested as suboptimal adherence to the diabetes regimen (Anderson, Vangsness, Connell, Butler, Goebel-Fabbri, & Laffel, 2002; Silverstein et al., 2005). However, adolescents whose parents maintain some guidance and supervision in the management of diabetes have shown better metabolic control (Follansbee, 1989; Grey, Boland, Yu, Sullivan-Bolyai, & Tamborlane, 1998; Silverstein et al., 2005).

Table 2.

Average Age for Diabetes Related Skills

<table>
<thead>
<tr>
<th>Skill</th>
<th>Average Age for Diabetes Related Skills (American Diabetes Association)</th>
<th>Average Age for Diabetes Related Skills (Survey of Care Providers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recognizes and Reports</td>
<td>8-10</td>
<td>4-9</td>
</tr>
<tr>
<td>Able to Treat</td>
<td>10-12</td>
<td>6-10</td>
</tr>
<tr>
<td>Anticipates/Prevents</td>
<td>14-16</td>
<td>7-11</td>
</tr>
<tr>
<td>Blood Glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testing (by meter)</td>
<td>8-10</td>
<td>7-11</td>
</tr>
<tr>
<td>Insulin Injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gives to Self (at least sometimes)</td>
<td>Not available</td>
<td>8-11</td>
</tr>
<tr>
<td>Draws 2 Types of Insulin</td>
<td>12-14</td>
<td>8-12</td>
</tr>
<tr>
<td>Able to Adjust Dose</td>
<td>14-16</td>
<td>12-16</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identifies appropriate pre-exercise snack</td>
<td>10-12</td>
<td>10-13</td>
</tr>
<tr>
<td>States role of diet in care</td>
<td>14-16</td>
<td>9-15</td>
</tr>
<tr>
<td>Able to alter food in relation to blood glucose</td>
<td>14-16</td>
<td>10-15</td>
</tr>
</tbody>
</table>

In terms of glucose monitoring specifically, Warzak, Majors, Ayllon, Milan and, Dellcher (1993) surveyed parents of children with T1D (n=38) to identify common and difficult obstacles to diabetes care. The participants ranged in age from 3-20; the mean age was 13 years and the median was 14 years. Parents completing the questionnaire rated items involving home monitoring as the most significant obstacle to good diabetes control (Number 1 - “My child will not monitor without prompts” and Number 3 - “My child will not monitor if he/she is not at home”). Recording blood glucose monitoring data also ranked highly as a significant obstacle to diabetes care (Number 8 - “My child monitors faithfully but fails to record the result without prompting”). While parents may perceive that it may be difficult to get their children and adolescents to perform blood glucose monitoring tasks, the study also demonstrated that parents still expect them to take the responsibility for carrying out their own blood glucose monitoring. Despite the emphasis on child responsibility for diabetes self-management, parental guidance and direction have been shown to relate to both treatment adherence and metabolic control in school-aged children with T1D (Anderson et al., 1997; Kovacs, Kass, Schnell, Goldston & Marsh, 1989) and adolescents living with T1D (Follansbee, 1989; Grey et al., 1998). However, these findings contrast with both a school-age child’s normal developmental striving toward "doing" and an adolescents need for their own identity and independence. Thus, it may be difficult and, at times, seem impossible for parents to provide guidance or be involved in diabetes management (Warzak et al., 1993).

During the crucial formative period of children's lives between the ages of 6 and 12, the school functions as the primary setting for the cultivation and social validation of cognitive competencies. School is the place where children develop the cognitive competencies and acquire the knowledge and problem-solving skills essential for participating effectively in the
larger society. Here their knowledge and thinking skills are continually tested, evaluated, and socially compared. As children master cognitive skills, they develop a growing sense of their intellectual efficacy (Bandura, 1994). For adolescents, increasing responsibilities for managing their own treatment enhances self-efficacy beliefs because they welcome the chance to exert control over their illness, while other adolescents with T1D may feel overwhelmed and helpless (Grossman, Brink, & Hauser, 1987). Self-efficacy has been shown to be an important factor for both short- and long-term changes in the health behaviours of children and adolescents (Holden, Moncher, Schimke, 1990; Holden, 1991). Self-efficacy has also been found to be one of the strongest predictors of children’s adherence to treatments for chronic illnesses, including asthma, arthritis, cystic fibrosis, and diabetes (Clark, Rosenstock, Hassan, Evans, Wasilewski, Feldman, & Mellins, 1988; McCaul, Glasgow, & Schaefer, 1987). Bandura (1977, 1982) defined self-efficacy as an individual’s belief in one’s ability to perform a specific behaviour and proposed that efficacy beliefs represent a final common pathway mediating behaviour change.

Reports of health literacy in diabetes as well as childhood adaptation to T1D have made use of social cognitive theory, specifically the concept of self-efficacy, to help explain adherence and adaptation to health behaviours and overall health outcomes (Agency for Healthcare Research and Quality, 2010; Ott, Greening, Palardy, Holderby, & DeBell, 2000; Whittemore, Jaser, Guo, Grey, 2010). Health literacy is the degree to which individuals can obtain, process, and understand the basic health information and services they need to make appropriate health decisions (Institute of Medicine, 2004). In their systematic review of the literature evaluating health literacy interventions and outcomes, the Agency for Healthcare Research and Quality (AHRQ, 2010) developed a logic model for their review.
The model suggests that health literacy leads to knowledge and accurate risk perception, which influences attitudes, social norms, and self-efficacy (AHRQ, 2010). Self-efficacy in turn has an effect on behavioural intent, which is a person’s stated likelihood of starting a behaviour, which results in the uptake of health skills (including seeking additional health information and accessing health care) and behaviour (such as taking medication, changing lifestyle activities, and monitoring one’s health). Adoption of these health behaviours influences adherence to healthy behaviours, which ultimately affects health outcomes, including disease prevention, the reduction of risk factors and improved quality of life (AHRQ, 2010).

Whittemore et al. (2010) developed a conceptual model describing factors that influence childhood adaptation to T1D. The framework suggests that a number of characteristics and responses lead to adaptation to T1D in children, defined as the degree to which an individual responds both physiologically and psychosocially to the stress of living with a chronic illness (Whittemore et al., 2010). They describe the individual and family characteristics (age, duration of diabetes, race/ethnicity, treatment modality, family environment), influence individual responses, including aspects of self-management and self-efficacy, which in turn influence metabolic control and overall quality of life. Several studies have demonstrated that higher self-efficacy is associated with improved self-management, family functioning, psychosocial adjustment, and metabolic control in children and adolescents diagnosed with T1D (Grossman et al., 1987; Iannotti, Schneider, Nansel, Haynie, Plotnick, Clark et al., 2006; Ott, Greening, Palardy, Holderby, & DeBell, 2000).

Grossman et al. (1987) examined various aspects of self-monitoring and self-management in adolescents with T1D in an attempt to develop a measure of diabetes self-efficacy, defined as “the self-perceptions or expectations held by persons with diabetes about
their personal competence, power, and resourcefulness for successfully managing their diabetes”. The participants included 68 adolescents with T1D between the ages of 12 and 16 years who were each given three measures within the first week of a diabetes camp. The self-efficacy for diabetes scale was constructed to evaluate how adolescents with diabetes perceive their efficacy or competence regarding their diabetes. They found that youth who expressed stronger self-efficacy for their diabetes also had greater self-esteem in general. In addition, diabetes self-efficacy was found to be associated with metabolic control. Specifically, those adolescents with higher self-efficacy beliefs also demonstrated improved metabolic control with better average blood glucose values.

In addition, a study aimed at the development and evaluation of measures of diabetes management self-efficacy in 168 children and adolescents with T1D between the ages of 10 and 16 (mean age 13.6 ± 1.92 years), Iannotti et al. (2006) found that children, who had confidence in their ability to manage their diabetes in a variety of challenging situations and believed in positive consequences of diabetes self-management, also adhered to their diabetes regimen and had better metabolic control. Self-efficacy for diabetes management, expected outcomes of adherence, and adherence to the diabetes regimen were evaluated using the Diabetes Self-Management Profile (DSMP), a 42-item scale evaluating diabetes self-management and adherence behaviours. Metabolic control was also assessed using HbA1c levels. Iannotti et al. (2006) used item analysis and eliminated 28 items from the long-form of the DSMP. An additional four items were eliminated due to overlapping content areas, which left 10 items on the self-efficacy for diabetes self-management (SEDM) scale. Iannotti et al. (2006) concluded that the SEDM covered the major areas of diabetes self-management and that these 10 areas could potentially reflect the various ways in which children can be challenged in terms of
maintaining good diabetes self-management. Overall, scores on the SEDM correlated significantly with child-reported diabetes self-management, parent-reported diabetes self-management, and metabolic control. Specifically, the Cronbach’s alpha for the 10-item version of the SEDM was 0.90, indicating that the SEDM has a high level of reliability.

Iannotti et al. (2006) reported that the new brief measure they developed exhibited good internal consistency and was consistent with Bandura’s social cognitive theory for assessing self-efficacy. This indicates that children and adolescents who have a stronger sense of capability and purpose are more successful in assuming responsibility for their own self-management and maintaining these behaviours over time, thus improving metabolic control for the long-term. However, the study had several limitations. The researchers used a cross-sectional design in order to evaluate predictive validity. As such, additional research would be required to evaluate prospective prediction of self-management of diabetes and its relationship to metabolic control.

Ott et al. (2000) applied Bandura’s self-efficacy theory to explore the process by which self-efficacy for managing pediatric diseases can be enhanced. Adolescents (n=143) diagnosed with T1D completed measures of adherence to diabetes treatment, self-efficacy for diabetes care, and personal responsibility for diabetes care. Self-efficacy was tested as a mediator variable for hypothesized relations between adherence to treatment and two methods proposed to enhance self-efficacy, mastery experience (responsibility for treatment) and social persuasion (supportive and non-supportive parental behaviours). They found that self-efficacy accounted for 89% of the variance in adherence to treatment using regression analysis. They proposed that this could suggest that self-efficacy is a significant mediator between personal responsibility in children and adherence to their diabetes treatment plan. Specifically, Ott et al. (2000) argued that the relationship between mastery experience, as defined by assuming personal responsibility for
treatment, and adolescent adherence was found to be explained by their perceptions of their own self-efficacy. They suggested that acquisition of health behaviours, which include diet, exercise, administering insulin, and frequent blood glucose monitoring, require strong self-efficacy beliefs. However, the researchers used a cross-sectional design and evaluation of the relationship between mastery and self-efficacy in relation to how adolescents adhere to their diabetes treatment regimen and would require further research. It could be that the relationship between responsibility for treatment and adherence is a function of being adherent to treatment rather than of mastery (Ott et al, 2000).

**Comparison of Self-Monitoring and Continuous Glucose Monitoring**

The following section reports the results of a systematic review of the studies evaluating children with T1D using continuous glucose monitoring compared to self-monitoring of blood glucose alone. Studies for inclusion in the review were accessed through a search of Medline (1946 to January week 2, 2015), EMBASE (1974 to January week 2, 2015), Health and Psychosocial Instruments (1985 to January 2015), and Ovid Healthstar (1966 to January, 2015). The search terms used included MeSH headings, subjects, text words, wild cards and/or keywords relevant to the following terms: ‘Type 1 Diabetes’, ‘T1D’, ‘child’, ‘adolescent’, ‘Continuous glucose monitoring’, ‘CGM’. Lastly, the limit feature was used to select only human and English language studies. The date of the last search attempt was March 2015. Reference lists from all identified appropriate papers and review papers were examined and then a hand search for other identified studies was conducted. No attempt was made to locate unpublished material or contact researchers for unpublished studies.
To be eligible, studies had to meet the following criteria:

1. The studies had to be published in peer-reviewed journals during the past 15 years (2000-2015).
2. The therapeutic intervention had to target children and adolescents with TID.
3. The study evaluated the use of continuous glucose monitoring.
4. The evaluation examined metabolic control (HbA1c) as one of the primary outcomes.
5. The study was a randomized controlled trial (RCT), quasi-randomized trial, before-and-after design, or retrospective study design. The typical inclusion criteria for systematic reviews was broadened beyond RCTs due to a lack of RCTs evaluating continuous glucose monitoring in children using continuous subcutaneous insulin infusion alone for diabetes management.
6. The study was published in English.

Electronic searches of major databases revealed 2109 papers, with 1161 papers removed after accounting for duplications, leaving 948 for further consideration. In terms of metabolic control as the primary outcome, 903 papers were removed as they were general or review articles or other non-continuous glucose monitoring-based interventions. Forty-five studies were identified as potentially applicable, of which 25 studies were excluded for reasons summarized in Figure 3, leaving 20 studies for assessment of methodological quality.
Figure 3. Study Selection for Metabolic Control Papers.

<table>
<thead>
<tr>
<th>2109 Papers identified and screened</th>
<th>1161 Duplicates</th>
</tr>
</thead>
<tbody>
<tr>
<td>948 Papers assessed for relevance</td>
<td>903 Papers excluded based on inclusion/exclusion criteria</td>
</tr>
<tr>
<td>45 Papers evaluating Metabolic Control using CGM</td>
<td>25 Papers evaluating Metabolic Control using CGM excluded based on:</td>
</tr>
<tr>
<td>20 Papers included for review</td>
<td></td>
</tr>
</tbody>
</table>

(Chase et al., 2001; Chase et al., 2003; Deiss et al., 2006; DirecNet Group, 2005; DirecNet Group, 2007; DirecNet Group, 2012a; DirecNet Group, 2012b; Gandrud et al., 2007; Halvorson et al., 2007; Hathout et al., 2005; JDRF, 2008; Jeha et al., 2004; Lagarde et al., 2006; Ludvigsson & Hanas, 2003; Ludwig-Seibold et al., 2012; Rasbach et al., 2014; Scaramuzza et al., 2011; Schaepeleynck-Belicar et al., 2003; Schiaffini et al., 2002; Yates et al., 2006)

**Intervention**
CSII compared to MDI using CGM, not CGM compared to SMBG = 11 (Alemzadeh et al., 2006; Buse et al., 2012; Davis et al., 2010; Deiss et al., 2004; DirecNet, 2009; Heptulla et al., 2004; Knight et al., 2009; Kordonouri et al., 2012; Raccah et al., 2009; Slover et al., 2012; Weintrob et al., 2004)

**Timing**
Simultaneous versus Delayed Start of CGM = 2 (Lawson et al., 2014; Olivier et al., 2014)

**Population**
Children and adults combined in single study = 8 (Battelino et al., 2012; Cemeroglu, et al., 2010; Deiss et al., 2006; Hirsch et al., 2008; Kaufman et al., 2001; Riveline et al., 2012; Salardi et al., 2002; Tubiana-Rufi et al., 2007)

**Design**
RCT using same subjects = 4 (same subjects as JDRF 2008 = 3; JDRF, 2009, 2010, 2011); (same subjects as ONSET 2012 = 1 (Kordonouri et al., 2010)
Study Characteristics

Nine randomized controlled trials, two of which were crossover trials, and eleven non-randomized controlled trials were found, involving 2938 children and adolescents from ages two to 19 years. The number of participants in each study ranged from 10 to 1395. Duration of diabetes ranged from 0.2 to 15 years and of the studies reporting method of insulin administration, 55% of children used continuous subcutaneous insulin infusion, while the remaining used multiple daily insulin injections for diabetes management. Three studies included only children using continuous subcutaneous insulin infusion (DirecNet, 2007; Halvorson et al., 2007; Scaramuzza et al., 2011), three included only children using multiple daily injections (Deiss, Hartmann, Schmidt, & Kordonouri, 2006; Jeha, Karaviti, Anderson, Smith, Donaldson, McGirk, & Haymond, 2004; Schiaffini, Ciampalini, Fierabracci, Spera, Borrelli, Bottazzo, et al., 2002), and the remaining studies (n=14) included children using either continuous subcutaneous insulin infusion or multiple daily injections (Figure 4).

All of the studies included both males and females in their samples. Three studies comprised mainly Caucasians [85% (DirecNet, 2005), 77% (DirecNet, 2012a), 96% (DirecNet, 2012b), 53% (Juvenile Diabetes Research Foundation, 2008), 59% (Hathout et al., 2005), and 65% (Lagarde, Burrows, Davenport, Kang, Guess, & Calikoglu, 2006)], and the remaining studies did not describe the participants’ ethnicity. The studies were carried out in pediatric academic hospitals and/or diabetes clinics in the United States (n=13), Germany (n=2), Italy (n=2), France (n=1), Sweden (n=1), and Australia (n=1). There was marked variability in the content and procedural aspects of the continuous glucose monitoring intervention, varying in type of device as well as the length, duration, and number of uses. The shortest intervention lasted 1.5 months and the longest was 3 years (mean of 6.8 months). For the studies reporting on
the use of sensors during the study (n=18), the frequency of continuous glucose monitoring use varied from six to 168 total sensor uses, with an average of 49 sensor days. The remaining two studies took place over 2.5 and 3 years and reported total sensor use only for all patients.

Figure 4. Types of Study Designs
Metabolic Control

**HbA1c.** Hemoglobin A1C (HbA1c), a long-term measure of metabolic control over the previous three months, was found to improve in children using continuous glucose monitoring compared to self-monitoring in all but five of the 20 studies reviewed. Significant improvements in HbA1c were found in only eight studies and the remaining 12 studies did not reveal significant improvements in HbA1c between groups (n=6) or between the first- and second-time point (n=6) (Table 3). Of nine randomized controlled studies of continuous glucose monitoring that used HbA1c to evaluate long-term metabolic control; the use of a continuous glucose monitor was associated with improved mean HbA1c levels in eight of nine studies. Despite an improvement in HbA1c, these levels reached statistical significance in only three of the nine randomized controlled trials. Seven of the eleven non-randomized, uncontrolled trials of continuous glucose monitoring have demonstrated improvements in HbA1c using a continuous glucose monitor compared to self-monitoring alone. Significant improvements were reported in only five of these eleven studies.

Despite a reduction in HbA1c in eight of the RCT studies reviewed, these levels did not reach Canadian Diabetes Association recommended levels of less than 7.5% for children ages 6-12 and less than 7.0% for children between the ages of 13-18 in the majority of these studies. Specifically, only three studies in which there was a significant reduction in HbA1c in the continuous glucose monitoring group compared to the self-monitoring group was within CDA recommended levels. In their randomized-controlled trial of 27 children Ludvigsson & Hanas (2003) reported HbA1c values were statistically significantly reduced from 7.7% at baseline to 7.3% (p = 0.023) following continuous glucose monitoring in their RCT crossover study of 27 children. Similarly, the DirecNet group (2007) used a before-after design (n=30) and revealed
CDA recommended HbA1c values in children using continuous glucose monitoring decreased from 7.1% at baseline to 6.8% at the end of the study (p = 0.02). The remaining study utilized a retrospective database review of 1395 children and adolescents and demonstrated a significant reduction in HbA1c values (p < 0.0309) within CDA recommended guidelines following use of CGM in children less than 6 years old (7.4%) and in children aged 6 to 12 years of age (7.7%). However, those between the ages of 12 and 18 did not reach CDA recommended HbA1c values and demonstrated HbA1c levels of 8.3%. Thus, despite statistically significant reductions in HbA1c levels in eight of 20 studies reviewed, these levels reached recommended targets set out by the Canadian Diabetes Association in only three of these studies.

Further, results from these studies must be viewed cautiously because a concurrent control group was not used in five of the studies, and contact with the participants and the clinical site often was more frequent than the amount that would occur in usual practice. In addition, 13 of 20 studies involved sample sizes of less than 40 children with T1D and as a result were underpowered to detect a statistically significant difference in HbA1c levels. In general, the studies included for review indicate that continuous glucose monitoring allows access to glucose values, trend data, and hypoglycemic and hyperglycemic alerts so that patients and their parents, with the aid of the diabetes team, may make adjustments to insulin doses to decrease mean glucose and HbA1c levels, and to reduce hypoglycemic and hyperglycemic episodes.
### Table 3.

Summary of the Effects of Continuous Glucose Monitoring on HbA1c Levels in Children

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Sample (F-M)</th>
<th>Age (Years)</th>
<th>Length of Study</th>
<th>Insulin Treatment</th>
<th>Intervention</th>
<th>ΔHbA1c (%) (Int/Cont)</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chase et al. (2001) USA</td>
<td>RCT</td>
<td>11 (5F-6M)</td>
<td>10-17</td>
<td>3 months</td>
<td>CSII + MDI</td>
<td>Experimental Group: (n=5) Asked to wear 6 sensors (18 total sensor days/user = 54 total sensor days) within a 30-day period</td>
<td>-0.36 vs -0.20 (p &gt; 0.05) (NS)</td>
<td>CGM helpful in detecting low BG, particularly at night</td>
<td>HbA1c showed improvement</td>
</tr>
<tr>
<td>Chase et al. (2003) USA</td>
<td>RCT</td>
<td>40 (19F-21M)</td>
<td>7-17</td>
<td>3 months</td>
<td>CSII + MDI</td>
<td>Experimental Group: (n=20) Given training on use of CGM and asked to wear the CGM for 2 daytime and 2 night-time applications per week</td>
<td>-0.5 vs 0.4 (p &lt; 0.05)</td>
<td>Well tolerated by children</td>
<td></td>
</tr>
<tr>
<td>Deiss et al. (2006) GERMANY</td>
<td>RCT Cross Over</td>
<td>30 (14F-16M)</td>
<td>2-17</td>
<td>6 months</td>
<td>MDI</td>
<td>Experimental Group: (n=15) Asked to wear CGM for 3 days (open access to glucose values) and asked to SMBG test 5 times daily</td>
<td>-0.2 vs 0.1 (p NR) (NS)</td>
<td>CGM provides information over a few days, but does not seem sufficiently representative, particularly in patients with marked day-by-day variability of glycemic profile</td>
<td>Use of MDI only</td>
</tr>
</tbody>
</table>

**Note.** NR = not reported; NS = not significant; F=Female and M=Male; BG = blood glucose levels; CGM = continuous glucose monitoring; CSII = continuous subcutaneous insulin infusion; DKA = diabetic ketoacidosis; HbA1c = glycosylated hemoglobin level; JDRF = Juvenile Diabetes Research Foundation; MDI = multiple daily injections; RCT = randomized controlled trial; SMBG = self-monitoring of blood glucose; TDD = total daily insulin dose
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<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DirecNet</td>
<td>RCT</td>
<td>200 (92F-108M)</td>
<td>7-17</td>
<td>6 months</td>
<td>CSII + MDI</td>
<td><strong>Experimental Group:</strong> (n=99) Provided with CGM and unlimited number of sensors Encouraged to use sensors as often as desired and instructed to use a minimum of 4 sensors during the first week and then at least 2 sensors a week thereafter, with at least one weekly use overnight Asked to SMBG 4 times per day <strong>Control Group:</strong> (n=101) Asked to perform 4 SMBG tests per day</td>
<td>+0.1 vs -0.0 (p=0.15) (NS)</td>
<td>Use of CGM did not improve glycemic control or reduce frequency of severe hypoglycemia Skin reactions led to decreasing sensor use over time</td>
<td>Randomization using permuted-blocks design stratified by clinical center and age group (7-12/12-18) Follow up visits were more frequent in both groups than what is provided in usual care Participants were compensated financially for each weekly CGM download made on time Large sample size 6 month duration of study Funding: NIH</td>
</tr>
<tr>
<td>(2005) USA</td>
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<tr>
<td>DirecNet</td>
<td>RCT</td>
<td>146 (67F-79M)</td>
<td>4-10</td>
<td>6 months</td>
<td>CSII + MDI</td>
<td><strong>Experimental Group:</strong> (n=74) Provided with CGM Encouraged to use sensors on a daily basis Asked to SMBG more than 4 times per day <strong>Control Group:</strong> (n=72) Asked to perform at least 4 SMBG tests per day</td>
<td>-0.1 vs -0.1 (p=0.79) (NS)</td>
<td>CGM use did not improve glycemic control, despite a high level of satisfaction from parents with CGM</td>
<td>Randomized using a permuted-blocks design stratified by clinical center Large sample size 6 month duration of study Funding: NIH</td>
</tr>
<tr>
<td>(2012) USA</td>
<td></td>
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<tr>
<td>JDRF (2008)</td>
<td>RCT</td>
<td>114 (56F-58M)</td>
<td>8-14</td>
<td>6 months</td>
<td>CSII + MDI</td>
<td><strong>Experimental Group:</strong> (n=56) Given instruction on how to use the data provided by the CGM to make real-time adjustments Asked to use the CGM device on a daily basis and to verify the accuracy of the glucose value with a home blood glucose meter <strong>Control Group:</strong> (n=58) Given blood glucose meters and asked to perform SMBG at least 4 times daily</td>
<td>-0.37 vs -0.22 (p = 0.29) (NS)</td>
<td>Lack of effectiveness of CGM in children and adolescents</td>
<td>Large sample size RCT used 6 month duration of study Funding: JDRF</td>
</tr>
<tr>
<td>USA</td>
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<th>Intervention</th>
<th>ΔHbA1c (%) (Int/Cont)</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lagarde et al. (2006) USA</td>
<td>RCT</td>
<td>27 (15F-12M)</td>
<td>7-17</td>
<td>6 months</td>
<td>CSII + MDI</td>
<td>Experimental Group: (n=18)</td>
<td>-0.6 vs -0.28 (p = 0.02)*</td>
<td>Results suggest that use of CGM improves metabolic control in children with T1D and are consistent with the few studies previously reported</td>
<td>Control group significantly older than intervention group; adolescents (difficult to manage)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Control Group: (n=9)</td>
<td></td>
<td></td>
<td>Both CSII and MDI</td>
</tr>
<tr>
<td>Ludvigsson &amp; Hanas (2003) SWEDEN</td>
<td>RCT Cross Over</td>
<td>27 (NR)</td>
<td>5-19</td>
<td>6 months</td>
<td>CSII + MDI</td>
<td>Experimental Group: (n=13)</td>
<td>-0.39 vs -0.1 (p = 0.023)*</td>
<td>Use of CGM facilitated an improved treatment</td>
<td>RCT with a crossover design</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Control Group: (n=14)</td>
<td></td>
<td></td>
<td>Funding: Medtronic MiniMed</td>
</tr>
</tbody>
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Note. NR = not reported; NS = not significant; F=Female and M=Male; BG – blood glucose levels; CGM – continuous glucose monitoring; CSII – continuous subcutaneous insulin infusion; DKA = diabetic ketoacidosis; HbA1c – glycosylated hemoglobin level; JDRF – Juvenile Diabetes Research Foundation; MDI – multiple daily injections; RCT – randomized controlled trial; SMBG – self-monitoring of blood glucose; TDD – total daily insulin dose
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<th>$\Delta$HbA1c (%) (Int/Cont)</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yates et al. (2006)</td>
<td>RCT</td>
<td>36 (23F-13M)</td>
<td>12-17</td>
<td>6 months</td>
<td>CSII + MDI</td>
<td>Experimental Group: (n=19) Had monitoring for 3 days every 3 weeks over a 3-month period in addition to traditional intermittent SMBG Control Group: (n=17) Had SMBG 4 to 6 times daily</td>
<td>-0.1 vs -0.1 (p=0.87) (NS)</td>
<td>CGM is no more useful than intermittent fingerstick SMBG and frequent review in improving diabetes control in reasonably well-controlled patients on near-physiological insulin regimens when used in an outpatient clinical setting</td>
<td>Random allocation used biased coin toss</td>
</tr>
</tbody>
</table>

**Note.** NR = not reported; NS = not significant; F=Female and M=Male; BG – blood glucose levels; CGM – continuous glucose monitoring; CSII – continuous subcutaneous insulin infusion; DKA = diabetic ketoacidosis; HbA1c – glycosylated hemoglobin level; JDRF – Juvenile Diabetes Research Foundation; MDI – multiple daily injections; RCT – randomized controlled trial; SMBG – self-monitoring of blood glucose; TDD – total daily insulin dose
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<tr>
<th>Study</th>
<th>Study Design</th>
<th>Sample (F:M)</th>
<th>Age (Years)</th>
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<th>Insulin Treatment</th>
<th>Intervention</th>
<th>ΔHbA1c (%) (Int/Cont)</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DirecNet (2007) USA</td>
<td>One Group Pre-test/ Post-test Design</td>
<td>30 (12F-18M)</td>
<td>4-17</td>
<td>3 months</td>
<td>CSII</td>
<td>Single Group: Children asked to use the CGM continuously and given written instructions on how to use the data to make real-time management decisions. Asked to download the CGM and SMBG readings at weekly intervals. Office visits were completed at 3, 7, and 13 weeks and phone calls were made between visits at 0.5, 2, 4, 8, and 10 weeks to review the downloaded glucose data.</td>
<td>-0.3 (p=0.02)*</td>
<td>Incorporating real-time CGM into the daily management of T1D in children is feasible and viewed as helpful by both patients and parents.</td>
<td>Did not include concurrent control group. Subject contact with clinical site more frequent than amount in usual practice. Follow-up was only for 3 months. Study included a select group of subjects who were all insulin pump users; excellent HbA1c at baseline.</td>
</tr>
<tr>
<td>DirecNet (2012) USA</td>
<td>One-Group Pre-test/Post-test Design</td>
<td>23 (8F/15M)</td>
<td>1-4</td>
<td>6 months</td>
<td>CSII + MDI</td>
<td>Single Group: Children were asked to use the CGM on a daily basis and given written instructions on how to use the sensor glucose data to make management decisions. Follow-up visits occurred at 1, 4, 8, 13, 19, and 26 weeks and phone calls with a parent were made between visits to review glucose data and adjust diabetes management.</td>
<td>+0.1 (p NR) (NS)</td>
<td>No change in mean HbA1c between baseline and 6 months, however, there was a high degree of parental satisfaction.</td>
<td>Did not include a control group. Contact with participants was more frequent than would occur in clinical practice. Longer duration of study (6 months). Number of participants was a convenience sample and represents a select group of families. Before-after design (not RCT). Funding: NR.</td>
</tr>
<tr>
<td>Gandrud et al. (2007) USA</td>
<td>One Group Pre-test/Post-test Design</td>
<td>19 (9F-10M)</td>
<td>1-7</td>
<td>6 months</td>
<td>CSII + MDI</td>
<td>Single Group: Children asked to wear the sensor for 3 days during approximately 6 months, but some continued with prolonged sensor wear. Families chose the number of sensor wears based on the time they were able to commit. Asked to perform 4 SMBG tests per day and one overnight</td>
<td>0.0 (p NR) (NS)</td>
<td>CGM tracings demonstrate frequent mild nocturnal hypoglycemia and significant postprandial hyperglycemia.</td>
<td>Both CSII and MDI used. Before-After design (not RCT). Funding: Glaser Pediatric Research Network; Weisgerber Foundation; Lucile Packard Foundation for Children’s Health.</td>
</tr>
</tbody>
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Note. NR = not reported; NS = not significant; F=Female and M=Male; BG – blood glucose levels; CGM – continuous glucose monitoring; CSII – continuous subcutaneous insulin infusion; DKA = diabetic ketoacidosis; HbA1c – glycosylated hemoglobin level; JDRF – Juvenile Diabetes Research Foundation; MDI – multiple daily injections; RCT – randomized controlled trial; SMBG – self-monitoring of blood glucose; TDD – total daily insulin dose.
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<tr>
<td>Halvorson et al. (2007) USA</td>
<td>One Group Pre-test/Post-test Design</td>
<td>10 (NR)</td>
<td>NR</td>
<td>1 month</td>
<td>CSII</td>
<td>Single Group: Children had four research visits at weekly intervals, wore 7 CGM sensors for an average of 3 days each and did 4 SMBG tests per day</td>
<td>-0.3 (p NR) (NS)</td>
<td>Able to use CGM to improve glycemia over short time</td>
<td>Before-After design (not RCT)</td>
</tr>
<tr>
<td>Hathout et al. (2005) USA</td>
<td>One Group Pre-test/Post-test Design</td>
<td>46 (26F/20 M)</td>
<td>2-18.5</td>
<td>3 months</td>
<td>CSII + MDI</td>
<td>Single Group: Protocol required 2 daytime and 2 nighttime 15-hour CGM wear periods. Children were asked to perform SMBG at least 4 times per day. Readings were uploaded weekly for 1 month, then monthly</td>
<td>-0.6 (p=0.1) (NS)</td>
<td>The reduction in HbA1c did not reach statistical significance</td>
<td>Did not include a control group</td>
</tr>
<tr>
<td>Jeha et al. (2004) USA</td>
<td>One Group Pre-test/Post-test Design</td>
<td>10 (8F-2M)</td>
<td>1-6</td>
<td>24 hours</td>
<td>MDI</td>
<td>Single Group: The CGM was inserted in each child by a certified diabetes educator. Asked to perform at least 4 SMBG tests daily. Each child underwent 2 72-hour monitoring periods 1 month apart using CGM</td>
<td>+0.5 (p=0.62) (NS)</td>
<td>CGM reveals trends in BG that current means of evaluating the adequacy of therapy (HbA1c and SMBG) are not able to discern</td>
<td>Lacked a control group with normal patients wearing the CGM</td>
</tr>
<tr>
<td>Ludwig-Seibold et al. (2012) GERMANY and AUSTRIA Database Review</td>
<td>1395 (NR)</td>
<td>6-18</td>
<td>2.5 years</td>
<td>CSII + MDI</td>
<td>Single Group: Data were analyzed from 144 385 sensor days from 1395 patients. Patients had regular visits at least every 3 months</td>
<td>(p&lt;0.0309)'</td>
<td>Glycemic control improved significantly possibly due to more intensive treatment and/or better diabetes education</td>
<td>Not a blinded randomized study</td>
<td></td>
</tr>
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<td>Rasbach et al. (2014) USA</td>
<td>One Group Pre-test/Post-test Design</td>
<td>122 (NR)</td>
<td>3 months</td>
<td>CSII + MDI</td>
<td>Single Group: Children received masked CGM use for 3 days, during which patients and their families completed a diary of blood glucose levels, insulin doses, food intake, and exercise during CGM use. Treatment recommendations were made based on CGM reports</td>
<td>-0.5% (p &lt; 0.001)</td>
<td>Children received an average of 3.1 + 1.1 treatment recommendations following review of CGM report. Metabolic control improved &gt; 0.5% in children who received recommendations regarding advanced insulin management (use of combination boluses/attend to active insulin)</td>
<td>Short duration of study</td>
</tr>
<tr>
<td>Scaramuzza et al. (2011) ITALY</td>
<td>Chart Review</td>
<td>622 (NR)</td>
<td>3 years</td>
<td>CSII</td>
<td>Experimental Group: Each center filled out a questionnaire for each eligible participant and data were collected from medical records. Children were utilizing sensor-augmented pump therapy. Control Group: Each center filled out a questionnaire for each eligible participant and data were collected from medical records. Children were using conventional insulin pump therapy.</td>
<td>-0.6 vs -0.3 (p=0.005)</td>
<td>Retrospective review of data shows a significant improvement in glycemic control for children CGM with insulin pump therapy compared with conventional insulin pump therapy (no CGM)</td>
<td>Provided a control group not using CGM</td>
</tr>
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<tr>
<td>Schaepeleyck-Belicar (2003) FRANCE</td>
<td>One Group</td>
<td>12 (5F-7M)</td>
<td>NR</td>
<td>2 months</td>
<td>CSII + MDI</td>
<td>Single Group:</td>
<td>-1.55%</td>
<td>Use of CGM achieved a significant improvement in metabolic control; accurate data for adjustment of insulin treatment and promoting patient communication and motivation</td>
<td>Sensor performance was sub-optimal due to patient- or device-related causes (40% of cases)</td>
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<tr>
<td></td>
<td>Pre-test/</td>
<td></td>
<td>16.2 ± 3</td>
<td></td>
<td></td>
<td></td>
<td>(p &lt; 0.05)*</td>
<td></td>
<td>Before-After design</td>
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<td></td>
<td>Post-test Design</td>
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<td></td>
<td>Short duration of study with a single sensor use</td>
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<td></td>
<td>Both CSII and MDI evaluated</td>
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<td>Funding: NR</td>
</tr>
<tr>
<td>Schiaffini et al. (2002) ITALY</td>
<td>One Group</td>
<td>18 (NR)</td>
<td>6-13</td>
<td>1.5 months</td>
<td>MDI</td>
<td>Single Group:</td>
<td>+0.1 (p NR) (NS)</td>
<td>Most patients demonstrated a reproducible daily glycemic pattern through which clinicians can adjust insulin therapy in order to improve metabolic control</td>
<td>Not an RCT</td>
</tr>
<tr>
<td></td>
<td>Pre-test/</td>
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<td>Infrequent use of CGM</td>
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<td></td>
<td>Post-test Design</td>
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<td>Only MDI evaluated</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Funding: MiniMed Inc.; Comar Cardio Technology Rome</td>
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**Hypoglycemia.** Continuous glucose monitoring has been used to assess hypoglycemia perception and to evaluate its’ use as a therapeutic tool to decrease the incidence and magnitude of hypoglycemia. All but one of the studies reviewed provided details related to the incidence of hypoglycemia (Table 4). Of the nine randomized trials, continuous glucose monitoring was associated with higher reported rates of hypoglycemia in five of the studies, lower rates of hypoglycemia in two studies, and no differences between groups in the remaining two studies. The additional eleven nonrandomized uncontrolled studies describing hypoglycaemia reported higher rates of hypoglycemia in three studies, lower rates of hypoglycemia in four studies, and no differences between the first- and second-time points in one study. The remaining two studies did not provide baseline values for rates of hypoglycemia to permit evaluation whether these rates increased, decreased, or remained the same following the use of continuous glucose monitoring and one study did not report on the frequency of hypoglycaemia.

Overall, hypoglycemia was identified more frequently in children using continuous glucose monitoring. However, this cannot be stated with certainty as two of the six before-after designs did not provide baseline rates of hypoglycemia and one study did not report on hypoglycemia frequency. This makes it impossible to evaluate whether or not there was an increase or decrease in terms of hypoglycemic episodes following use of continuous glucose monitoring. The remaining five nonrandomized uncontrolled designs reported a combination of higher, lower, and no difference in terms of rates of hypoglycemia. Despite the use of an RCT design in the remaining nine studies evaluating rates and frequency of hypoglycemia, five of these studies revealed an increase in the number of episodes of hypoglycemia, two studies reported a decrease, and the remaining two studies reported no difference in terms of rates of hypoglycemia, therefore making any conclusions related to this variable much more difficult.
**Hyperglycemia and diabetic ketoacidosis.** Children with T1D with high levels of blood glucose, or hyperglycemia, over a long period of time are at risk for long-term health complications including microvascular conditions, such as retinopathy, neuropathy, and nephropathy. Rates of hyperglycemia, as well as diabetic ketoacidosis were reported in fewer than half of the studies (n=8). Of the nine randomized controlled trials, only four reported on the frequency of hyperglycemia. Two of these studies reported an increase in the frequency of hyperglycemia, one study reported a decrease, and the remaining study did not provide baseline values. Of the eleven additional nonrandomized uncontrolled studies, only four reported on the rates of hyperglycemia. Only one study provided baseline values of the rate of hyperglycemia prior to use of the continuous glucose monitor, revealing a decrease in hyperglycemia when continuous monitoring was used. The remaining three studies did not report baseline values to permit a comparison in whether or not hyperglycemia increased or decreased following the use of continuous glucose monitoring.

With regards to Diabetic Ketoacidosis, five of the 20 studies reviewed calculated the frequency of such episodes. Of the nine randomized controlled trial designs, only three studies evaluated DKA. One study reported no difference between groups (zero incidences in both groups) and the other study reported one case of DKA in the group using a continuous glucose monitor. Similarly, of the eleven nonrandomized uncontrolled study designs, only two studies reported on the frequency of DKA and one study reported no episodes of DKA following the use of a continuous glucose monitor and the other study reported a slight decrease in episodes of DKA following continuous glucose monitoring.
With fewer than half of the studies reporting on hyperglycemia and DKA (3/20 studies), there is limited information available. However, it is apparent that hyperglycemia is relatively common in children with T1D in general, whereas severe episodes of hyperglycemia resulting in DKA are relatively rare. Due to the lack of reported rates of hyperglycemia before the study commenced in the majority of the before-after study designs reporting on this variable it is impossible to determine whether rates and frequency of hyperglycemia increased, decreased, or remained the same from the start of the study to the end. Despite the importance of this aspect of metabolic control, the findings from these studies are difficult to interpret due to diverse methods of reporting the frequency of hyperglycemia.

**Glycemic excursions and variability.** Reducing glycemic excursions and variability might also be an important aspect of glucose management and was reported in eleven of the twenty studies reviewed (Table 4). Five of the eight randomized controlled trials and six of the eleven nonrandomized uncontrolled studies reported on various aspects of blood glucose levels, including glycemic excursions and variability. However, as a result of the varying ways in which data related to glucose levels were reported, including percentages of overall glucose values, time spent in hypo- and/or hyper-glycemic range, frequency of glucose excursions, and area under the curve (above and below a certain range) as well as the differences in types of intervention used, length of studies, and varying sample sizes, it is not possible to draw general conclusions about the effects of continuous glucose monitoring versus self-monitoring on overall glucose levels.
**Insulin dose and insulin dose changes.** Aspects of insulin dose requirements, including dosage changes as well as total daily insulin dose requirements were calculated and reported in over half of the studies (n=11) (Table 4). Of the nine randomized controlled trials, changes to insulin dose and frequency of changes were reported in five of these studies. Two of these trials reported only on the frequency of insulin dose changes, two studies reported only on changes to insulin dose levels, and the remaining study reported on both changes to insulin dose and frequency of insulin dose changes. Increased rates of insulin dose changes were reported in children using continuous glucose monitoring in one study and increased rates of insulin dose changes were reported in the self-monitoring group in the other study. The three studies to report on changes to insulin dose levels found similar rates between groups. Six of the additional eleven nonrandomized uncontrolled trials reported on changes to insulin dose levels and frequency of changes to insulin dose. Four of these nonrandomized uncontrolled studies reported on changes to insulin dose levels and two reported on both changes to insulin dose levels and frequency of changes. However, three studies do not provide baseline values to provide comparisons of whether continuous glucose monitoring had an effect on insulin dose between the first and second time point. The three remaining studies did provide baseline values, with two studies reporting no differences in insulin dose between the first and second monitoring episodes and the remaining study reporting insulin requirement decreased only in patients using continuous monitoring, . Overall, descriptions of insulin dose were reported in eleven of the 20 studies reviewed. As a result of the varying ways in which insulin dose was analyzed and reported in these studies and due to only half of the studies reporting on this variable, it is not possible to draw conclusions about the effects of the two types of blood glucose monitoring on insulin dosage.
Table 4.

Summary of the Effects of Continuous Glucose Monitoring on Other Metabolic Control Outcomes in Children

<table>
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<tr>
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<th>Sample (F-M)</th>
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<th>Insulin Treatment</th>
<th>Hypoglycemia (Int/Cont)</th>
<th>Hyperglycemia (Int/Cont)</th>
<th>DKA (Int/Cont)</th>
<th>Blood Glucose Levels (Int/Cont)</th>
<th>Insulin Dose (Int/Cont)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chase et al. (2001) USA</td>
<td>RCT</td>
<td>11 (5F-6M)</td>
<td>10-17</td>
<td>3 months</td>
<td>CSII + MDI</td>
<td>12.8/person vs 6.7/person (p = 0.001)’</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>11.5 ± 1.5 insulin dose changes per participant vs 5.2 ± 0.9 insulin dose changes per participant (p=0.001)’</td>
</tr>
<tr>
<td>Chase et al. (2003) USA</td>
<td>RCT</td>
<td>40 (19F-21M)</td>
<td>7-16</td>
<td>3 months</td>
<td>CSII + MDI</td>
<td>7.7 events/100 person hrs vs 4.4 events/100 person hrs (p &lt; 0.0005)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Insulin dose changes slightly more in control group (p &gt; 0.05) (NS)</td>
</tr>
<tr>
<td>Deiss et al. (2006) GERMANY</td>
<td>RCT Cross Over</td>
<td>30 (14F-16M)</td>
<td>2-17</td>
<td>6 months</td>
<td>MDI</td>
<td>4 episodes per month vs 4 episodes per month (p = 0.84) (NS)</td>
<td>620 minutes spent &gt; 180mg/dL vs 720 minutes spent &gt; 180mg/dL (p=0.191) (NS)</td>
<td>NR</td>
<td>220mg/dL during day vs 208mg/dL during day (p=0.917) (NS)</td>
<td>Insulin dose as well as number of injections was not different between the groups (p &gt; 0.10) (NS)</td>
</tr>
<tr>
<td>DirecNet (2005) USA</td>
<td>RCT</td>
<td>200 (92F-108M)</td>
<td>7-17</td>
<td>6 months</td>
<td>CSII + MDI</td>
<td>7 total vs 2 total (p=0.10)’</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Insulin dose increased in both groups 0.1 ± 0.2 vs 0.1 ± 0.2 (p&lt;0.001) (NS)</td>
</tr>
<tr>
<td>DirecNet (2012) USA</td>
<td>RCT</td>
<td>146 (67F-79M)</td>
<td>4-10</td>
<td>6 months</td>
<td>CSII + MDI</td>
<td>8.6 events/100 person years vs 17.6 events/100 person years (p = 0.80) (NS)</td>
<td>23 mg/dL vs 22 mg/dL (% median BG &gt; 250 mg/dL) (p NR) (NS)</td>
<td>0 vs 0 (NS)</td>
<td>46 mg/dL vs 47 mg/dL (% median BG 71-80 mg/dL) (p NR) (NS)</td>
<td>NR</td>
</tr>
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<th>Blood Glucose Levels (Int/Cont)</th>
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<tr>
<td>JDRF (2008) USA</td>
<td>RCT</td>
<td>114 (56F-58M)</td>
<td>8-14</td>
<td>6 months</td>
<td>CSII + MDI</td>
<td>17.9 events/ 100 person years vs 24.4 events/ 100 person years (p = 0.64) (NS)</td>
<td>745 minutes &gt; 180mg/dL vs 671 minutes &gt; 180mg/dL (p=0.58) (NS)</td>
<td>0 vs 0 (NS)</td>
<td>646 minutes spent between 71-180mg/dL vs 710 minutes spent between 71-180mg/dL (p=0.53) (NS)</td>
<td>NR</td>
</tr>
<tr>
<td>Lagarde et al. (2006) USA</td>
<td>RCT</td>
<td>27 (15F-12M)</td>
<td>7-17</td>
<td>6 months</td>
<td>CSII + MDI</td>
<td>1.2 ± 2.2/ person vs 0.67 ± 1.0/person (p = 0.24)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ludvigsson &amp; Hanas (2003) SWEDEN</td>
<td>Cross Over</td>
<td>27 (NR)</td>
<td>5-19</td>
<td>6 months</td>
<td>CSII + MDI</td>
<td>26/27 patients experienced &lt;3.0mmol/L (0.8 episodes/day, duration 58 ± 29 minutes, 5.5% of total time)</td>
<td>1.5 episodes/day of high glucose and 0.6 episodes/night</td>
<td>NR</td>
<td>Dawn phenomena (5.3% of days in 10 patients)</td>
<td>NR</td>
</tr>
<tr>
<td>Yates et al. (2006) AUSTRALIA</td>
<td>RCT</td>
<td>39 (26F-13M)</td>
<td>13-15</td>
<td>6 months</td>
<td>CSII + MDI</td>
<td>0.4 vs 0.3 (p NR) (NS)</td>
<td>One subject in CGM group admitted for DKA (thought to be due to insulin omission)</td>
<td>AUC &gt; 9mmol/L weakly associated with initial HbA1c; did not significantly change from the first to the last cycle (p=0.098) (NS)</td>
<td>No significant correlation between change in AUC &gt; 9mmol/L and change in HbA1c (p=0.41) (NS)</td>
<td>Increase in insulin dose was 0.01 vs 0.03 (p=0.69) (NS)</td>
</tr>
</tbody>
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<th>Length of Study</th>
<th>Insulin Treatment</th>
<th>Hypoglycemia (Int/Cont)</th>
<th>Hyperglycemia (Int/Cont)</th>
<th>DKA (Int/Cont)</th>
<th>Blood Glucose Levels (Int/Cont)</th>
<th>Insulin Dose (Int/Cont)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DirecNet (2007) USA</td>
<td>One Group Pre-test/Post-test Design</td>
<td>30 (12F-18M)</td>
<td>4-17</td>
<td>3 months</td>
<td>CSII</td>
<td>4.5% versus 5.5% of all BG values (p NR) NS</td>
<td>NR</td>
<td>NR</td>
<td>Percentage of values between 71-180mg/dL rose from 52% to 60% (p=0.01)</td>
<td>NR</td>
</tr>
<tr>
<td>DirecNet (2012) USA</td>
<td>One Group Pre-test/Post-test Design</td>
<td>23 (8F-15M)</td>
<td>1-4</td>
<td>6 months</td>
<td>CSII + MDI</td>
<td>Four severe hypoglycemic episodes in one subject during study (p NR) (NS)</td>
<td>NR</td>
<td>NR</td>
<td>50% of participants between 71-180 mg/dL/day</td>
<td>NR</td>
</tr>
<tr>
<td>Gandrud et al. (2007) USA</td>
<td>One Group Pre-test/Post-test Design</td>
<td>19 (9F-10M)</td>
<td>1-7</td>
<td>6 months</td>
<td>CSII + MDI</td>
<td>1.1 ± 1.7 episodes per 24 hours; frequency and duration did not change over time (p NR) (NS)</td>
<td>NR</td>
<td>NR</td>
<td>Mean blood glucose and % time &gt;11mmol/L significantly associated with HbA1c % time &lt;3.9mmol/L not significantly associated with HbA1c (p &lt;0.001 for both) (NS)</td>
<td>NR</td>
</tr>
<tr>
<td>Halvorson et al. (2007) USA</td>
<td>One Group Pre-test/Post-test Design</td>
<td>10 (NR)</td>
<td>NR</td>
<td>1 month</td>
<td>CSII</td>
<td>Reduced from 9.4 ± 21.7 five-minute blocks to 5.3 ± 15.1 five-minute blocks at end (p NR) (NS)</td>
<td>NR</td>
<td>0 episodes</td>
<td>198 ± 38 vs. 200 ± 45 mg/dL (p = 0.8) (NS)</td>
<td>3.2 insulin dose changes/patient made following CGM 42% increase insulin rate, 15% decrease insulin rate, 30% increased insulin:carb ratio, 9% increase insulin in algorithm, 4% altered insulin for exercise</td>
</tr>
</tbody>
</table>

Note. NR = not reported; NS = not significant; F=Female and M=Male; BG – blood glucose levels; CGM – continuous glucose monitoring; CSII – continuous subcutaneous insulin infusion; DKA = diabetic ketoacidosis; HbA1c – glycosylated hemoglobin level; JDRF – Juvenile Diabetes Research Foundation; MDI – multiple daily injections; RCT – randomized controlled trial; SMBG – self-monitoring of blood glucose; TDD – total daily insulin dose.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Sample (F-M)</th>
<th>Age (Years)</th>
<th>Length of Study</th>
<th>Insulin Treatment</th>
<th>Hypoglycemia (Int/Cont)</th>
<th>Hyperglycemia (Int/Cont)</th>
<th>DKA (Int/Cont)</th>
<th>Blood Glucose Levels (Int/Cont)</th>
<th>Insulin Dose (Int/Cont)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hathout et al. (2005)</td>
<td>One Group Pre-test/Post-test Design</td>
<td>46 (26F-20M)</td>
<td>2-18.5</td>
<td>3 months</td>
<td>CSII + MDI</td>
<td>42 episodes detected by CGM; 33 confirmed by meter (79% sensitivity)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>No changes in daily weight-adjusted insulin used</td>
</tr>
<tr>
<td>Jeha et al. (2004)</td>
<td>One Group Pre-test/Post-test Design</td>
<td>10 (8F-2M)</td>
<td>1-6</td>
<td>24 hours</td>
<td>MDI</td>
<td>Duration median of 4.7 hours vs. 4.2 hours per monitoring period (p = 0.4) (NS)</td>
<td>3 episodes per subject per 24 hours (p NR) (NS)</td>
<td>NR</td>
<td>Spent 7% of 24-h period &lt;60mg/dL, 64% with a glucose value greater than 150mg/dL, and only 24% of their time with acceptable values</td>
<td>No difference between insulin dose (0.7 ± 0.1 vs 0.7 ± 0.2 units/kg/day) recorded during the first and second monitoring episodes</td>
</tr>
<tr>
<td>Ludwig-Seibold et al. (2012)</td>
<td>Database Review (NR)</td>
<td>1395 (NR)</td>
<td>6-18</td>
<td>2.5 years</td>
<td>CSII + MDI</td>
<td>More hypoglycemia in children wearing CGM for &lt;30 days (p &lt; 0.0011)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rasbach et al. (2014)</td>
<td>One Group Pre-test/Post-test Design</td>
<td>122 (NR)</td>
<td>NR 14.3 ± 3.9</td>
<td>3 months</td>
<td>CSII + MDI</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Note.** NR = not reported; NS = not significant; F=Female and M=Male; BG – blood glucose levels; CGM – continuous glucose monitoring; CSII – continuous subcutaneous insulin infusion; DKA = diabetic ketoacidosis; HbA1c – glycosylated hemoglobin level; JDRF – Juvenile Diabetes Research Foundation; MDI – multiple daily injections; RCT – randomized controlled trial; SMBG – self-monitoring of blood glucose; TDD – total daily insulin dose
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<th>Study</th>
<th>Study Design</th>
<th>Sample (F-M)</th>
<th>Age (Years)</th>
<th>Length of Study</th>
<th>Insulin Treatment</th>
<th>Hypoglycemia (Int/Cont)</th>
<th>Hyperglycemia (Int/Cont)</th>
<th>DKA (Int/Cont)</th>
<th>Blood Glucose Levels (Int/Cont)</th>
<th>Insulin Dose (Int/Cont)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scaramuzza et al. (2011)</td>
<td>Chart Review</td>
<td>622 (NR)</td>
<td>1-18</td>
<td>3 years</td>
<td>CSII</td>
<td>Severe hypoglycemia decreased only in patients using CGM (11.9 vs 4.1 events/100 patients/year [p = 0.04] and 6.6 vs 3.9 events/100 patients/year [p NS])</td>
<td>NR</td>
<td>No difference in DKA episodes (0.5 vs 0.3 events/100 patients/year [p = NS] and 0.5 vs 0.4 events/100 patients/year [p NS])</td>
<td>NR</td>
<td>Insulin requirement showed decrease only in patients using CGM (0.88 ± 0.25 vs 0.79 ± 0.23 U/kg/day) (p = 0.005)*</td>
</tr>
<tr>
<td>Schaeperyck-Belicar (2003)</td>
<td>One Group Pre-test/</td>
<td>12 (5F-7M)</td>
<td>NR</td>
<td>2 months</td>
<td>CSII + MDI</td>
<td>4 episodes total in 4 patients</td>
<td>In 10 patients, a total of 24 episodes of postprandial hyperglycemia were observed</td>
<td>NR</td>
<td>Large excursions of glycemia unrecognized by SMBG found in all 12 patients</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Post-test Design</td>
<td></td>
<td>16.2 ± 3</td>
<td></td>
<td></td>
<td></td>
<td>In 5 patients seven prolonged episodes of hyperglycemia were recorded during the night period</td>
<td></td>
<td>Significant decrease in mean frequency of glycemic excursions from 3.5 ± 1.3 to 2.08 ± 1.37 per patient</td>
<td></td>
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<tr>
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<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>In 4 patients, a total of six episodes of dawn phenomenon were observed</td>
<td></td>
<td>In 3 patients, the number of daily insulin injections was increased from 2 to 3</td>
<td></td>
</tr>
<tr>
<td>Schiaffini et al. (2002)</td>
<td>One Group Pre-test/</td>
<td>18</td>
<td>6-13</td>
<td>1.5 months</td>
<td>MDI</td>
<td>Higher number of asymptomatic hypoglycemic events revealed by CGM compared to SMBG (3.6 ± 2.3 vs 0.7 ± 0.972 hours/patient) (p &lt; 0.0001)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Total daily insulin intake were maintained (0.93 ± 0.15 vs 0.98 ± 0.19 IU/kg/day (p NR) (NS)</td>
</tr>
<tr>
<td></td>
<td>Post-test Design</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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**Note.** NR = not reported; NS = not significant; F=Female and M=Male; BG – blood glucose levels; CGM – continuous glucose monitoring; CSII – continuous subcutaneous insulin infusion; DKA = diabetic ketoacidosis; HbA1c – glycosylated hemoglobin level; JDRF – Juvenile Diabetes Research Foundation; MDI – multiple daily injections; RCT – randomized controlled trial; SMBG – self-monitoring of blood glucose; TDD – total daily insulin dose
Metabolic Control using Continuous Subcutaneous Insulin Infusion with Continuous Glucose Monitoring versus Self-Monitoring of Blood Glucose

No randomized controlled trials were found which compared continuous glucose monitoring to self-monitoring in children with T1D who were using continuous subcutaneous insulin infusion. Therefore the inclusion criteria were broadened to include other research designs and studies which enrolled both children and young adults. Of the 20 studies comparing these two forms of glucose monitoring, only three studies evaluated continuous subcutaneous insulin infusion alone with the use of continuous glucose monitoring (Table 5). Two studies were before-after designs and one study was a retrospective chart review.

The first reported study evaluating continuous glucose monitoring with continuous subcutaneous insulin infusion alone used a before-after design (n=10) to evaluate whether using the real-time glucose values, glucose trend data, and hypoglycemic and hyperglycemic alerts available on continuous glucose monitoring devices improved metabolic control and reduced episodes of hypoglycemia and hyperglycemia over time (Halvorson et al., 2007). Children had four research visits at weekly intervals, wore seven glucose sensors for an average of three days each (numbered Sensor 1 to 7) and performed four self-monitoring checks per day. The mean HbA1c was 8.1% ± 0.9% at baseline and 7.8% ± 0.9% at study end (p not reported); indicating improved metabolic control though not a clinically important reduction in HbA1c levels. The mean number of 5-minute blocks of hypoglycemia was reduced from 9.4 ± 21.7 for sensor 1 to 5.3 ± 15.1 for sensor 7 per patient (p not reported) and the mean number of 5-minute blocks of hyperglycemia decreased from 64.9 ± 36.8 for sensor 1 to 44.7 ± 38.4 for sensor 7 (p not reported), demonstrating reduced frequency of both hypoglycemia and hyperglycemia.
The second study by DirectNet (2007) examined the feasibility of daily use of continuous glucose monitoring in children with T1D using a before-after design. After a masked continuous glucose monitoring device was used for 4 to 7 days to establish baseline level of metabolic control, 30 continuous subcutaneous insulin infusion users with T1D were asked to use the continuous glucose monitor daily for 13 weeks. For the 28 participants completing the 13-week visit, HbA1c values dropped significantly from 7.1% ± 0.6% at baseline to 6.8% ± 0.7% at 13 weeks (p=0.02). Although none of the participants had a severe hypoglycemic episode during the study, the frequency of hypoglycemia experienced increased from 4.5% to 5.5% (p = 0.07) and the frequency of hyperglycemia decreased from 6.2% to 3.1% (p = 0.004), indicating improved metabolic control with a modest increase in risk of hypoglycemia, but reduced hyperglycemia. However, these results must be viewed cautiously, because the study did not include a concurrent control group, subject contact with the clinical site was more frequent than the amount that would occur in usual practice, follow-up was only for one month, and the sample size was small. Further, the results cannot be generalized to all children with T1D because the study included a group of participants whose mean HbA1c levels at baseline were quite good (DirectNet, 2007).

The additional and most recent study assessed metabolic control as well as the usefulness and safety of continuous glucose monitoring and insulin pump therapy in a large population of pediatric patients with T1D evaluated at baseline and after three years through the use of a before-after chart review and questionnaire (Scaramuzza et al., 2011). The primary end point was the change in HbA1c between baseline and the end of the observation period for children using insulin pump therapy with the addition of continuous glucose monitoring compared to conventional pump therapy (without continuous monitoring). One hundred and twenty nine
children (13.5 ± 3.8 years old and a duration of diabetes of 6.3 ± 3.4 years) using an insulin pump with CGM were compared with 493 patients (12.9 ± 3.4 years old, with a disease duration of 6.2 ± 3.3 years) using conventional insulin pump therapy evaluated as the control group.

They reported that after six months to three years, HbA1c significantly improved in insulin pump and continuous monitoring users and in controls (8.0 ± 1.5% vs 7.4 ± 0.8%, \([p = 0.002]\) and 8.0 ± 1.6% vs 7.7 ± 1.1%, \([p = 0.006]\), respectively). However, the improvement in metabolic control was significantly better in the children using continuous glucose monitoring with their insulin pump (0.6% vs 0.3% \([p=0.005]\)). In addition, no differences were observed in DKA episodes during the follow up period in both groups (0.5 vs 0.3 events/100 patients/year \([p = \text{not significant}]\) and 0.5 vs 0.4 events/100 patients/year \([p = \text{not significant}]\), respectively), whereas severe hypoglycemia significantly decreased only in patients using insulin pump therapy with continuous monitoring (11.9 vs 4.1 events/100 patients/year \([p=0.04]\) and 6.6 vs 3.9 events/100 patients/year \([p = \text{not significant}]\), respectively). However, due to the use of a retrospective study design, it is not possible to determine if the decline in HbA1c was directly related to continuous glucose monitoring use, or if other factors, such as more frequent contacts with the providers from the clinic and/or motivation to use new technological advances could have affected the results.
Table 5.

Summary of the Effects of Continuous Glucose Monitoring with CSII on Metabolic Control in Children

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Sample (F-M)</th>
<th>Age (Years)</th>
<th>Length of Study</th>
<th>Insulin Treatment</th>
<th>Intervention</th>
<th>ΔHbA1c (%) (Int/Cont)</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DirecNet (2007)</td>
<td>One Group Pre-test/ Post-test Design</td>
<td>30 (12F-18M)</td>
<td>4-17</td>
<td>3 months</td>
<td>CSII</td>
<td>Single Group: Children were asked to use the CGM continuously and were given written instructions on how to use the data to make real-time management decisions. Asked to download the CGM and SMBG readings at weekly intervals. Office visits were completed at 3, 7, and 13 weeks and phone calls to children/caregivers were made between visits at 0.5, 2, 4, 8, and 10 weeks to review the downloaded glucose data.</td>
<td>-0.3 (p=0.02) *</td>
<td>Incorporating real-time CGM into the daily management of T1D in children is feasible and viewed as helpful by both patients and parents</td>
<td>Did not include concurrent control group; Subject contact with clinical site more frequent than amount in usual practice; Follow up was only for 3 months; Study included a select group of subjects who were all insulin pump users; excellent HbA1c at baseline</td>
</tr>
<tr>
<td>Halvorson et al. (2007)</td>
<td>One Group Pre-test/ Post-test Design</td>
<td>10 (NR)</td>
<td>14.1 ± 2.6</td>
<td>1 month</td>
<td>CSII</td>
<td>Single Group: Children had four research visits at weekly intervals, wore 7 CGM sensors for an average of 3 days each and did 4 SMBG tests per day.</td>
<td>-0.3 (p NR) (NS)</td>
<td>Able to use CGM to improve glycemia over short time; CGM might enable more children to avert complications</td>
<td>Before-After design (not RCT); Contact with clinic site was more frequent than usual</td>
</tr>
<tr>
<td>Scaramuzza et al. (2011)</td>
<td>Chart Review</td>
<td>622 (NR)</td>
<td>1-18</td>
<td>3 years</td>
<td>CSII</td>
<td>Experimental Group: Data were collected from medical records. Children were utilizing sensors and insulin pumps. Control Group: Data were collected from medical records. Children were using conventional insulin pumps.</td>
<td>-0.6 vs -0.3 (p=0.005) *</td>
<td>Retrospective review of data shows a significant improvement in glycemic control for children CGM with insulin pump therapy compared with conventional insulin pump therapy (no CGM).</td>
<td>Provided a control group not using CGM; Data collected retrospectively from medical records; Very long duration; Only CSII evaluated</td>
</tr>
</tbody>
</table>

Note. NR = not reported; NS = not significant; F=Female and M=Male; BG = blood glucose levels; CGM = continuous glucose monitoring; CSII = continuous subcutaneous insulin infusion; DKA = diabetic ketoacidosis; HbA1c = glycosylated hemoglobin level; JDRF = Juvenile Diabetes Research Foundation; MDI = multiple daily injections; RCT = randomized controlled trial; SMBG = self-monitoring of blood glucose; TDD = total daily insulin dose
**Fear of Hypoglycemia**

Only two studies have evaluated the effect of continuous glucose monitoring on fear of hypoglycemia in children and adolescents (Table 6). Neither of these studies evaluated the use of continuous subcutaneous insulin infusion alone. Chase et al. evaluated whether the use of continuous glucose monitoring improves blood glucose control in children using the CGM (2001) or the GlucoWatch 2 Biographer (2003). In both studies, fear of hypoglycemia was assessed with the Hypoglycemic Fear Survey (Cox et al., 1987).

Chase et al. (2001) evaluated metabolic control and fear of hypoglycaemia in eleven children with T1D whose HbA1c values were greater than 8.0% (range 8.3 – 10.3%) over the previous six months. Children were randomized either to continuous glucose monitoring or the control group. The children receiving continuous monitoring were each asked to wear six sensors (18 total sensor days) within a 30-day period. Each participant completed the Hypoglycemic Fear Survey (HFS) and the DCCT Quality of Life (QoL) questionnaire (DCCT, 1988) at the start, after one month, and after three months of study. The range for the HFS and QOL questionnaires were 27 to 135 and 44 to 220, respectively, with lower totals, meaning less fear or greater QOL, respectively. There were no significant differences in results for the Fear of Hypoglycemia or the QOL measures between the test and control participants at any time. There were also no significant differences in outcomes before versus one or three months of study for either group. The mean group total for the HFS decreased slightly (meaning less fear) from 61.8 at the beginning of the study to 56.6 at three months for the continuous glucose monitoring group (p > 0.05). However, no additional mean scores or test statistics were provided.
Similarly, in their study of 40 children between the ages of 7-16, Chase et al. (2003) explored the use of continuous glucose monitors and their potential impact on glucose control in children and adolescents with T1D. Children were randomized to one of two groups and treated for three months (intervention phase). The intervention group used the GlucoWatch 2 biographer as an adjunctive measure to conventional glucose monitoring; the control group used only conventional self-monitoring of blood glucose levels. Each participant completed the Hypoglycemic Fear Survey and the DCCT Quality of Life questionnaires initially, after one month, and after three months of the study. There were no significant differences in either the Hypoglycemic Fear Survey or the Quality of Life scores between the control and GlucoWatch 2 biographer groups during the intervention phase of the study. The scores were 59 ± 14.3 versus 56.4 ± 9.6 after three months for the Hypoglycemic Fear Survey scale and 81.3 ± 11.7 versus 79.8 ± 15.5 for the Quality of Life scores, respectively.
### Table 6.

Summary of the Effects of Continuous glucose monitoring on Fear of Hypoglycemia in Children

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Sample (F-M)</th>
<th>Age (Years)</th>
<th>Length of Study</th>
<th>Insulin Treatment</th>
<th>FOH (Int/Cont)</th>
<th>QOL (Int/Cont)</th>
<th>Satisfaction (Int/Cont)</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chase et al. (2001) USA</td>
<td>RCT</td>
<td>11 (5F-6M)</td>
<td>10-17</td>
<td>3 months</td>
<td>CSII + MDI</td>
<td>HFS</td>
<td>DCCT QOL</td>
<td>NR</td>
<td>The ability for patients to read their glucose values, as well as to have alarms for high and low glucose levels, will likely result in the routine use of CGM</td>
<td>Method of random allocation not identified; Small sample size; Funding: Children’s Diabetes Foundation; CGM Supplier: Medtronic MiniMed Inc.</td>
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<tr>
<td>Chase et al. (2003) USA</td>
<td>RCT</td>
<td>40 (19F-21M)</td>
<td>7-16</td>
<td>3 months</td>
<td>CSII + MDI</td>
<td>HFS</td>
<td>DCCT QOL</td>
<td>NR</td>
<td>Well tolerated by children; Alarms led to greater detection of hypoglycemia than occurs with conventional glucose monitoring</td>
<td>Small sample size; Use of GW2B that is no longer available for use; Funding: Children with Diabetes Foundation; Children’s Diabetes Foundation</td>
</tr>
</tbody>
</table>

*Note.* NR = not reported; NS = not significant; F=Female and M=Male; BG – blood glucose levels; CGM – continuous glucose monitoring; CSII – continuous subcutaneous insulin infusion; DKA = diabetic ketoacidosis; HbA1c – glycosylated hemoglobin level; JDRF – Juvenile Diabetes Research Foundation; MDI – multiple daily injections; RCT – randomized controlled trial; SMBG – self-monitoring of blood glucose; TDD – total daily insulin dose; CGM Questionnaire: Researcher-developed questionnaire; DCCT QOL: Diabetes Control and Complications Trial Quality of Life - Possible range of scores 0-230; higher scores indicate less favourable quality of life; HFS: Hypoglycemic Fear Scale - Possible range of scores 0-115; higher scores indicate more diabetes-related anxiety.
Summary of Studies Evaluating Metabolic Control and Fear of Hypoglycemia in Children with Type 1 Diabetes using Continuous Glucose Monitoring

Twenty studies evaluating metabolic control and two evaluating fear of hypoglycemia in children with T1D using continuous glucose monitoring compared to self-monitoring of blood glucose alone published in peer-reviewed journals were identified. However, of these twenty studies, only three evaluated continuous subcutaneous insulin infusion alone for diabetes management. Two studies utilized a before-after design and one study used a retrospective chart review rather than an RCT design. Taken together, the findings from all twenty studies suggest that children and adolescents generally experience improved metabolic control following use of continuous glucose monitoring and potentially a reduction in terms of psychological concerns, including fear of hypoglycemia. However, ascertaining the efficacy and effectiveness of continuous glucose monitoring for metabolic control and other health outcomes, including reduction of fear of hypoglycemia, has been difficult because of differences in use of the device, as well as methodological issues such as selection bias, lack of controls, and inadequate power.

Of the nine studies utilizing an RCT design, only four studies described the method for randomization. Randomization was accomplished using a permuted-blocks design stratified by clinical center and age group (7-12 and 12-18) in the study by DirecNet (2005) and in the study by DirecNet (2012). Lagarde et al. (2006) assigned children 2:1 into an intervention group using a computer-generated randomization list created by a statistician. Lastly, Yates et al. (2006) made use of a biased coin randomization with group allocation blinded using opaque sealed envelopes; however, there was no mention of who created the envelopes or enrolled the participants. In terms of studies evaluating continuous glucose monitoring versus self-monitoring, seven utilized an RCT design and two utilized an RCT crossover study design.
The remaining eleven studies utilizing a before-after design (n=9) or retrospective chart review (n=2) provide a description of the experiences of children with T1D using continuous glucose monitoring. However, these types of studies lack a comparison control group, instead using the subject as his or her own control, potentially introducing a bias of history and maturation. These biases may make evaluation of the efficacy of continuous glucose monitoring compared with self-monitoring more difficult (Wilson, Buckingham, Kunselman, Sullivan, Paguntalan, & Gitelman, 2005). With regards to fear of hypoglycemia experienced by children with T1D using continuous glucose monitoring, only two studies have evaluated this variable, with both utilizing an RCT design. However, neither of these two studies evaluated continuous subcutaneous insulin infusion alone, rather evaluated children using CSII or MDI for insulin administration.

Previous systematic reviews exploring the effects of continuous glucose monitoring compared to self-monitoring of blood glucose on metabolic control have also found mixed evidence for their effectiveness (DeBlock, Manuel-y-Kennoy, & Van Gaal, 2008; Edelman & Bailey, 2009; Golicki, et al., 2008; Hoeks, Greven, & de Valk, 2010; Klonoff, 2005; Pickup, 2011; Verheyen et al., 2010). The most recent meta-analysis by Pickup (2011) analyzed individual patient data from six randomized controlled trials in adults. They showed that when management of T1D included real time continuous glucose monitoring compared with self-monitoring, the overall reduction in HbA1c was 0.30%. More specifically, the improvement in metabolic control with continuous glucose monitoring was greatest in those with the highest baseline HbA1c and those who used the sensor most frequently. However, of these previous reviews, only one involved children (Golicki et al., 2008), while the remaining four reviews combined child, adolescent, and adult populations in the same review. The current systematic
review included the same child studies identified in the previous reviews, in addition to more recent studies that had not been carried out at the time of publication of these earlier reviews.

Overall, the studies evaluated in the current systematic review of the literature revealed some improvement in metabolic control in children and adolescents using continuous glucose monitoring compared to self-monitoring, similar to the results reported in the review in adults. In general, HbA1c levels improved and the number of insulin dose changes increased in the pediatric population in the studies reviewed when using continuous glucose monitoring compared to self-monitoring. These results indicate that continuous glucose monitors may be beneficial for children with T1D in attempts to improve overall metabolic control. However, as a result of the various methods used to report on metabolic control, variations in sample sizes, duration of study, types of continuous glucose monitoring devices used, as well as use of both continuous subcutaneous insulin infusion and/or multiple daily injections together in the same sample for diabetes management, as well as the lack of a concurrent control group in half of the studies, it is impossible to draw any real conclusions.

Despite a number of studies being performed in the past, many had one or more deficiencies. These include some studies being only observational, inadequately powered and/or too short in duration. Thus, a well-designed randomized controlled trial is critically needed to evaluate children with T1D using continuous subcutaneous insulin infusion for diabetes management with continuous glucose monitoring compared to self-monitoring of blood glucose alone. A well-controlled RCT design may provide additional evidence towards the usefulness of this form of technology in an effort to improve metabolic control through reductions in HbA1c levels, as well as hypo- and hyperglycaemic episodes. In addition, the potential effects on increasing or decreasing fear of hypoglycemia, may also be revealed.
Chapter 3
Conceptual Framework

A conceptual framework was developed for this pilot trial using concepts from the review of the literature and provides a model to explain how metabolic control, specifically HbA1c levels, can be affected by use of the continuous glucose monitoring intervention in this trial.

Conceptual Framework Definition of Terms

*Continuous glucose monitoring* comprise a disposable subcutaneous glucose sensing device is connected to a transmitter, which wirelessly transmits the data to the monitor. The system takes a glucose measurement every 10 seconds and stores an average value every one to five minutes, depending on the device, for up to seven days (ranging from 3 to 7 days).

*Current glucose values* are measured using a subcutaneous sensor that monitors interstitial glucose levels every 10 seconds and sends the information to the continuous glucose monitor.

*Average glucose value* is an average of the last five minutes of glucose readings which are then sent to the continuous glucose monitor.

*Glucose trends* are the direction and rate of change that glucose levels are currently undergoing. Arrows indicate whether glucose levels are going up (hyperglycemia) when glucose levels increase above a certain level, or going down (hypoglycemia) when glucose levels decrease below a certain level. These arrows also reveal how fast the change is happening to provide an idea of how quickly children must intervene to prevent the current upward or downward trend.

*Glucose trend graphs* show the effects that meals (diet), physical activity, insulin, and other medications can have on glucose levels.

*Self-efficacy* is an individual’s belief in one’s ability to perform a specific behaviour (Bandura, 1997).
Hypoglycemia is a low glucose level < 4.0mmol/L (72mg/dL) for those treated with insulin with the development of autonomic (trembling, sweating, hunger, nausea) or neuroglycopenic symptoms (confusion, weakness, vision changes, headache, dizziness) that respond to the administration of carbohydrate (CDA, 2013).

Hyperglycemia is a high glucose level > 14mmol/L (252mg/dL) for those treated with insulin with positive serum and/or urine ketones (CDA, 2013).

Glucose excursion or variability is the fluctuations of glucose levels experienced over a given time period (ie day, night, week, and month) (Rodbard, 2009).

Fear of Hypoglycemia is a psychological state in which people with T1D exhibit anxiety about developing hypoglycemia and may engage in over-compensatory behaviours, including prematurely treating hypoglycemia and taking less insulin or to avoid hypoglycemia (Wild et al., 2007).

HbA1c also known as glycated or glycosylated hemoglobin is formed in a non-enzymatic glycation pathway by hemoglobin’s exposure to plasma glucose. Normal levels of glucose produce a normal amount of glycosylated hemoglobin. As the average amount of plasma glucose increases, the fraction of glycosylated hemoglobin increases in a predictable way.

Metabolic control is represented by the amount of glycosylated hemoglobin in the blood and HbA1c levels are used to provide an estimate of the metabolic control, specifically how well diabetes is being managed over the long-term. In children between the ages of 6 and 12, the recommended level of HbA1c is less than 8.0% which is indicative of good metabolic control for this age group.
Description

Figure 5 is a diagrammatic representation of the pathway by which HbA1c levels, an indication of metabolic control, may be reduced in children with Type 1 diabetes in the Continuous glucose monitoring and HbA1c In Long-term Diabetes Management (CHILD) study.

Figure 5. Conceptual Model for the Definitive Trial

The description to follow provides an interpretation of the conceptual model in Figure 5. Similar to a biofeedback system, in which people are alerted to potential problems in his or her body that may not normally be noticeable, through the use of the continuous glucose monitoring intervention in this study, the child with T1D will be provided with current glucose information, with a glucose level reading every minute and a five minute average glucose level, for a total of 288 measurements each day. The continuous glucose monitoring also provides three-hour and
24-hour glucose trend information via graphs that show children the effects of meals, physical activity, insulin, and other medications on glucose levels. Trend arrows point up or down to clearly show children the direction and rate of change (how fast or slow) in glucose levels (Medtronic, 2010). Together, the additional information provided by the continuous glucose monitoring related to current, average, and future glucose trends provides the child with T1D increased glucose awareness within their own body that is not available when using self-monitoring of blood glucose alone. Thus, the continuous glucose monitor sensors shift the focus of diabetes management to the child, enabling them to react to subcutaneous glucose readings in a “biofeedback” fashion (Danne & Kordonouri, 2008). The effects of continuous glucose monitoring on fear of hypoglycemia are unclear. Increased information provided by the continuous glucose monitor may help children with T1D reduce their fear of hypoglycemia because they receive information about the current, average, and future trends toward low glucose levels. In contrast, the additional information provided by continuous monitoring may also result in information overload and actually increase fear of hypoglycemia.

Nevertheless, simply having increased knowledge and awareness of glucose levels does not guarantee children will act on this information. Despite the underlying assumption that increased knowledge influences behaviour, which subsequently influences metabolic control, research has demonstrated that this is an oversimplified assumption and the link between knowing something and doing something is an extremely complex personal process (Whittemore, 2000). Changing behaviour through education and increasing knowledge alone has been shown to be ineffective (Bloomgarden, Karmally, Metzer, Brothers, Nedheinas, Bookman et al., 1987; Kulzer, Hermanns, Reinecker, & Haak, 2007; Mazzuca, Moorman, Wheeler, Norton, Fineberg, Vinicor et al., 1986). However, behavioural strategies derived from
social learning theories (Bandura, 1986; Fishbein & Ajzen, 1975; Prochaska, 1979) have improved diabetes knowledge and self-reported behaviours such as glucose testing and medication use (Norris, Engelgau, & Narayan, 2001; Whittemore, 2000).

According to Social Cognitive Theory (SCT), an individual’s behaviour constantly interacts with internal personal characteristics such as cognition, affect, biological factors and the environment (1986). A major construct in this theory is self-efficacy, which states that change and maintenance behaviours are related to expectations about one’s ability to perform a particular behaviour and one’s expectations of the outcomes. An individual’s sense of self-efficacy is strengthened by four information sources: (1) vicarious experiences (role modeling), (2) performance accomplishment, (3) social persuasion, and (4) somatic and emotional states (Bandura, 1994; 1997). Vicarious experience is gained from seeing peer models master a particular behaviour and social persuasion strengthens people’s belief that they have what it takes to succeed. People also rely partly on their somatic and emotional states in judging their capabilities. They interpret their physical reactions as signs of performance (Bandura, 1994). However, for this study, the focus will be on performance accomplishments.

Performance accomplishments are derived from personally mastering certain tasks and may be achieved through the use of continuous glucose monitoring. Children in the school age years, between 6 and 12, begin to develop their sense of industry, as well as build upon their physical and social skills and further develop the ability of “doing things on their own” (Erikson, 1950). It is during this time that many children with T1D may be able to initiate some of their diabetes self-care tasks on their own (Anderson & Laffel, 1997). Further, the adolescent should also gradually assume more responsibility in terms of their own diabetes management (Silverstein et al., 2005). However, parents continue to play a significant role in the management
of diabetes care in younger children and adolescents, which may also influence the frequency and type of changes made to diabetes management aspects. Parents may continue to provide direction in terms of insulin administration, diet, and exercise in children with T1D and ultimately affect the ways in which children and adolescents make these changes. Pond et al. (1995) identified the significance of Erikson’s psychosocial stages of development for children with T1D. They concluded that the separation from parents caused by school is similar to the child’s growing ability to separate the self from others. In terms of psychosocial development, the child begins to recognize their ability to do more on their own during the stage of Industry versus Inferiority. This greater sense of independence can be used to help a child cope effectively with their chronic illness, but also to maintain some control and take part in their own self-care for diabetes management. In terms of adolescents, Karlsson, Arman, & Wikblad (2008) also draw upon Erikson’s stages of psychosocial development in terms of management of diabetes-related tasks for older children with T1D. They suggest that during adolescence, children begin the stage of Identity versus Role Confusion, which is a period where the childhood position of dependence begins to change into feelings of increased autonomy and self-reliance. During this time, parents play an important role in encouraging their child’s autonomy by allowing them to continue carrying out much of their own diabetes self-care, but at the same time they need to help adolescents manage their diabetes and make appropriate decisions about diabetes management and metabolic control through collaboration, rather than control.

In their review of health literacy research, the Agency for Healthcare Research and Quality (2010) described that the awareness of information related to health (health literacy) influences knowledge and accurate risk perception, which affects self-efficacy. Self-efficacy in turns influences behavioural intent resulting in uptake of health skills and behaviour. These
behaviours have potential effects on adherence of healthy behaviours, which ultimately influences health outcomes, including the reduction of risk factors, such as HbA1c. Glucose alarms, continuously updated glucose data, and short-term trend graphs on the continuous glucose monitor provide immediate feedback to the user on the effects of food, medications, physical activity, stress, and other variables on glucose control. The instantaneous feedback increases the likelihood that the participants will take action to correct glucoses that are above or below their target (Block, 2008). The increased glucose awareness can enhance diabetes management by illustrating increases and decreases in glucose levels as well as the duration of this effect following physical and dietary activities (Allen, Jacelon, & Chipkin, 2009). Since performance accomplishment or actually doing an intended behaviour enhances self-efficacy (Bandura, 1997), the continuous glucose monitor alerts, glucose values, and graphs can enhance self-efficacy for managing glucose levels with diet and physical activity behaviours (Allen et al., 2009). Seeing the continuous glucose monitoring data can reinforce a sense of performance accomplishment for diabetes management behaviours and help users to understand how diet and physical activity are interrelated with glucose levels. The visual feedback can allow children and adolescents to recognize how daily events are related to higher or lower glucose levels and make the need to alter insulin, physical and dietary behaviours real to them and increase the likelihood they will engage in these changes (Allen et al., 2009).

Interventions aimed at middle childhood (6-12 years of age) and adolescence (12-18 years of age) usually involve a much larger component directed to the child rather than the parent, than do interventions for younger children (Ievers-Landis & Witherspoon, 2009). Children in this middle age group are at the concrete-thinking stage of cognitive development and benefit from direct information and practice in performing healthy behaviours. Adolescents
begin to enter the formal operational stage of cognitive development and are able to use symbols related to abstract concepts and can begin to formulate hypothesis and to consider various possibilities and outcomes in terms of decision-making, in particular health decisions as well (O’Brien & Bush, 1997). Actions to prevent hypoglycemia may include decreasing insulin dose, changing the time insulin is given, increasing carbohydrate intake, and avoiding physical activity until glucose levels rise. To prevent hyperglycemia, children may increase insulin dose, change the time insulin is given, reduce carbohydrate intake, and engage in physical activity, thus reducing the likelihood of experiencing high glucose levels. Children can utilize the trend information and alarms to intervene and prevent glucose from dropping below or rising above the threshold (Block, 2008).

With increased and immediate information related to current and future (trend) glucose information provided by the continuous glucose monitor, children and adolescents can then act upon this knowledge to prevent a further trend towards hypo- or hyper-glycemia, thus avoiding the symptoms associated with these conditions. With a reduction in the frequency and time spent in hypo- or hyperglycemia, children and adolescents with T1D may experience a reduction in glucose excursion or variability, with fewer glucose fluctuations, and ultimately an improvement in metabolic control as shown by a reduction in HbA1c levels. Frequent hypoglycemic and hyperglycemic episodes can increase HbA1c levels in children with T1D as a result increase the risk for both long-term microvascular complications, including neuropathy, nephropathy, and retinopathy as well as macrovascular complications such as cardiovascular and coronary artery disease (DCCT, 1993; Epidemiology of Diabetes Interventions and Complications, 2005).
If continuous glucose monitoring can improve metabolic control, as demonstrated by a reduction in HbA1c, via any of the posited pathways, it may also reduce or limit the occurrence of short-term complications, including frequency and time spent in hypo- and/or hyper-glycemia, reduce fluctuations in blood glucose levels, reduce risk of long-term health complications, and use of health care resources. However, before an adequately powered trial on metabolic control outcomes is undertaken, a number of key questions must be answered. A description of the conceptual model for the CHILD pilot trial is described below (Figure 6.)

Figure 6. Conceptual Model for the CHILD Pilot Trial

As in the conceptual model for a larger trial, children and adolescents with T1D using continuous glucose monitoring were provided with 288 glucose measurements each day compared to three provided by self-monitoring of blood glucose alone. The increased information provided by the continuous glucose monitor may have positive or negative or no effects on the level of fear of hypoglycemia in children with T1D. Increased glucose awareness could help children reduce their fear because they have increased knowledge of glucose levels.
However, the added information could also result in information overload and alternatively increase levels of fear of hypoglycemia, or be perceived by the children as irrelevant. Providing children with T1D additional information related to glucose levels may allow for increased changes to be made to their diabetes regimen in terms of insulin administration, diet, and/or exercise. These changes may lead to decreased rates of glucose variability, including decreased levels of hypoglycemia and hyperglycemia, which ultimately leads to improved metabolic control overall, as indicated by decreased HbA1c levels.

This pilot study addressed the feasibility and acceptability of a larger trial, including an estimation of recruitment rates as well as assessment of compliance and satisfaction with allocated treatment. Research on the effectiveness of continuous glucose monitoring on metabolic control in children and adolescents with T1D using continuous subcutaneous insulin infusion has been limited. Therefore, a pilot clinical trial was designed to provide preliminary indicators of the feasibility and acceptability of continuous glucose monitoring on metabolic control and addressed the following objectives.

**Research Objectives**

The pilot RCT was carried out in order to address the following:

1. provide preliminary indicators of the effects of continuous glucose monitoring compared to self-monitoring of blood glucose alone on a) metabolic control and b) fear of hypoglycemia.

2. provide an estimate of recruitment rates

3. assess compliance with allocated treatment, and;

4. determine participants’ satisfaction with allocated treatment.
Research Questions

This pilot trial was not powered to answer the following research questions. The questions were designed to provide preliminary indicators which would inform the sample size calculation for the larger trial.

Primary Question

What is the effect of continuous glucose monitoring use by children and adolescents with T1D on metabolic control, as demonstrated by a reduction in HbA1c levels, at three months when compared with children and adolescents using self-monitoring of blood glucose alone?

Secondary Questions

1. What is the effect of continuous glucose monitoring compared to self-monitoring in children and adolescents with T1D on levels of fear of hypoglycemia?
2. What is the effect of continuous glucose monitoring compared to self-monitoring in children and adolescents with T1D on:
   (a) Frequency of severe hypoglycemia?
   (b) Frequency of diabetic ketoacidosis?
Chapter 4
Research Design and Methods

Study Design

A randomized, multi-site pilot trial of continuous subcutaneous insulin infusion with continuous glucose monitoring versus self-monitoring of blood glucose was carried out at pediatric diabetes centres in Whitby, ON and Barrie, ON. Outcomes of continuous glucose monitoring, the intervention in this study, were compared with those of usual care.

Study Sample

Inclusion Criteria

1. Children aged 6-18 years;
2. T1D for greater than one year;
3. Willing to perform at least three self-monitoring blood glucose tests per day;
4. Has been using continuous subcutaneous insulin infusion for more than one month, and;
5. English speaking.

Exclusion Criteria

1. Presence of celiac disease, which can cause malabsorption of nutrients affecting metabolic control and increasing the frequency of hypoglycemia;
2. Use of corticosteroids that have systemic effects and are known to affect glucose levels;
3. Currently using continuous glucose monitoring, and;
4. Cognitively unable to self-manage, based on parent’s and/or care provider’s opinion.
Recruitment and Eligibility

The study was introduced to the clinicians, including the diabetes nurse educators, dietitians, social workers, and endocrinologists through presentations at the pediatric diabetes centres in Whitby, ON and Barrie, ON. Posters with information about the study were also placed on display in visible areas within each of the pediatric diabetes centres. In addition, an explanation of the study was mailed to eligible children and their families in advance of their upcoming clinic appointment.

Prior to clinic visits that occur every three months, a clinic staff member identified consecutive eligible patients by age (6-18 years) from clinic lists and an eligibility screening form (Appendix A) was completed by the staff member to assess their eligibility. When the criteria for enrolment were met (see above), a clinic staff member introduced the study using the Introduction to Prospective Participants Form (Appendix B). The clinic staff member then obtained verbal consent for the child and his or her family to listen to an explanation of the study by the PI. If the family agreed, the PI explained the study to the child and their family during this clinic visit, study information material was distributed, and time was provided to make their decision about participating in the study. There was also an option available for parents to go away and think about participation and return for a subsequent appointment if they chose to participate. Subsequently, written informed consent was obtained from the parents (Appendix C) and assent was sought from the child (Appendix D). All children and their families were informed about the potential uncertainties related to the benefits of continuous glucose monitoring for metabolic control improvement, and that they had an equal chance of being assigned to the experimental group or the usual care group.
Baseline Data Collection

Baseline data related to the child included: birth date, sex, race, and date of diabetes diagnosis. Baseline assessment of fear of hypoglycemia was obtained using the Children’s Hypoglycemia Index (CHI). Assessment of baseline metabolic control was measured with HbA1c, a measure of long-term blood glucose control over the previous three months at the pediatric diabetes centres.

Randomization

A colleague from the Lawrence S. Bloomberg Faculty of Nursing in the University of Toronto used a website (www.randomizer.org) to generate a list of group assignments which were then placed in sequentially numbered sealed opaque envelopes and centrally located at the Lawrence S. Bloomberg Faculty of Nursing in the University of Toronto. Participants were randomly assigned to one of two groups: (1) the experimental group, receiving the intervention under investigation (continuous glucose monitoring), and (2) the comparison or control group, receiving usual care (self-monitoring of blood glucose). While the group assignment could not be blinded due to the nature of the intervention, HbA1c level is an objective outcome measure which was used in both the experimental and control group, and both groups had the same glycemic goals. The goals for these children were: a preprandial (before-meal) glucose target of 4.0-10.0mmol/l (18-180mg/dL) and a bedtime target of 10mmol/l (180mg/dL), with an overall HbA1c target less than 8.0% for children aged 6-12 and 7.0% for adolescents between 13 and 18 years as outlined by the Canadian Diabetes Association Clinical Practice Guidelines (2008).

On the day of randomization, the PI completed the study Entry Form (Appendix E) with data retrieved from the participant and their health records kept at the pediatric diabetes centres and the participant completed the CHI. The PI assigned the participant identification code and
secondary identifier and telephoned the Lawrence S. Bloomberg Faculty of Nursing, University of Toronto to receive the group allocation, which could not be altered or reassigned. The PI then documented the group assignment on the Entry Form, prior to introducing the study condition to the participant.

**Interventions**

**Both Groups**

All children used continuous subcutaneous insulin infusion (either the MiniMed® Paradigm™ or MiniMed® Veo™) for administration of rapid-acting insulin and received usual care. Continuous subcutaneous insulin infusion requires the use of an insulin pump, which is a battery-operated device worn on a belt or inside a pocket that continuously delivers rapid-acting insulin subcutaneously through a cannula inserted into the abdomen. The pump automatically delivers insulin at a steady basal rate that is pre-programmed into the pump by the user and is delivered continuously over 24 hours. The basal rate is set to the minimum insulin needed to suppress gluconeogenesis and ketogenesis, while keeping blood glucose levels within the normal range without inducing hypoglycemia (Weintrob, Shalitin, & Phillip, 2004). A top-up of bolus (meal-time) insulin can be manually programmed into the pump. The boluses are calculated by an algorithm and depend on the caloric and nutritive composition of the meal, the blood glucose concentration before the meal, and the anticipated level of physical activity after the meal (Weintrob et al., 2004).

All standard medical care for diabetes management, including all clinical and laboratory assessments for child well being, were provided for both study groups. For both groups, as part of usual care, children were asked to test their blood glucose levels three times each day, which were recorded in their blood glucose meter. The children and their parent(s) then attended a
regularly-scheduled appointment three months after randomization, during which the child had his/her HbA1c measured, continuous glucose monitor and blood glucose meter downloaded to a computer, and completed the CHI. A brief review of self-monitoring of blood glucose levels was provided for each child, which took approximately 15 minutes. Accurate technique and appropriate test sites for checking blood glucose levels, as well as calibrating the blood glucose meter itself using the code provided on the test strip bottle were discussed.

**Continuous Glucose Monitoring (Experimental Group)**

Children allocated to the continuous glucose monitoring group and at least one parent attended an information appointment lasting approximately 30 minutes at the pediatric diabetes centre, in which they received the continuous glucose monitor and details regarding the use of the device. Specifically, information about the technical aspects of continuous glucose monitoring, such as sensor insertion, sensor settings and alarms, the interpretation and use of data in terms of trends and graphs created by the device and their use for adjustments to insulin dose, activity levels, diet, and/or medication were explained in detail. A guide to continuous glucose monitoring was also provided to each child and their parents/caregivers to take home with contact information included in case of questions. Children were then asked to engage in their normal everyday activities and to call the pediatric diabetes centre; if they had questions related to their continuous glucose monitor and/or experienced an adverse event. Children were asked to perform three self-monitoring of blood glucose checks using his/her glucometer for calibrating the continuous glucose monitor.
Children were provided with the MiniLink™ transmitter and Sof-sensors™, which provide up to 288 glucose measurements every 24 hours in real-time and were used to measure an average blood glucose level every five minutes for three days (Figure 7). A tiny glucose-sensor was inserted just beneath the skin of the abdomen and measured the level of glucose in the tissue every 10 seconds (A) and sent the information via a wireless transmitter to the continuous subcutaneous insulin infusion pump (B) attached to a belt or the waistline of the participants’ pants, where insulin was delivered through a cannula into the abdomen (C). The device also featured a low glucose alert threshold that could not be set below 5mmol/L (90mg/dL). This feature is intended to provide pediatric patients with additional warning time to react to potential hypoglycemia. While this feature is designed to provide an additional measure of safety, it also has the potential to create more frequent alerts. To help children manage alerts, a “snooze” feature is available, which allows children to silence low glucose alerts for up to one hour while children and their families get the blood glucose levels back in range (Medtronic, 2010). Alarms are designed to warn children of high glucose levels, indicating hyperglycemia and provide them with an opportunity to adjust insulin dose and/or dietary or physical activity changes to lower glucose levels into normal range.
The accuracy and efficacy of the MiniMed Paradigm REAL-Time CGM™ device has been evaluated in two studies. A retrospective analysis was carried out evaluating 60,050 paired sensor values taken during an outpatient ambulatory study investigating the efficacy of a sensor-augmented pump system in adults and adolescents (Mastrototaro, Shin, Marcus, & Sulur, 2008). Sensor accuracy and performance was evaluated using three different methods and determined in adolescent participants, 71.2% of the overall readings were within ±20% and 83.8% were within ±30% of comparative glucose readings. The highest rate of agreement between paired sensor and meter occurred in the 13-22mmol/L range, whereas 74.3% of the readings agreed within ±20% and 88.2% agreed within ±30%. Overall, this indicates good agreement between self-monitoring of blood glucose values and continuous glucose monitoring values. The mean absolute relative difference (MARD) for the adolescents was 18.0% and median absolute relative difference for children was 12.4%. The MARD measures the average difference between the sensor and the reference measurement provided by self-monitoring. The lower the MARD, the
more accurate the device is considered. A previous study by the Food and Drug Administration (2004) evaluating the MARD of the same continuous glucose monitor demonstrated a value of 19.4%, which is higher than the MARD of 18.0% obtained in Mastrototaro et al. study (2008). This shows improved accuracy of the continuous glucose monitor since the previous study was carried out. Lastly, the majority of blood glucose values fell within 20% of the reference sensor measurements and indicates good accuracy of the estimates of blood glucose values achieved by self-monitoring and CGM.

**Self-Monitoring of Blood Glucose (Control Group)**

Children allocated to the self-monitoring group were asked to continue to use self-monitoring of blood glucose levels, i.e. asked to test three times daily (before each meal) and to carry out a bedtime and 3:00am blood glucose reading if blood glucose levels had been unusually high and/or low throughout the day, which was consistent with usual care (Figure 8). Children were asked to engage in their normal everyday activities and to call the pediatric diabetes centre; if they had any questions related to the study and/or experienced an adverse event.
Primary Outcome

HbA1c

Data related to the primary outcome, metabolic control was collected at three months and was measured using glycosylated hemoglobin (hemoglobin A1c; HbA1c), a form of hemoglobin used to identify the average plasma glucose concentration over prolonged periods of time. This served as a marker for average blood glucose levels over the previous three months prior to the measurement and provides a long-term indicator of control over blood glucose levels. HbA1c was measured using the DCA 2000 clinical analyzer (Bayer). This point-of-care diabetes management instrument measures the concentration of HbA1c and the concentration of total hemoglobin and the ratio of the two is displayed as %HbA1c (John, 2003). The analyzer uses a method based on inhibition of latex agglutination and performs both HbA1c and microalbumin/creatinine tests. The analyzer has demonstrated good performance with many laboratory-based immunoassay instruments for the measurement of HbA1c and has been found...
to give reliable results (Greaves, Northfield, and Cameron, 2005). Specifically, John, Edwards, and Price (1994) demonstrated a within-batch coefficient of variation (CV) between 1.9-3.1% imprecision and a between-batch CV of 2.2% imprecision. In addition, the analyzer has been found to correlate well with agar electroendosmosis (r = 0.93), affinity chromatography (r = 0.97), high-performance liquid chromatography (HPLC) (r = 0.90) and Enzyme Immunoassay (EIA) (r = 0.98). In order for a commercial method or a laboratory to be considered certified by the National Committee of Clinical Laboratory Standards (NCCLS), the total imprecision must be below 4% (Little, 2003; NCCLS Standards, 1999).

In order to ensure accuracy of the device, a quality control check was run by a diabetes nurse educator at each clinic the week that participant samples were to be tested. If the control results were out-of-limits, the nurse educators were asked not to do the analysis until a control check was completed within acceptable limits. The sample was then re-done to ensure accuracy.

In order to obtain HbA1c levels, a blood sample was obtained by finger-stick at baseline and at the three month clinical visit and results were available in six minutes using the DCA2000. HbA1c values were recorded on the Outcomes Form (Appendix E).

Secondary Outcomes

Fear of Hypoglycemia

Fear of hypoglycemia was measured at baseline and again at three months. The PI administered the questionnaire at baseline and a diabetes nurse educator administered the questionnaire at the three month appointment. The PI provided an explanation of the instrument for each child. For children who were unable to complete the child self-report due to young age or difficulty reading, the PI administered the questionnaire to the child on an individual basis and
provided further explanation of the questions, if necessary (without prompting the child to answer in a certain way). The score for the instrument was recorded on the questionnaire.

Fear of hypoglycemia was evaluated using the Children’s Hypoglycemia Index (CHI), a newer scale to measure fear of hypoglycemia in children (Kamps, Roberts, & Varela, 2005). The CHI is a self-report instrument that measures fear of hypoglycemia in children with diabetes and consists of a situation, general fears, and a behavioural subscale. Items on the CHI assess general fears related to hypoglycemia and its consequences (eight items), fear related to specific situations in which hypoglycemia might occur (seven items), and specific behaviours designed to address hypoglycemia or avoid it out of fear for its consequences (nine items). The CHI contains 24 items and requires the child to respond on a five-point Likert scale the extent to which a given statement characterizes their actions and emotions surrounding hypoglycemia, ranging from 1 – not afraid, 2 – a little afraid, 3 – afraid, 4 – very afraid, and 5 – extremely afraid; or 1 – never, 2 – hardly ever, 3 – sometimes, 4 – most of the time, and 5 – all the time. Scores range between 25 and 125 and the higher the score indicating greater levels of fear.

Kamps et al. (2005) evaluated the psychometric properties of the CHI in 109 children (42 male and 67 female) diagnosed with T1D, ranging in age from 8 to 16 years with a mean age of 11.9 ± 2.3 years. Internal consistency was calculated using Cronbach’s alpha coefficient using scores from the first administration of the CHI. The alpha coefficient for the total subscale was 0.89. Test-retest reliability was assessed by calculating Pearson correlation coefficients for the CHI scores two weeks following camp. Two-week test-retest reliabilities were 0.76 for the Total scale. The authors also evaluated the stability of the instrument over time with a high test-retest reliability at a two-week interval. The validity of the CHI was evaluated using confirmatory factor analysis, which demonstrated excellent fit between actual and proposed factors. In
addition, the CHI was significantly correlated with other established measures of anxiety and fear of hypoglycemia in children. However, it should be noted that the Behaviour scale of the CHI was found not to be related to the frequency of severe hypoglycemic episodes. Kamps et al. (2005) proposed that children’s thoughts and feelings regarding diabetes may be more sensitive to change by severe hypoglycemic episodes compared to their diabetes management behaviour, which may be influenced more greatly by caregivers.

Construct validity of the CHI was examined using a maximum-likelihood confirmatory factor analysis on data collected prior to camp. It was intended to test the hypothesis that the CHI measures three independent factors indicating three separate constructs (general fears, situation, and behaviour). The Bentler-Bonnet non-normed fit index (NNFI) was used (Bentler, 1985) and indicated that this three-factor model was not rejected $\chi^2 (24) = 35.37, p < 0.05$. As well, the Bentler-Bonnet normed-fit index of 0.98 showed a good fit between the hypothesis and the data. The CHI demonstrated good convergent validity shown by significant correlation between the different subscales. The Situation subscale was positively correlated with the General Fears ($r=0.79, p < 0.01$) and Behaviour ($r=0.50, p < 0.01$) subscales. In turn, the Behaviour and General Fears subscales were positively correlated with each other ($r=0.47, p < 0.01$). The authors also evaluated criterion-related validity. Kamps et al. (2005) used the Revised Children’s Manifest Anxiety Scale (RCMAS) and the Children’s Hypoglycemic Fear Survey (CHFS) to examine the relationship between the CHI and other established measures of anxiety and fear. The RCMAS is a widely-used self-report measure that assesses anxiety levels in children and adolescents between the ages of 6 and 19 years (Reynolds & Richmond, 1997). To assess fear of hypoglycemia, the CHFS was used. This scale consists of 23 self-report items and measures worries that are related to hypoglycemia and behaviours associated with diabetes
management (Green et al., 1990). The CHI total score was positively correlated with the RCMAS total \((r = .25, p < .05)\), the CHFS Total \((r = .69, p < .01)\), the CHFS Worry \((r = .63, p < .01)\), and the CHFS Behaviour subscales \((r = .38, p < .01)\). Further, the CHI General Fears subscale was positively correlated with the RCMAS Total \((r = .27, p < .01)\), RCMAS Worry subscale \((r = .36, p < .01)\), and CHFS Worry subscale \((r = .59, p < .01)\). The CHI appears to demonstrate adequate psychometric properties and contains items that are derived from the literature and clinical practice with children and adolescents with diabetes (Kamps et al., 2005).

**Adverse Effects**

**Frequency of severe hypoglycemia.** Hypoglycemia is defined by the presence of a low blood glucose level of 4.0mmol/L(72mg/dL) for patients treated with insulin (CDA, 2008, 2013) and was classified as severe hypoglycemia when any hypoglycemic or suspected hypoglycemic event (when blood glucose measurement was not taken) required any assistance from another person to recover. This variable was further subcategorized to determine the frequency of severe hypoglycemic events that resulted in a seizure or coma. Children and their parents/caregivers were instructed to report severe hypoglycemic events within 24 hours of their occurrence to the diabetes nurse educator at the pediatric diabetes centres and these were recorded by the nurse educator on an Adverse Event Form.

In order to assess the frequency of severe hypoglycemia, continuous glucose monitor and blood glucose meter profiles (experimental group) and blood glucose meter profiles (control group) were reviewed at baseline and the conclusion of the study. For both the experimental group using continuous glucose monitoring and the control group, using self-monitoring of blood glucose alone, a software program (CareLink Pro by Medtronic) was used to generate an episode summary report, which provides a list of severe hypoglycemic events experienced by the
participant including the number of episodes as well as the preceding events leading up to the severe hypoglycemic episode (Medtronic, 2011). The frequency of severe hypoglycemia was recorded on an Outcomes Form (Appendix E) at the three month clinic visit.

**Frequency of severe hyperglycemia and diabetic ketoacidosis.** Diabetic ketoacidosis occurs in approximately 15% to 67% of children with newly diagnosed diabetes and at a rate of one to 10 episodes per 100 patient years in children who have established diabetes (Levy-Marchal, Patterson, & Green, 2001) and is the leading cause of morbidity and mortality in children with diabetes (Dahlquist & Kallen, 2005). Hyperglycemia was defined as a blood glucose level greater than 11mmol/L (198mg/dL) (CDA, 2013) and Diabetic Ketoacidosis was defined as an acidotic event that required an emergency department or hospital admission in which the arterial blood pH is <7.30 and the blood glucose level is greater than 14mmol/L (252mg/dL) (CDA, 2013). Children were instructed to perform ketone testing during periods of acute illness accompanied by elevated BG, when preprandial blood glucose levels remained greater than 14.0 mmol/L (252mg/dL) or in the presence of symptoms of DKA (CDA, 2013). Children and their parents/caregivers were instructed to report DKA episodes within 24 hours of their occurrence to the diabetes nurse educator at the pediatric diabetes centres as part of standard practice at the clinic. These events were recorded by the nurse educator on an Adverse Event Form each time the child and/or family notified the clinic of any DKA event.

In order to assess the frequency of DKA, continuous glucose monitor and blood glucose meter profiles (experimental group) and blood glucose meter profiles (control group) were reviewed at baseline and the conclusion of the study (Appendix E). For both the experimental group and the control group, a software program (CareLink Pro by Medtronic) was used to generate an episode summary report.
The report provided a list of the DKA episodes experienced by the participant including the number of episodes as well as the preceding events leading up to the DKA episodes (Medtronic, 2011). The frequency of DKA was recorded on an Outcomes Form (Appendix E) at the three month clinic visit.

**Frequency of skin reactions.** Skin reaction using continuous subcutaneous insulin infusion can include irritation, inflammation, scabbing, dry skin, changes in pigmentation, and potentially lipoatrophy (CDA, 2013). Participants experiencing any of these skin reactions were asked to report the incidence to the diabetes nurse educator at the pediatric diabetes centres and these were recorded on an Adverse Event Form. Participants were also asked to report the occurrence of any skin reactions requiring the discontinuation of the continuous glucose monitoring device within 24 hours of their occurrence, to the diabetes nurse educator at the pediatric diabetes centres and these were recorded on the Adverse Event Form. Infusion site problems as well as injection site reactions were assessed at the final clinic visit and the frequency of skin reactions were recorded on the Outcomes Form.

**Psychological distress.** Psychological distress as expressed by the child or the parents was also monitored. Any participants and their family members who experienced psychological distress were asked to report the incidence to the diabetes nurse educator at the pediatric diabetes centres and this was recorded on an Adverse Event Form.

**Frequency of illness.** As illness can affect glucose levels in children with T1D, participants were asked to report the occurrence of any episode of illness including colds, throat infections (strep throat/tonsillitis), ear infections, the flu, urinary tract infections, and any other illnesses on the Post-Study Questionnaire (Appendix E).
Monitoring Compliance

The child’s compliance with the allocated study group condition was verified by reviewing data on use of continuous glucose monitoring and self-monitoring per day and number of days per week, collected at the three month clinical appointment. The process of collecting compliance data were the same for both treatment groups and occurred at the conclusion of the study. For children in both the experimental group and the control group, the PI downloaded information related to the number of uses of continuous glucose monitoring and the number of self-monitoring of blood glucose checks from the Carelink program. Despite the recommended use of a written blood glucose log to document each self-monitoring of blood glucose level carried out, use of a logbook was not part of the protocol as it has been shown to be associated with problems of missing data and compliance issues, and it has been shown that a high percentage of entries are made retrospectively (Stone, Shiffman, Schwartz, Broderick & Hufford, 2003).

Compliance with the intervention (continuous glucose monitoring) was defined as use of the continuous glucose monitor for three days each week for the duration of the study. The manufacturer of the continuous glucose monitoring device recommends replacing the sensors every three days in order to reduce the likelihood of skin reactions (Medtronic, 2010). However, there is no clear indication whether a minimal frequency is required to achieve any improvements in metabolic control or anxiety that might be observed. In addition, children using the continuous glucose monitor were asked to perform three self-monitoring of blood glucose calibration checks each day for optimal glucose sensor accuracy (Medtronic, 2010). As long as children carried out a minimum of three blood glucose checks per day, for a period of three months, they were considered compliant with their assigned condition, as measured by computer
download of the insulin pump and blood glucose meter at the three month clinic visit. Children assigned to the self-monitoring group were asked to perform at least three blood glucose readings per day. As long as children carried out three blood glucose checks per day, for a period of three months, they were considered compliant with their assigned control condition, as measured by computer download of the blood glucose meter and insulin pump at the three month clinic visit. Once all of the data were collected, a note of appreciation and a gift card was provided to the participant to demonstrate the research team’s appreciation. All participants received a note of thanks and a gift card regardless of whether or not they provided complete data.

**Participant Satisfaction**

In order to assess participant satisfaction for the study, children completed the Post-Study Questionnaire for Children in the Continuous Glucose Monitoring Group or Post-Study Questionnaire for Children in the Self-Monitoring of Blood Glucose Group (Appendix E) at the three month clinic appointment. Both questionnaires included four forced-choice questions regarding satisfaction with study participation and preferences for future use. For those participants in the continuous glucose monitoring group, they were required to wear a continuous glucose monitor for a three month period. Thus, it was necessary to find out how children felt about using this technology during the study. Six questions about the experience of using continuous glucose monitoring were included in the Post-Study Questionnaire for Continuous glucose monitoring Group. These questions utilized Likert type scales, anchored with a low score of 0 if “not at all” and 5 if “very much so”. In addition, parents’ satisfaction was assessed using the Post-Study Questionnaire for Parents in the Continuous glucose monitoring Group or Post-Study Questionnaire for Parents in the Self-monitoring of Blood Glucose Group (Appendix E), which was completed immediately following the conclusion of the study. Both
questionnaires included a series of four forced-choice questions regarding satisfaction with study participation and preferences for future use. For parents of children in the continuous glucose monitoring group, six items assessing parents experiences with use of the continuous glucose monitoring device were included in the Post-Study Questionnaire for Continuous glucose monitoring Group. Again, all of these were Likert type scales, anchored with a low score of 0 if “not at all” and 5 if “very much so”.

**Contamination**

Children in the self-monitoring group did not attend the continuous glucose monitoring information appointment and did not have access to the verbal or written information provided during this appointment. In addition, children randomized to the self-monitoring group were asked not to initiate continuous glucose monitoring until the three month study period was over. Children in the continuous glucose monitoring group were not introduced to the specifics of the self-monitoring of blood glucose condition. Some children and their families may have been allocated to a group other than the one to which they had hoped and an item on the Post Study Questionnaire (Appendix E), administered at the three month clinic appointment, the conclusion of the study, provided data as to the extent to which such disappointments occurred.

**Co-Interventions**

In order to control for influences in relation to attention given to participants, the time spent and the frequency of contact between the participant and the staff at the diabetes clinics was designed to be consistent for both groups, although the content of the interaction may have been different depending on the child’s group assignment. Children in the experimental group may have received an additional 15 minutes of attention related to the 30 minute information appointment they had to attend related to use of the continuous glucose monitoring device.
Other than the information appointment for children in the continuous glucose monitoring group, all children who participated in the study were not required to attend any additional appointments to the pediatric diabetes centres in Whitby, ON or Barrie, ON.

**Losses to Follow Up**

In an effort to minimize loss to follow-up, a number of methods were used in this pilot RCT. First, children using the continuous glucose monitoring intervention were asked to use the device for a minimum of three days per week. However, children were permitted to use the device for a total of seven days. This increased the likelihood that children would continue to engage in daily continuous glucose monitoring for as long as they were in the study. Second, children and their families were provided with a telephone number, and encouraged to call the PI if difficulties arose with the assigned study condition or to contact clinical staff at the pediatric diabetes centres if difficulties occurred with the use of the continuous glucose monitor. Third, the questionnaires were completed at times when the PI was present. Fourth, measurement of HbA1c takes six minutes using the DCA2000 analyzer (Bayer) and is typically measured every three months for pediatric diabetes patients and took place at a regularly scheduled appointment, therefore few HbA1c data were missing. Lastly, the CHI required ten minutes or less to complete, thus data related to fear of hypoglycemia were not expected to be missing.

**Sample Size Justification**

The sustained lowering of HbA1c levels by 0.4-0.8% is clinically important and relevant (Ahern et al., 2002; Sulli & Shashaj, 2006). Results of the Diabetes Control and Complications Trial (DCCT) indicate that this degree of improvement in metabolic control, as evaluated by HbA1c levels, can result in a 30-40% reduction in the risk for development and progression of diabetic retinopathy (DCCT, 1995) and a 21-49% decreased risk of microvascular complications,
including nephropathy and neuropathy (DCCT, 1996; Rohlfing, Wiedmeyer, Little, England, Tennill, & Goldstein, 2002). A sample size of 40 (in a two-group design) had greater than 99% power to detect a mean difference of 0.8 in HbA1c levels with a maximum standard deviation of 0.4 in HbA1c, or a 56% power to detect a mean difference of 0.4 with a standard deviation of 0.8 in HbA1c (Table 7).

Table 7.

Power Calculation for RCT

<table>
<thead>
<tr>
<th>If the standard deviation of differences between groups is:</th>
<th>Power to detect a difference of 0.8% in HbA1c</th>
<th>Power to detect a difference of 0.4% in HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>1.000</td>
<td>.986</td>
</tr>
<tr>
<td>0.5</td>
<td>1.000</td>
<td>.923</td>
</tr>
<tr>
<td>0.6</td>
<td>.999</td>
<td>.807</td>
</tr>
<tr>
<td>0.7</td>
<td>.996</td>
<td>.676</td>
</tr>
<tr>
<td>0.8</td>
<td>.986</td>
<td>.556</td>
</tr>
</tbody>
</table>

The aim was to enrol 46 children, to allow for 15% loss to follow-up. Initially, the plan was for a single site study. At the outset of the study, the initial study site followed approximately 110 children under the age of 18 using continuous subcutaneous insulin infusion, and an additional 3-4 children were started on various types of continuous subcutaneous insulin infusion per month. When recruitment was slower than anticipated, a second Ontario site was recruited. The second centre followed approximately 55 children between the ages of 1 and 18 years using continuous subcutaneous insulin infusion, with another 1-2 children started on various types of continuous subcutaneous insulin infusion per month.
Data Management

Data were collected prior to randomization (baseline) and again at three months. The timing of data collection coincided with regularly scheduled clinic visits, which occur every three months, when metabolic control is typically evaluated for standard diabetes care, using an HbA1c measure. Linking metabolic control and impact of disease assessments to planned follow-up visits was intended to help improve patient compliance and decrease the number of missing data forms and questionnaires.

In order to ensure that children were eligible for the study and that duplicate study numbers were not used, the PI verified inclusion and exclusion criteria as well as generated unique patient identification numbers. A visual aid (a thermometer) was placed in the waiting rooms in both pediatric centres and was used to represent the current number of participants enrolled in the study as well as providing a track record of the number of participants needed to achieve the desired sample size.

A file folder was created for each child enrolled in the study to store the data entry form and participant questionnaires prior to data being entered into Microsoft ACCESS © and was kept in a locked filing cabinet at each study site. A second file folder was also created containing participant contact data as well as consent and assent forms for each child enrolled in the study (Appendix E). This form was used to keep track of which data forms and questionnaires had been completed and picked up from the research sites. Alternative contact information for all children included in the study (another relative phone number and address) was also recorded on the Patient Contact Sheet in case the child moved and follow up was required. This identifying information was kept in the patient file and held separate from the data kept at the data collection sites. This file ensured that enrolment confirmation was achieved and that children were not lost.
to follow-up in the event the family moved. This folder was kept in a separate locked filing cabinet at the study site and was only accessible to the PI. All paper data forms and questionnaires were collected by the PI from the study sites. The date the form was completed was recorded on each page of all forms in order to keep track of what data had been received and to identify which data were not available. This allowed for a record of overdue data but ensured that the study sites were not bothered about data that would not be available.

Data collected by the insulin pump and continuous glucose monitoring device itself were collected and downloaded to the computer prior to any re-programming of these devices, which included changes to insulin dose and/or regime. The data were also downloaded to the computer following any changes made to help ensure minimal loss of data collected by the pump and continuous glucose monitor, as part of usual care provided to children attending the pediatric diabetes clinics.

**Data Entry**

All data were entered into Microsoft Office ACCESS ©. Queries were made to check for logic problems. An ACCESS © form was developed to track which forms had been received from the research site. The patient identification number, enrolment date, and the child’s date of birth were included on the form to ensure data were entered about the correct patient. Checkboxes were used to identify which forms were received. These forms were updated as they were received from the research site. In an effort to prevent missing data forms, a calendar was kept in Microsoft Outlook with reminders to send email messages to the research sites to ensure missing data forms were submitted as soon as possible. Keeping track of unobtainable data in the ACCESS © form prevented the research sites from being bothered about data that would not be available.
Paper data forms, including entry, clinic visit, and adverse event form were developed to document data obtained at each clinic visit or reported to the research site. A form to collect the data was developed in ACCESS © to resemble the paper form used at the research sites. This helped to ensure familiarity with the forms to avoid errors during data entry. All data for one participant could be viewed at a time in the ACCESS © database, thus helping to avoid entering data on the wrong line. Several ACCESS © tables were used to hold data from the different forms used to collect data at baseline and from the clinic visit at three months. A unique identification number in each table was used so that the tables could be linked together when queries for logic and range checks were used to check data entered into the databases.

Data Safety

In an effort to protect data, all paper forms and questionnaires were kept in a locked filing cabinet within a locked office space. As well, the computer where data were entered for the study into the ACCESS © database was also placed in a locked office space. As data were entered it was saved on the computer’s hard-drive, as well as stored on a USB and stored in another locked location. In order to ensure data on the forms and databases could not be changed except by the individual entering the data, the ACCESS © databases were locked.

Data Analyses

Data were entered into Microsoft ACCESS © and analyzed using an intent-to-treat model (Lachin, 2008) with SAS (version 9.4; Cary, NC). Baseline characteristics, including demographic variables were presented as frequencies, means, and medians. The primary outcome, HbA1c levels, and secondary outcome, fear of hypoglycemia, were tested using a two-sample t test of the mean differences between pretest and posttest. Frequency comparisons of all other outcomes, including episodes of severe hypoglycemia, DKA, and psychological distress, as
well as adverse skin reactions, and illness were made using $\chi^2$ test. Results were expressed as means +/- standard deviations (SD), with a significance level of 0.05, unless otherwise indicated. Feasibility issues, including retention, withdrawal, and refusal rates, as well as the number of losses to follow-up were monitored and reported as frequencies and percents. Feasibility and acceptability questions were developed to prepare for an adequately powered trial. Data from this pilot study provided insight into how practical the use of continuous glucose monitoring is to the child and their family and offers justification for a larger trial in the future. The following acceptability parameters were set to determine whether a larger trial is warranted (Table 8).

Table 8.
Acceptability Parameters for a Larger Trial

<table>
<thead>
<tr>
<th>Acceptability Parameter</th>
<th>Predefined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of eligible children/families agree to participate</td>
<td>50%</td>
</tr>
<tr>
<td>Monthly recruitment rate</td>
<td>1/week$^a$</td>
</tr>
<tr>
<td>Total amount of time to train participants in continuous glucose monitoring</td>
<td>30 minutes (information session)</td>
</tr>
<tr>
<td>Total number of children that used continuous glucose monitoring three times per week</td>
<td>&gt;75%</td>
</tr>
<tr>
<td>Total number of children that performed 3 self-monitoring checks per day</td>
<td>&gt;75%</td>
</tr>
<tr>
<td>Percentage of children who would choose to participate in the larger trial</td>
<td>80%</td>
</tr>
<tr>
<td>Percentage of children in the experimental group who would use the intervention again in the future</td>
<td>&gt;75%</td>
</tr>
</tbody>
</table>

Note. $^a$ one/week at a small diabetes centre would allow recruitment of several hundred children per year with multiple sites
Ethical Considerations

Prior to beginning the study, ethics approval was obtained from the Human Subjects Review Committee at the University of Toronto. In addition, the pediatric diabetes centre in Barrie, ON had their own Research Ethics Board and prior to beginning the study at this research site, ethics approval was obtained from this board. Children and their families were informed of the study during a regularly scheduled visit to the pediatric diabetes centres and were invited to participate if eligible. Informed assent was sought from all children and signed informed consent was sought from all parents of eligible participants. Participants and their families received verbal and written explanations of the study, including potential risks and benefits, and a copy of the consent. The children and their families were informed that they may withdraw from the study at any time without penalty to themselves. All participant data were kept confidential, with each child being assigned a unique identifying code and only group data were reported. All data were kept in secure locked filing cabinets, including paper forms and the computer holding the data entry tables and only accessible by study staff. Self-monitoring of blood glucose was required during the study for both the control and experimental group in order to calibrate the sensor. This was done because the effectiveness of continuous glucose monitoring in improving overall metabolic control has not been confirmed. Any changes to insulin, including timing and dose, as well as any alterations in diet were based on continuous glucose monitor readings, however, at least three self-monitoring readings were also required to ensure accuracy of the continuous glucose monitor. Insulin dose changes were instituted by the diabetes nurse educators and/or the endocrinologists as clinically indicated. Therefore, participants were not at any additional health risk as a result of study participation. Any child exhibiting evidence of severe hypoglycemia and/or DKA during the study was required to notify the PI and/or diabetes
nurse educators at the pediatric diabetes centres. Severe hypoglycemia was defined as any hypoglycemic or suspected hypoglycemic event (when blood glucose measurement was not taken) requiring any assistance from another person to recover and DKA was defined as an acidotic event that required an emergency department or hospital admission in which the arterial blood pH was <7.30.

The trial protocol was registered at ClinicalTrials.gov, identifier number NCT02137031.
Chapter 5

Results

The following chapter provides a review of the study results related to the derivation of the sample, including randomization, attrition, and compliance of participants, a description of the sample according to demographic characteristics obtained at baseline, and the primary and secondary research questions.

The Sample

Recruitment

A total of 485 children were assessed by the staff at two pediatric diabetes centres. Figure 9 provides the flow diagram for the trial. The majority of the children (402 of the 485) were ineligible for the study because they were not currently using an insulin pump (n=326) or were using an incompatible insulin pump for use with a Medtronic continuous glucose monitoring system (n=76). An additional 37 children declined to participate, and a further six were found not to be eligible for the following reasons: celiac disease (n = 4), the current use of CGM (n = 1), and a learning disability which made the use of CGM difficult (n = 1).
Figure 9. Flow Diagram

Assessed for eligibility (n = 485)

402 ineligible
  Not using CSII (n = 326)
  Using incompatible CSII (n = 76)

Declined to participate (n = 37)
  Did not meet inclusion criteria (n= 6)
  Celiac disease (n = 4)
  Using CGM (n = 1)
  Learning disability (n = 1)

Eligible (n = 83)

Declined to participate (n = 37)
  Did not meet inclusion criteria (n= 6)
  Celiac disease (n = 4)
  Using CGM (n = 1)
  Learning disability (n = 1)

Baseline

Completed demographic baseline questionnaire, Fear of Hypoglycemia questionnaire

Randomized (n = 40)

Usual Care Group (n = 16)

Experimental Group (n = 24)

Lost to Follow Up (n = 1)
  Did not attend follow up despite multiple contact attempts

Follow Up (n = 15)

Follow Up at 3 Months

Follow Up (n = 23)

Withdrew from study (n = 1)
  Due to other health problems
  Discontinued intervention (n = 2)
  Skin Reaction; CGM (n = 1)
  DKA; no CGM (n = 1)

Analyzed (n = 15)

Analysis

Analyzed (n = 23)

Reasons for declining
  Did not want a second site (n = 16)
  Too busy (n = 5)
  Other health problems (n = 4)
  Competitive athlete (n = 3)
  Struggling on pump (n = 2)
  Felt child was too young (n = 2)
  Not interested (n = 2)
  Felt they were too thin (n = 1)
  Seen by TeleNurse (n = 1)
  Felt they did not need CGM (n = 1)
Randomization

Of the 83 children determined to be eligible by study personnel, 48% (n = 40) agreed to participate, gave consent, and were randomized. Twenty-four children were randomly assigned to the continuous glucose monitoring group and 16 were randomly assigned to the self-monitoring group.

Attrition

Prior to beginning treatment, one child in the experimental group declined to participate due to other health problems and withdrew from the study and one child in the usual care group did not attend the three month follow up appointment. Therefore, no primary outcome data were available for either participant. In addition, two children in the experimental group experienced health difficulties during the study and discontinued use of the continuous glucose monitor temporarily at first and then permanently. One of the participants discontinued using the device permanently after 30 days of use and the second participant after 43 days of use.

Compliance

Compliance in the continuous glucose monitoring group was defined as use of the continuous glucose monitor for three days each week and performing three self-monitoring checks each day for the 12 week duration of the study to ensure accuracy of the continuous glucose device. For the self-monitoring group, participants were considered to be compliant when they performed at least three blood glucose readings per day each week, for a period of three months. For the continuous monitoring group, only nine (39.1%) participants used the device for three days per week for the entire 12 week study duration. Of these nine participants, three were compliant with self-monitoring for the study duration as well. Fifteen participants (65%) in the continuous glucose monitoring group completed 12 weeks of continuous glucose
monitoring use. Use of the device declined over the course of the study from 21 participants (91.3%) utilizing continuous glucose monitoring at any time in the first week to 15 (65.2%) uses at any time in the final week of the study (Table 9). Five children notified the PI that they were experiencing issues using the continuous glucose monitor and indicated they were not compliant with wearing the device for various reasons. The other nine participants did not notify the PI of any problems with the monitor and upon review of the continuous glucose monitoring report at the conclusion of the study were found to be non-compliant use as outlined in the study protocol. Reasons for non-compliance are listed in Table 10.

Table 9.

Participants Using Continuous Glucose Monitoring by Week of Study

<table>
<thead>
<tr>
<th>Week</th>
<th>Number of Participants Using Continuous Glucose Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
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<td>5</td>
<td>20</td>
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<td>6</td>
<td>20</td>
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<td>7</td>
<td>18</td>
</tr>
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<td>8</td>
<td>17</td>
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<td>9</td>
<td>17</td>
</tr>
<tr>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>12</td>
<td>15</td>
</tr>
</tbody>
</table>
Table 10.

Reasons for Non-Compliance with Continuous Glucose Monitoring System Use

<table>
<thead>
<tr>
<th>Reason for Non-Compliance</th>
<th>Number of Non-Compliant Participants (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participating in sports and felt it was interfering with sporting activity</td>
<td>n = 2</td>
</tr>
<tr>
<td>Experienced health difficulties during the study</td>
<td></td>
</tr>
<tr>
<td>Severe skin reaction</td>
<td>n = 1</td>
</tr>
<tr>
<td>DKA episode (not wearing CGM at the time of occurrence)</td>
<td>n = 1</td>
</tr>
<tr>
<td>Experiencing technical difficulties with the CGM device</td>
<td>n = 1</td>
</tr>
<tr>
<td>No reason given</td>
<td>n = 9</td>
</tr>
</tbody>
</table>

Only five participants (22%) in the continuous glucose monitoring group and two in the self-monitoring group (13%) were compliant with self-monitoring for the entire 12 week duration of the study (Table 11).

Table 11.

Compliance with Glucose Monitoring During the Study

<table>
<thead>
<tr>
<th></th>
<th>Continuous Glucose Monitoring Group (n=23) No. (%)</th>
<th>Self-Monitoring Group (n=15) No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number who wore continuous glucose monitoring for three days each week for 12 weeks</td>
<td>9 (39.1)</td>
<td>N/A</td>
</tr>
<tr>
<td>Number who performed at least three self-monitoring glucose checks per day each week for 12 weeks</td>
<td>5 (21.7)</td>
<td>2 (13.3)</td>
</tr>
</tbody>
</table>
Baseline Characteristics

Baseline characteristics of both study groups are outlined in Table 12. Participants ranged in age from 7 to 18 years, with a mean of $14.0 \pm 3.2$ years. Duration of diabetes ranged from 1 to 15 years, with a mean duration of $6.4$ years (SD $3.1$) and a median duration of $6.0$ years. Mean baseline HbA1c for both groups was $8.70 \pm 1.10\%$ (range $6.90\%$ to $11.50\%$). The majority of the sample was Caucasian, which was representative of the population from which the sample was drawn. Two-thirds of the sample were males and adolescents between the ages of 13 and 18. Fear of hypoglycemia scores at baseline ranged from 27 to 72 with a mean of $48.0 \pm 12.6$. Participants in both groups reported similar Fear of Hypoglycemia scores at baseline.

Table 12.

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Continuous Glucose Monitoring Group (n = 24)</th>
<th>Self-Monitoring Group (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-12</td>
<td>$14.6 \pm 3.1$</td>
<td>$13.1 \pm 3.3$</td>
</tr>
<tr>
<td>13-18</td>
<td>$6 \ (25.0)$</td>
<td>$7 \ (43.8)$</td>
</tr>
<tr>
<td></td>
<td>$18 \ (75.0)$</td>
<td>$9 \ (56.3)$</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>$22 \ (95.7)$</td>
<td>$13 \ (76.5)$</td>
</tr>
<tr>
<td>South Asian</td>
<td>$0$</td>
<td>$1 \ (5.9)$</td>
</tr>
<tr>
<td>More than one</td>
<td>$1 \ (4.3)$</td>
<td>$3 \ (17.6)$</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>$15 \ (62.5)$</td>
<td>$12 \ (75.0)$</td>
</tr>
<tr>
<td>Female</td>
<td>$9 \ (37.5)$</td>
<td>$4 \ (25.0)$</td>
</tr>
<tr>
<td>Duration of Diabetes (years)</td>
<td>$7.03 \pm 3.54$</td>
<td>$5.54 \pm 2.16$</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>$8.71 \pm 1.22$</td>
<td>$8.68 \pm 0.94$</td>
</tr>
<tr>
<td>Fear of Hypoglycemia</td>
<td>$48.0 \pm 12.3$</td>
<td>$47.8 \pm 13.4$</td>
</tr>
</tbody>
</table>

Note. Percentages may not total 100 due to rounding
Research Questions

Primary Research Question

Mean changes in HbA1c levels. Table 13 presents results for the primary outcome.

There was no statistically significant difference between groups in changes in mean HbA1c.

Table 13.

Comparison of Mean Changes in HbA1c from Baseline to End of Intervention Period

<table>
<thead>
<tr>
<th></th>
<th>Continuous Glucose Monitoring Group</th>
<th>Self-Monitoring Group</th>
<th>Between-Treatment Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 23</td>
<td>n = 15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>[95% CI]</td>
</tr>
<tr>
<td><strong>HbA1c Baseline</strong></td>
<td>8.71 ± 1.22</td>
<td>8.68 ± 0.94</td>
<td></td>
</tr>
<tr>
<td><strong>HbA1c At 12 Weeks</strong></td>
<td>8.39 ± 0.60</td>
<td>8.59 ± 0.80</td>
<td></td>
</tr>
</tbody>
</table>

According to the 2008 Canadian Diabetes Association Clinical Practice Guidelines

children between the ages of six and 12 should have HbA1c targets less than 8.0% and for

adolescents between the ages of 13 and 18, HbA1c values should be less than 7.0%. In 2013, the

Canadian Diabetes Association updated their Clinical Practice Guidelines and recommended
lower HbA1c levels for children between 6 and 12 years old, changing from HbA1c levels less than 8.0% to less than 7.5% in 2013. Recommended HbA1c values for adolescents (13-18 years old) remained the same. Table 14 summarizes the numbers of participants who achieved target HbA1c levels by the end of the study according to Clinical Practice Guidelines produced in 2008 and updated in 2013. Very few participants (n = 4) achieved targeted levels by study conclusion, according to either set of guidelines.

Table 14.

Number of Participants Achieving Target HbA1c Levels According to Canadian Diabetes Association Clinical Practice Guidelines (2008, 2013)

<table>
<thead>
<tr>
<th></th>
<th>Continuous Glucose Monitoring Group (n=23) No. (%)</th>
<th>Self-Monitoring Group (n = 15) No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achieved Final HbA1c Target (2008)</td>
<td>1 (4.3)</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>Achieved Final HbA1c Target (2013)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Secondary Research Questions

**Fear of hypoglycemia.** There was a statistically significant difference between groups, favouring the continuous glucose monitoring group, in changes in mean Children’s Fear of Hypoglycemia scores as measured using the Children’s Hypoglycemia Index (CHI) (Table 15).
Table 15.

Comparison of Mean Changes in Fear of Hypoglycemia Scores from Baseline to End of Study

<table>
<thead>
<tr>
<th></th>
<th>Continuous Glucose Monitoring Group n = 22 Mean (SD)</th>
<th>Self-Monitoring Group n = 15 Mean (SD)</th>
<th>Between-Treatment Group Difference [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear of Hypoglycemia Score Baseline</td>
<td>48.0 ± 12.33</td>
<td>47.8 ± 13.41</td>
<td></td>
</tr>
<tr>
<td>Fear of Hypoglycemia Score At 12 Weeks</td>
<td>42.4 ± 11.97</td>
<td>51.8 ± 19.34</td>
<td></td>
</tr>
<tr>
<td>Change in Mean Fear of Hypoglycemia Scores</td>
<td>-5.00 ± 6.89</td>
<td>3.13 ± 10.49</td>
<td>8.13 [-13.92, -2.34]</td>
</tr>
</tbody>
</table>

**Adverse Effects**

**Frequency of severe hypoglycemia.** There were no episodes of severe hypoglycemia reported by any participant in either of the two treatment groups.

**Frequency of severe hypoglycemia and diabetic ketoacidosis.** One participant reported a single episode of DKA in the continuous glucose monitoring group in week eight of the study. The participant was not wearing the continuous glucose monitoring device prior to or during this episode. As per usual care and the study protocol, the participant performed self-monitoring of blood glucose, tested for ketones, and spoke to a clinician at the Charles H. Best Centre. The participant was advised to go to the Emergency Department. The mother reported the episode of DKA to the clinic within the 24 hour period and an Adverse Event Form was submitted.
completed by a clinic staff. The PI was notified of the event and the Human Subjects Review Committee at the University of Toronto was also notified.

**Frequency of skin reactions.** Fifteen participants reported skin reactions at the conclusion of the study, 14 (61%) from the continuous glucose monitoring group and one from self-monitoring group (7%). The majority of skin reactions were minor in nature and consisted of irritation from the adhesive tape used to hold the insulin infusion cannula and continuous glucose monitoring cannula in place or rash/bumpy skin/chafing and/or dry skin. There was one major skin reaction reported by a participant in the continuous glucose monitoring group and it occurred at the continuous glucose monitoring site and resulted in a localized skin infection. The participant was advised on how to treat the infection and it resolved following treatment. The participant discontinued continuous glucose monitoring temporarily.

**Psychological distress.** No episodes of psychological distress were reported by any participant in either group.

**Frequency of illness.** Fourteen children reported an episode of illness. Five children from the self-monitoring group reported at least one episode of illness, one of these participants reported two episodes during the study period. The remaining nine children from the continuous glucose monitoring group reported at least one episode of illness, with four of the children reporting more than two episodes of illness during the study. The illnesses ranged from cold with cough, throat infection, dehydration, urinary tract infection, and influenza. A single participant reported five episodes of dehydration and another participant reported two episodes of urinary tract infection.
Other Outcomes Related to Study Objectives

Measuring the Primary Outcome at 3 Months

Thirty eight (95%) of the 40 children randomized for the study completed 12 weeks of study participation. One participant in the continuous glucose monitoring group withdrew from the study after randomization and prior to starting treatment and therefore did not provide primary outcome data. One participant in the self-monitoring group did not attend the three month follow up appointment at the conclusion of the study and did not have his HbA1c measured at the conclusion of the study.

Estimate of Recruitment Rates

Centre recruitment. Initially, the CHILD Study was carried out at a single pediatric diabetes centre. The full sample size was estimated to take approximately 12 months to recruit with approximately three to four children randomized per month. However, less than a quarter of the sample (n = 8) had been recruited after a seven month period. As a result, four additional pediatric diabetes centres were contacted and invited to take part in the study as a recruitment site, with one site agreeing to participate.

Estimated and actual recruitment rate. Recruitment of 40 participants took 16 months. The first pediatric diabetes centre met their monthly recruitment goal of randomizing participants to the study for three of the 16 months. The second pediatric diabetes centre met their monthly recruitment goal of randomizing one to two children per month for each of the five months during which it recruited participants. A graph of cumulative recruitment is shown in Figure 10.
Figure 10. Recruitment of Study Participants

**Participant Satisfaction**

**Participant likes and dislikes.** At the three month follow up appointment, participants were asked their opinions about their satisfaction and experiences in the CHILD study on a Post-Study Questionnaire. They were asked to respond and mark all that apply to four forced-choice questions related to what they liked and disliked about being in the study, whether or not they would choose to be in the study again, and what they would prefer to use for glucose monitoring in the future. Thirty seven of the 40 children (92.5%) completed the Post-Study Questionnaire at their three month follow up appointment. One child in the self-monitoring group did not attend the three month follow up appointment and did not complete the questionnaire, despite several attempts at follow up with the child/adolescent and their family by mail and with phone calls. One participant from the continuous glucose monitoring group withdrew from the study prior to initiating treatment and therefore did not complete the post-study questionnaire and one
participant attended the final appointment and completed her HbA1c and pump download, but did not complete the Post-Study Questionnaire.

The aspect that was most commonly identified by participants in both groups that they liked about taking part in the study was meetings with research staff (Principal Investigator, PI) at the pediatric diabetes centres, n = 16 (43.2%) and being put into the group that they wanted, n = 15 (40.5%). Four participants (two in each group) responded that they liked nothing about the study (10.8%). Just over half of the children in both groups (51.4%; n = 19) responded that there was nothing they disliked about the study, with 80% of respondents in the self-monitoring group reporting this and 31.8% in the continuous glucose monitoring group choosing this response. Table 16 provides an outline of children’s responses evaluating their experiences during the CHILD trial.
Table 16.

Children’s Evaluations of Their Experiences During the Study

<table>
<thead>
<tr>
<th>Likes about participating in the trial:</th>
<th>Continuous Glucose Monitoring Group (n=22) No. (%)</th>
<th>Self-Monitoring Group (n=15) No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meetings with research staff</td>
<td>12 (54.5)</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Randomized to group wanted</td>
<td>11 (50.0)</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Being in study helped feel less afraid</td>
<td>6 (27.2)</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Nothing extra they had to do</td>
<td>4 (18.2)</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>Helped to answer important research questions</td>
<td>7 (31.8)</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Liked nothing</td>
<td>2 (9.1)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Other likes*</td>
<td>6 (27.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dislikes about participating in the trial:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meetings with research staff</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Not randomized to group wanted</td>
<td>1 (4.5)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Being in study made me feel more afraid</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Extra things they had to do</td>
<td>4 (18.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Disliked nothing</td>
<td>7 (31.8)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>Other dislikes**</td>
<td>11 (50.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Participate in the study again:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definitely yes</td>
<td>9 (40.9)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Probably yes</td>
<td>8 (36.4)</td>
<td>8 (53.5)</td>
</tr>
<tr>
<td>Definitely not</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Probably not</td>
<td>3 (13.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Not sure</td>
<td>2 (9.1)</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Future preferences for blood glucose monitoring:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGM</td>
<td>14 (63.6)</td>
<td>7 (46.7)</td>
</tr>
<tr>
<td>SMBG</td>
<td>8 (36.4)</td>
<td>8 (53.5)</td>
</tr>
</tbody>
</table>

Note. Percentages may not total 100 due to rounding

*Other likes included: trying new things (n=1), being great for monitoring sports (n=1), decreased A1c (n=1), being easier, being able to check glucose levels anytime (n=1), and that constant monitoring and access to trends got them to check blood sugars more (n=1)

**Other dislikes included: the sensor falling out (n=1), hard to get used to the sensor (n=1), technical problems with the sensor (n=1), the sensor beeping at night (n=1), disliking putting the sensor in (n=5), and disliking the big or long needle (n=2)
**Children’s ratings of continuous glucose monitoring.** Participants in the continuous glucose monitoring group were asked about their experience of using the Continuous glucose monitoring device during the study on their Post-Study Questionnaire. Children were asked to rate their use of the device in six different areas on a Likert Scale of zero to five, with zero representing “not at all” and five indicating “very much so”. Overall, participants indicated a positive experience with the continuous glucose monitoring device. Most of the children chose Likert values of 0 or 1 for the statements that the continuous glucose monitor did not cause them to worry (n = 15; 68.2%) and just over half reported that it did not interfere with their activities (n = 12; 54.5%). Fourteen participants (63.6%) reported Likert scores of two or three with regards to the level of discomfort that the continuous glucose monitor caused them, indicating a moderate level of discomfort with the machine. The majority of the children (n = 19; 86.4%) chose scores of four or five on the Likert scale, indicating that instructions about the device were easy or very easy to follow.

**Future preferences for participant use of glucose monitoring.** Participants were asked to respond to a question about their preferences for glucose monitoring at the three month follow up appointment. Fifty seven percent of participants (n = 21) responded that they would prefer continuous glucose monitoring if they had a future choice. Of these, seven (33.3%) were in the self-monitoring group and 14 were in the continuous glucose monitoring group (Table 19).

**Participants’ willingness to take part in the CHILD pilot trial again.** The Post-Study Questionnaire also asked participants to indicate whether they would choose to take part in the CHILD study again if they could make the decision for a second time (Table 19). Choices on the questionnaire ranged from Definitely Yes to Not Sure. The majority of participants (n = 27 - 17 from the experimental group and 10 from the control group; 73.0%) indicated that they would
“definitely” or “probably” say yes to taking part in the study again. No participants indicated that they would “definitely not” take part in the study again.

Parent/Caregiver Satisfaction

Parent/Caregiver likes and dislikes. At the three month follow up appointment, the parents and/or caregivers were also asked their opinions about the level of satisfaction and experiences of their child taking part in the study. They were asked to respond and mark all that apply to the same four forced-choice questions related to their likes and dislikes about the study. Thirty five of the 40 parents/caregivers (87.5%) completed the Post-Study Questionnaire at their three month follow up appointment. Similar to the child responses, the aspect that was most commonly identified by parents and caregivers in both groups that they liked most about taking part in the study was meetings with research staff (PI) at the pediatric diabetes centres (n = 22; 62.9%) and having their child put into the group that they wanted (n = 18; 51.4%). Only one parent/caregiver indicated that they liked nothing about their child taking part in the study, this parent was from the self-monitoring group. More than half (62.9%; n = 22) indicated that there was nothing they disliked about their child participating in the CHILD study. Forty seven percent (n = 7) of parents/caregivers from the self-monitoring group reported disliking that their child was not put into the group they wanted. Table 17 provides a summary of responses to the Parent/Caregiver Satisfaction Post-Study questionnaire based on their evaluations of their experiences during the study.
Table 17.

Parent/Caregiver Evaluations of their Experiences During the Study

<table>
<thead>
<tr>
<th>Liked:</th>
<th>Continuous Glucose Monitoring Group (n=20)</th>
<th>Self-Monitoring Group (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Meetings with research staff</td>
<td>13 (65)</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Child randomized to group wanted</td>
<td>14 (70)</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Child being in study helped feel less afraid</td>
<td>9 (45)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Nothing extra their child had to do</td>
<td>2 (10)</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Helped to answer important research questions</td>
<td>10 (50)</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Liked nothing</td>
<td>0 (0)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Other likes*</td>
<td>3 (15)</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Disliked:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meetings with research staff</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Child not randomized to group wanted</td>
<td>0 (0)</td>
<td>7 (46.7)</td>
</tr>
<tr>
<td>Child being in study made me feel more afraid</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Extra things their child had to do</td>
<td>2 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Disliked nothing</td>
<td>14 (70)</td>
<td>8 (53.3)</td>
</tr>
<tr>
<td>Other dislikes**</td>
<td>4 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Participate in the study again:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definitely yes</td>
<td>14 (70)</td>
<td>7 (46.7)</td>
</tr>
<tr>
<td>Probably yes</td>
<td>4 (20)</td>
<td>7 (46.7)</td>
</tr>
<tr>
<td>Definitely not</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Probably not</td>
<td>1 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Not sure</td>
<td>1 (5)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Future preferences for blood glucose monitoring:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGM</td>
<td>17 (85)</td>
<td>10 (66.7)</td>
</tr>
<tr>
<td>SMBG</td>
<td>3 (15)</td>
<td>5 (33.3)</td>
</tr>
</tbody>
</table>

Note. Percentages may not total 100 due to rounding
*Other likes included: participating may help with diabetes management for their child (n=1), being part of an important study (n=1), and lower HbA1c (n=1)
**Other dislikes included: the size of the needle on the sensor (n=1), putting the sensor in (n=1), when the sensor did not work (n=1), and keeping the sensor in (n=1).
Parent/Caregiver ratings of continuous glucose monitoring. Parents and caregivers were asked to provide details about their children’s experience with the continuous glucose monitoring system during the CHILD trial. Again, a five-point Likert scale was used to evaluate six areas about the device. Similar to their children’s responses, parents reported an overall positive experience with the continuous glucose monitoring device. Most parents chose Likert values of 0 to 1 for the statements that the device did not cause them to worry (n = 17; 85.0%) and did not interfere with their child’s activities (n = 15; 75.0%). Importantly, 65% (n = 13) of parents reported their child did not dislike wearing two machines. Nine parents (45.0%) reported low levels of discomfort for their child with a Likert score of zero or one. Six parents (30%) reported high levels of discomfort for their child, with Likert scores of four or five. Ninety percent (n = 19) of all parents/caregivers scored four or five on the Likert scale, indicating that the instructions were easy or very easy to follow.

Parent/Caregiver opinion about future preferences for use of continuous glucose monitoring. Parents and caregivers were asked about their future preferences for use of glucose monitoring for their child. Twenty seven parents (77.1%) indicated that they would prefer their child/adolescent use continuous glucose monitoring if they had a future choice. Of these, 17 parents had their child in the continuous glucose monitoring group and the remaining 10 had their child in the self-monitoring group.

Parent/Caregiver willingness to take part in the CHILD pilot trial again. Overall, parents and caregivers were very willing to have their child/adolescent take part in the study again. A total of 32 (91.4%) parents indicated on their Post-Study Questionnaire at the three month follow up appointment that they would definitely or probably agree to have their child participate in the CHILD study again. Of these, 18 of 23 were parents of children in the
continuous glucose monitoring group and the remaining 14 of 15 were parents of children in the Self-monitoring group. No parents in either group responded that they would definitely not have their child take part if given the choice again and only one parent/caregiver indicated that they would probably not have their child participate in the study again. This parent had their child in the continuous glucose monitoring group and previously indicated that they did not like the extra things their child had to do during the study.

**Acceptability Parameters for a Larger Trial**

A number of acceptability parameters were set for a future larger trial, prior to initiating the CHILD pilot trial. These included the percentage of eligible children and families that agree to participate in the larger trial, the recruitment rate, training time for use of the continuous glucose monitor, usage of continuous glucose monitoring, performance of self-monitoring of blood glucose, the percentage of children who would take part in the larger trial and would use continuous glucose monitoring again. Table 18 shows the pre-set acceptability parameters compared with the post-study results. Only the time to train children/parents on use of the continuous glucose monitoring reached the pre-set acceptability parameters. The enrollment rate (48%) and the percentage of children who would take part in a larger trial (n = 27; 71%) approached the pre-set acceptability parameters, but the remaining aspects did not.
Table 18.

Acceptability Parameters for a Larger Trial

<table>
<thead>
<tr>
<th>Acceptability Parameter</th>
<th>Predefined</th>
<th>Actual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of eligible children/families agree to participate</td>
<td>50%</td>
<td>48%</td>
</tr>
<tr>
<td>Monthly recruitment rate</td>
<td>1/week(^a)</td>
<td>0.6/week</td>
</tr>
<tr>
<td>Total amount of time to train participants in continuous glucose monitoring</td>
<td>30 minutes (information session)</td>
<td>30 minutes (information session)</td>
</tr>
<tr>
<td>Total number of children who used continuous glucose monitoring three times per week</td>
<td>&gt;75%</td>
<td>39%</td>
</tr>
<tr>
<td>Total number of children who performed 3 self-monitoring checks per day</td>
<td>&gt;75%</td>
<td>18%</td>
</tr>
<tr>
<td>Percentage of children who would choose to participate in the larger trial</td>
<td>80%</td>
<td>73%</td>
</tr>
<tr>
<td>Percentage of children in the experimental group who would use the intervention again in the future</td>
<td>&gt;75%</td>
<td>64%</td>
</tr>
</tbody>
</table>

Note.
\(^a\) one/week at a small community diabetes centre would allow recruitment of several hundred children per year with multiple sites
\(^b\) Minimum number of uses the continuous glucose monitor is to be worn/week
Chapter 6
Discussion

The discussion begins with a description of the methodological strengths and limitations of the trial, a discussion of the feasibility of the trial protocol and the acceptability of the intervention. Although this pilot trial was not powered to determine significant group differences, the effects of continuous glucose monitoring versus self-monitoring are discussed and the results relative to the currently available research evidence are reviewed.

**Strengths and Limitations of the Study**

**Strengths**

The CHILD pilot trial used a centrally, controlled, concealed method of random allocation, an objective primary outcome measure, and a validated questionnaire to measure the secondary outcome. The primary outcome, HbA1c level, has been used consistently for evaluating overall metabolic control and the effectiveness of long-term diabetes management (ADA, 2014; CDA, 2008; 2013; Koga, 2014). Treatment outcomes may be influenced by expectancies from either the participant or the diabetes clinic staff members. Because the continuous glucose monitoring intervention could not be masked, the primary outcome was objectively measured and recorded using a standardized measure (HbA1c), limiting bias on study outcomes. HbA1c is an objective measure that cannot be influenced by the diabetes nurse educators who perform the test or the child who is receiving the test. In order to ensure greater accuracy of the primary outcome measure, the DCA 2000+ Analyzer device that was used to measure HbA1c was the same brand of machine used at both research sites and was calibrated prior to each participant having their HbA1c measured.
Fear of Hypoglycemia, the secondary outcome, was measured using the Children’s Hypoglycemia Index. The questionnaire demonstrated very good psychometric properties, including sufficient internal consistency, test-retest reliability, and validity. In addition, the development of the items on the questionnaire came from both clinical practice as well as the literature (Kamps et al., 2005), thereby improving its relevance and usefulness in assessing fear of hypoglycemia in children with diabetes.

Very few participants were lost to follow up; the attrition rate was 5%. There were complete data for the primary outcome measure for 38 of the 40 participants, one of which withdrew from the study prior to starting their treatment. An alternate phone number, mailing address, and email address were obtained to assist with participant follow-up and all strategies were used to help ensure participants attended their final appointment at the conclusion of the study. Therefore, attrition bias was not a concern for the CHILD pilot trial. An intent-to-treat analysis was used in which the data from all children randomized in the study were analyzed in the group to which they were assigned. All of the study data were entered into Microsoft Office ACCESS ©. Queries were made for logic and range checks to ensure accuracy of the data entered into the database.

Limitations

The website (www.randomizer.org) was used to assign group allocation, with 24 participants assigned to the continuous glucose monitoring group and 16 to the self-monitoring group. Block randomization should have been done, using random block sizes of two or four, in order to avoid the assignment of an uneven number of participants in each group. This would ensure a balance in the number of participants allocated to each group (Akobeng, 2005). However, the baseline data were very similar between groups, despite the unequal group sizes.
Feasibility and Acceptability

Several feasibility and acceptability issues including an estimate of recruitment rates, assessment of compliance with allocated treatment group, and satisfaction with treatment allocation were evaluated in the CHILD pilot trial.

Recruitment Rates

Recruitment is crucial to the success of research studies, but remains a challenge in many clinical trials and often occurs more slowly than intended (Ramm, Daws, & Schadewaldt, 2013; Ulrich, James, Walker, Stine, Gore, Prestidge et al., 2010). One of the largest feasibility issues for the CHILD trial was recruitment of the sample. The majority of the children (n=402; 82.9%) were ineligible to participate in the study because they were not currently using continuous subcutaneous insulin infusion or were using an incompatible form of continuous insulin infusion. However, 48% of eligible children chose to participate in the trial, which was just below the 50% acceptability parameter set out for a larger trial. This suggests that children with T1D were interested in using the intervention and taking part in the study. Over the course of the CHILD trial, additional continuous subcutaneous insulin systems were developed which were then compatible with continuous glucose monitoring. Future studies should consider the use of these different devices to increase the number of eligible children to participate in evaluating metabolic control in children using continuous glucose monitoring compared to self-monitoring of blood glucose alone.

Compliance with Allocated Treatment

Very few children (n=2; 13.3%) in the self-monitoring group consistently performed three self-monitoring checks per day for the three month duration of the study. This finding is similar to previous studies demonstrating low compliance rates for self-monitoring, ranging from
26% to 54% of children reporting monitoring three or more times per day (Greening, Stoppelbein, Konishi, Jordan & Moll, 2007; Hood, Peterson, Rohan, & Drotar, 2009; Wing, Lamparski, Zaslow, Betschart, Siminerio, & Becker, 1985), with self-monitoring often declining throughout the study duration (Riveline et al., 2012).

Only nine participants in the experimental group (39.1%) wore the continuous glucose monitoring device for three days per week as required by the study protocol. This was well below the predefined 75% acceptability parameter for a larger trial. However, previous studies have demonstrated that despite a high level of satisfaction with the continuous glucose monitoring device itself, children do not wear the sensors regularly (DirecNet, 2005; JDRF, 2008; Riveline et al., 2012), which may imply an increased treatment burden (Formosa & Matyka, 2012). Further, use of the continuous glucose monitoring device declined over the course of the study from greater than 90% of children using the device in the first week to 65% of children using continuous glucose monitoring in the final week of the study. Similar to the DirecNet group (2005), the Juvenile Diabetes Research Foundation (2008), Kordonouri et al. (2010), and Mauras et al., (2012), declining use of the continuous glucose monitoring device was observed over the duration of their study periods. In addition, there were very few participants in the experimental group who performed the minimum three self-monitoring of blood glucose checks per day (n = 5; 21.7%), which is similar to the finding in the self-monitoring group and in line with previous studies demonstrating low rates of compliance with self-monitoring for children with T1D (Greening et al., 2007; Hood et al., 2007; Borus & Laffell, 2010; Ziegler et al., 2011). Overall, only 18% (n=7) of participants were compliant with self-monitoring for the 12 week duration of the CHILD pilot trial.
Efforts to improve compliance with self- and continuous monitoring of glucose may require increased follow up with children to ensure the checks are being carried out three times per day and the device is being worn three times per week. Requiring the children to upload their continuous subcutaneous insulin infusion and blood glucose records on a regular basis could assist in improving compliance by making sure the children are being held accountable for performing their blood glucose and continuous glucose monitoring checks. However, this is usually only done when children are first diagnosed, are ill, have recently started continuous glucose monitoring, or are undergoing insulin dosage changes. This is not necessarily a part of usual care and would require increased contact with participants, which has been typically observed in randomized controlled trials of continuous glucose monitoring in children (Chase et al., 2001; Chase et al., 2003; DirecNet 2005; Lagarde et al., 2006; Yates et al., 2006). The use of mobile health (mHealth) interventions may be useful in helping to improve adherence to blood glucose measurement in children, as they have been shown to improve health outcomes in adults with T2D (Cafazzo, Casselman, Hamming, Katzman, & Palmert, 2012). The mHealth app provides prompts for users to check blood glucose levels and intervene based on an algorithm related to current blood glucose levels. Children are provided with rewards (free apps and music) when they intervene as recommended. This may be a useful addition to ensure compliance that is acceptable and appealing for children with T1D. In addition, improved sensor accuracy, smaller needles and size of the device itself were also mentioned as reasons for non-compliance with study protocol and improvements to these may also help in improving compliance.

**Satisfaction with the Study and Allocated Treatment**

Children and parents/caregivers reported high levels of satisfaction with both the study and acceptability of continuous glucose monitoring. Despite the lack of significant improvement
in metabolic control in children using continuous glucose monitoring, 64\% \,(n = 14)\) of children and 85\% \,(n = 17)\) of parents in the experimental group who responded to the post-study questionnaire would choose to use continuous glucose monitoring again. This is close to the predefined acceptability parameter of 75\% for a larger trial and is interesting, in light of the lack of significant improvement in HbA1c. Chase et al. (2010), the JDRF (2008), and Mauras et al., (2012) described that children and their parents reported favourable views in terms of the benefits of continuous glucose monitoring for improving diabetes management and overall metabolic control. Only three children reported high levels of discomfort with the continuous glucose monitor, reporting that the large size of the device and inserting the sensor were items they disliked. This is contrast with earlier studies reporting negative effects of continuous glucose monitoring including the sensor feeling too big and irritation from the sensor insertion (Cemeroglu et al., 2010; Chase et al., 2005; Ludvigsson & Hanas, 2003).

Overall, 73\% of children and 86\% of parents stated that they would definitely or probably choose to participate in the study again if they were given the choice. Again, this is close to the predefined acceptability parameter of 80\% for a larger trial. It is remarkable to note such high levels of interest in taking part in a study where children are required to insert a second device and continue to self-monitor their blood glucose levels a minimum of three times per day. However, low compliance rates for use of continuous glucose monitoring despite positive views of the device itself are common (Chase et al., 2010; DirecNet, 2006; Ludvigsson & Hanas, 2003). Further evaluation of low compliance rates and methods to ensure increased compliance are necessary, including increased follow up with participants, submission of blood glucose records to ensure accountability, or use of mHealth interventions may help improve compliance rates. Other than being randomized to the group they wanted, the two most common items that
participants and parents liked about the study was meetings with research staff and helping answer important questions. Still, it is important to note that this is somewhat lower than expected. It may be that because meetings with participants and their families were held only at baseline and study conclusion, the development of a relationship between research staff and participants and emphasizing the importance of the research questions being asked was problematic because the meetings were short in duration and infrequent. In future studies, with recommended increased follow up and interaction with participants to ensure compliance, the creation of a more in-depth relationship may be possible, where more discussion about the research and the importance of the study outcomes can be elaborated upon.

**Delivery of Intervention**

Participants and their family member(s) in the continuous glucose monitoring group attended a 30 minute information session where they received instruction on how to use the continuous glucose monitor as well as review self-monitoring. The participants in the self-monitoring group received a 15 minute review of self-monitoring to ensure appropriate testing. The additional attention that the continuous glucose monitoring group received is not considered a limitation of this pilot study. An extra 15 minutes of attention has not been shown to change behaviour or other long-term outcomes. A number of meta-analyses evaluating the effects of psychoeducational interventions on patient outcomes have concluded that patients receiving research-based nursing interventions and additional information can improve knowledge (Devine, 1992; Devine & Reifschneider, 1995; Heater, Becker, & Olson, 1988; Theis & Johnson, 1995). However, education and increased knowledge alone has been shown to be ineffective in causing behavioural changes (Bandura, 1982; Bloomgarden, Karmally, Metzer, Brothers,

**Primary Research Question**

**Effect of continuous glucose monitoring on metabolic control (HbA1c).** The primary research question addressed the effect of continuous glucose monitoring compared with self-monitoring on metabolic control, as measured by HbA1c levels, at three months post-randomization. Although there was no statistically significant difference between groups in changes in mean HbA1c, there was a trend toward improved metabolic control in the continuous glucose monitoring group. Participants in the experimental group recorded a mean decrease in HbA1c of 0.32% compared to a decrease of 0.05% in the self-monitoring group. This finding is similar to the 0.36% reduction in HbA1c reported by Chase et al. (2001) and the 0.37% reduction in HbA1c found by the JDRF (2008). The sustained lowering of HbA1c values by 0.4% is clinically important (Ahern et al., 2002; Sulli & Shashaj, 2006) and can result in reductions in the risk of neuropathy, nephropathy, and retinopathy (DCCT, 1995; 1996; Rohlfing et al., 2002). Participants using continuous glucose monitoring in the CHILD pilot trial group demonstrated a reduction in HbA1c that approached a clinically important decrease, which would be encouraging if confirmed in an adequately powered trial. However, only four children and zero adolescents achieved targeted levels set out by the CDA Clinical Practice Guidelines (2008 and 2013) by the end of the study. Only an adequately-powered trial can determine if a clinically important reduction in HbA1c levels can be obtained with CGM. As the main objective of this pilot study was to determine if an adequately powered RCT of continuous glucose monitoring was feasible, rather than evaluating the effectiveness of the intervention itself, a sample size of
244 children would be required in a larger trial, using a two-sided hypothesis test, with an alpha level of 0.05 and 80% power to detect a clinical significant difference of 0.32% in HbA1c levels.

To date there have been no other randomized controlled trials evaluating the use of continuous glucose monitoring compared with self-monitoring in children using continuous subcutaneous insulin infusion alone for insulin administration. In line with the conceptual framework developed for the CHILD pilot trial, a reduction in the frequency and time spent in hypo- or hyperglycemia may result in children with T1D experiencing a reduction in glucose variability and fluctuations, which ultimately results in an improvement in overall metabolic control, as measured by HbA1c levels. The information provided by the continuous glucose monitor in terms of continuous feedback about current and future glucose trends is potentially very beneficial for children and permits the opportunity to intervene when they begin to experience hypoglycemia or hyperglycemia. The information is readily available and can be easily observed on the insulin pump screen. Previous research has indicated that providing immediate glucose level feedback does increase the likelihood that children will respond and intervene to make changes in terms of diet and/or exercise in order to achieve appropriate blood glucose levels (Block, 2008). However, it is important to remember that simply having such information available does not necessarily ensure that action is taken to compensate for either hypo- or hyperglycemic trends. It may be that participants in both the before-after designs and the CHILD pilot trial did not necessarily respond to the glucose trend information provided by the continuous glucose monitoring device and therefore, glucose variability was not reduced, which did not lead to a significant or substantial reduction in HbA1c. Future studies may wish to further explore the importance of increased follow up and/or reporting of blood glucose records in order to ensure compliance with continuous glucose and self-monitoring and to emphasize the
importance of intervening when relevant glucose information is provided. Frequent reminders to take action either by adjusting diet and/or exercise when hypo- and hyperglycemic values occur may be a necessary component during follow up conversations or in-person visits to help ensure that reductions in glucose variability and overall HbA1c levels meet target values provided by the CDA.

**Secondary Research Questions**

**Effect of continuous glucose monitoring on fear of hypoglycemia.** The secondary research question addressed the effect of continuous glucose monitoring compared with self-monitoring, on fear of hypoglycemia at 12 weeks post-randomization. There was a statistically significant difference between groups in changes in mean scores on the Children’s Hypoglycemic Index evaluating fear of hypoglycemia in the CHILD pilot trial. Participants using continuous glucose monitoring reported a five-point decrease in fear of hypoglycemia scores compared with a three-point increase in participants in the self-monitoring group. When participants in the continuous glucose monitoring group wore the device they received glucose averages every five minutes and close to 300 total glucose values each day. They were able to observe glucose trends by looking at a screen which would indicate with arrows whether their glucose values were going high or low without having to perform self-monitoring and were able to respond in advance of becoming hypoglycemic.

The majority of children (63.6%) using continuous glucose monitoring reported decreased fear of hypoglycemia scores compared to less than half of the participants (46.7%) in the self-monitoring group. It is important to note that fear of hypoglycemia was reduced significantly, despite a low level of compliance with participants using the device in the intervention group. It is important to evaluate this further as the responses that children have
with regards to fear of hypoglycemia can affect their diabetes management and may influence compliance. It has been shown that children may take less insulin than they should or overeat in order to keep their blood glucose levels high in an attempt to avoid hypoglycemia (DiBattista, Hart, Greco, & Glozier, 2009; Patton, Dolan, Henry, & Powers, 2008; Wild et al., 2007), but also that parents may endorse behaviours such as feeding their child large snacks at bedtime, trying to keep blood glucose levels high when their child may be away from them, at a long social or school event, or simply to be on the safe side (Patton, Dolan, Henry, & Powers, 2007). Reporting a decreased fear of hypoglycemia is beneficial for children with T1D and their parents because fear of hypoglycemia can lead to unhealthy behaviours which ultimately could result in increased HbA1c levels, indicative of poor metabolic control. This poor control puts children at risk of long term health complications, including neuropathy, nephropathy, and retinopathy associated with diabetes (CDA, 2013).

This was the first time that fear of hypoglycemia in children using continuous glucose monitoring versus self-monitoring was measured using the Children’s Hypoglycemia Index (Kamps et al., 2005). Fear of hypoglycemia scores were reduced significantly in the continuous glucose monitoring (-5.00 + 6.89) compared with the self-monitoring group (3.13 ± 10.49). The participants in the control group actually reported increased fear of hypoglycemia scores, indicating the children felt more fear at the end of the study than at baseline. Previous randomized controlled trials (Chase et al., 2001; Chase et al., 2003) have measured fear of hypoglycemia using the Hypoglycemic Fear Survey and reported reductions in fear of hypoglycemia scores in children using continuous glucose monitoring, although no significant differences between groups were found.
The conceptual framework developed for the CHILD pilot trial emphasized the importance of acting upon information related to hypo- and hyperglycemic glucose values, either by making changes to the participant’s diet or current exercise pattern in order to increase or decrease glucose values as necessary. Previous studies and the CHILD pilot trial all indicated a reduction in fear of hypoglycemia in children using continuous glucose monitoring compared to self-monitoring. However, it is impossible to determine whether fear of hypoglycemia decreased as a result of the actions taken by the children using continuous glucose monitoring as this was not evaluated in the CHILD pilot trial or the other studies evaluating fear of hypoglycemia. It is necessary to determine in future studies whether children indeed took action to intervene depending on the glucose alarms and future trend graphs provided by the continuous glucose monitoring device and the effect this may have on fear of hypoglycemia.

**Frequency of glycemic and adverse events.** There were no episodes of severe hypoglycemia or DKA reported in the self-monitoring group. There were no reported episodes of severe hypoglycemia and only a single episode of DKA in the continuous glucose monitoring group. The participant was not wearing the continuous glucose monitor at the time of the incident and there were no episodes of severe illness leading up to the DKA event. Participants in the continuous glucose monitoring group lowered their HbA1c levels without increasing their risk of hypoglycemia, which is important to note. A total of 15 skin reactions were reported and were mostly mild in nature. There were no reports of psychological distress in any child or adolescent participating in the CHILD trial. Fourteen episodes of illness were reported during the study period. More children from the continuous glucose monitoring group reported illness compared to the self-monitoring group, but in general, the illnesses were minor and included colds, ear infections, and sore throats, and a few more serious illnesses including urinary tract
infection, dehydration, and influenza. Illness in children with T1D may result in an increased risk of severe hypoglycemia and diabetic ketoacidosis. However, the difference in illness rates did not translate into increased rates of hypoglycemia and DKA in either group. Taken together, these findings indicate that continuous glucose monitoring is safe to use and does not result in reports of negative psychological distress. Future studies may wish to evaluate the psychological effects that the use of continuous glucose monitoring may have on children with T1D through the use of more in-depth questionnaires and/or open-ended questions related to psychological issues. The results from these studies may shed light on whether psychological issues have an impact on feelings of treatment burden and the subsequent effects this may have on compliance rates.

**Feasibility of a Future Randomized Controlled Trial**

The CHILD pilot trial focused on evaluating important feasibility and acceptability questions for a larger future randomized controlled trial. This study provided preliminary evidence that supports the use of the Children’s Hypoglycemia Index to evaluate fear of hypoglycemia in children in a future RCT. Through the use of an adequate number of research study sites, increased funding to provide payment for a trial coordinator and paid research staff at each site, as well as expanding the scope to include non-Medtronic insulin pumps, the issues surrounding recruitment can be overcome to ensure an adequate study sample can be achieved. The acceptability of the device reported by both the children and their parents and the recent development of different subcutaneous insulin infusion devices that are compatible with continuous monitoring are encouraging. However, as a result of the low compliance with the use of the continuous glucose monitoring device observed in this study, the feasibility of a larger trial remains questionable. Additional research is necessary to develop and test methods to improve
compliance with the intervention before an RCT is feasible and warranted. This may involve further evaluation of mHealth technology which prompts children to act in accordance to current blood glucose values and rewards them for following through on the actions they are requested to do. In addition, further accountability may also be beneficial in which children are required to submit their continuous glucose monitoring records each week to ensure the device is being worn and children are intervening when required. The following chapter provides specific recommendations for future research and practice implications.
Chapter 7
Summary, Implications, and Conclusions

Summary of the Project

Continuous glucose monitoring is a promising form of technology that is easily used in children with T1D. However, there has been inconsistent evidence regarding its effectiveness in terms of improving metabolic control by lowering HbA1c levels in this population. The CHILD pilot trial was the first randomized controlled trial evaluating the use of continuous glucose monitoring compared with self-monitoring on overall metabolic control and fear of hypoglycemia in children using continuous subcutaneous insulin infusion alone for insulin administration. The conceptual framework of this study focused on the roles that additional information from continuous glucose monitoring along with the concept of self-efficacy have in assisting children to make changes in their diabetes management in order to achieve improved overall metabolic control.

The CHILD pilot trial was a two-site study, in which 40 children were randomly allocated to the continuous glucose monitoring group (n = 24) or the self-monitoring, usual care group (n = 16). Participants were considered similar at baseline and were primarily male, Caucasian, adolescents between the ages of 13 and 18. Participants in the experimental group were provided with a continuous glucose monitoring system and instructed on its use. They were asked to use the device for a minimum of three days per week. Both groups were asked to continue self-monitoring three times per day for the 12 week duration of the study. Metabolic control was measured using HbA1c and fear of hypoglycemia was measured using the Children’s Hypoglycemia Index at study conclusion. An intent-to-treat analysis was performed. No significant differences were found in metabolic control at the conclusion of the study. Mean
scores for fear of hypoglycemia were significantly reduced in the continuous glucose monitoring group (-5.00 ± 6.89) compared to the self-monitoring group, which actually reported increased fear of hypoglycemia scores (+3.13 ± 10.49) (p = 0.007). There were no reports of severe hypoglycemia or psychological distress, a single report of diabetic ketoacidosis, and low rates of adverse skin reactions.

Continuous glucose monitoring was generally well accepted by children and their families in the continuous glucose monitoring group. As mentioned previously, feasibility issues in terms of low recruitment rates, which can be overcome and low compliance with the continuous glucose monitoring device, need to be addressed before a larger randomized controlled trial can be considered feasible and are discussed in the following section.

Implications

**Implications for Research**

At baseline, participants in the CHILD trial reported high HbA1c levels, above those recommended by the CDA (2008; 2013). Further research examining the use of continuous glucose monitoring in children with significantly elevated HbA1c levels is important as it has been shown that those using continuous glucose monitoring consistently and starting with the highest HbA1c levels stand to benefit the greatest (Pickup et al., 2011). There is an underlying assumption that by simply having additional knowledge children will utilize the additional information provided by continuous glucose monitor to make changes to their diabetes management behaviours, which in turn has an effect on metabolic control. However, research has demonstrated that this is not necessarily the case, and that there is a deeper connection between “knowing” and “doing” (Whittemore, 2000). Thus, further studies exploring the underlying mechanism by which children using continuous glucose monitoring utilize the
increased glucose information available to them and in turn alter their behavioural response towards current and future glucose levels may also be valuable. Perhaps the recommended increase in follow up as well as the addition of technology which prompts children to act upon their current glucose levels and rewards them when they do so, should be incorporated into future research, before engaging in a larger RCT. These techniques may help to improve compliance with use of CGM, which was one of the largest issues in the current pilot study.

The concept of self-efficacy has been evaluated in many areas of research, including education and health. However, specific assessment of the ways in which self-efficacy can be improved in children with T1D using continuous subcutaneous insulin infusion with continuous monitoring, may help to promote compliance with but CGM and acting upon the information provided by CGM. The conceptual framework developed for the CHILD pilot trial is a useful one to explain how continuous glucose monitoring can help improve overall metabolic control. Research has shown that immediate feedback regarding blood glucose levels does improve the chances that children will respond and take action (Block, 2008). However, the specific mechanisms by which children make decisions to follow through on such actions needs additional evaluation. The conceptual framework developed for the CHILD pilot trial may be helpful in the development of interventions, by showing where interventions are required and what types of interventions may be useful to increase self-efficacy, compliance, and overall metabolic control. These interventions may include the design of prompts and reminders, rewards, and submission of records, which are necessary in order to increase action taken by the child, improve compliance with the use of continuous glucose monitoring, which in turn improves the child’s HbA1c level.
As well, further investigation of the effects of continuous glucose monitoring on fear of hypoglycemia are warranted. Increased information provided by the device may help children with T1D reduce their fear of hypoglycemia because they have access to increased information about current, average, and future glucose trends. However, this extra information may also result in information burden and actually increase fear of hypoglycemia, although this was not the case in the CHILD trial. Further, if participants are not compliant with using the continuous glucose monitoring device, additional research evaluating the effects that increased blood glucose information has on levels of fear of hypoglycemia in those that are not wearing the device are warranted. Despite the low levels of compliance in this study, an important and relevant outcome was the finding that 27.2% (n=6) of participants and 45.0% (n=9) of parents/caregivers reporting that taking part in the CHILD pilot trial made them feel less afraid. It may be that simply participating in a study helped to reduce the fear of hypoglycemia that children with T1D may experience. This is a concept that should be evaluated in future research.

**Implications for a Larger Randomized Controlled Trial**

The findings from the CHILD pilot trial provide guidance for future research evaluating the use of continuous glucose monitoring for the management of T1D. Most notably, sufficient funding for a larger multi-site study would be vital in order to carry out randomized controlled trials of continuous glucose monitoring in pediatric populations. Specifically, having the ability to provide financial compensation for a designated research assistant at each site would be very useful to ensure that an adequate amount of time and effort is spent on recruitment of potential study participants and that follow-up care can be provided consistently. As well, different types of continuous subcutaneous insulin infusion systems have been developed and are now compatible with continuous glucose monitoring. Additional randomized controlled trials should
consider the use of these different devices which will help increase the number of eligible participants.

Use of the continuous glucose monitor steadily declined over the duration of the three-month study period and hindered accurate data collection. In addition, poor overall compliance in terms of self-monitoring of blood glucose values was also observed. With usual care following the initiation of continuous glucose monitoring, frequent follow up care is provided by the health care team following initiation of the use of continuous glucose monitoring, often bi-weekly and then monthly for the first several months. These follow up appointments were not implemented for the CHILD pilot trial. However, future studies may find it necessary to follow up more frequently to ensure that adequate self-monitoring checks are being performed and appropriate compliance with the use of the device is achieved. Furthermore, having the child submit their monitoring records to the study site each week may also encourage children to remain compliant by being held accountable for completing their records. The use of mHealth interventions using the latest technology may also be very helpful and more appealing to children and adolescents with Type 1 diabetes. These applications provide prompts for children to intervene in a certain way and participants are rewarded for acting upon these recommendations. This may help ensure increased rates of compliance in this population which needs to be the focus of future randomized trials prior to focusing on the use of continuous glucose monitoring for improving metabolic control.

The findings from this study indicated that the measurement of the primary outcome of metabolic control (HbA1c levels) after three months was feasible due to the low attrition rate found in the CHILD trial. This time frame coincides with regularly scheduled follow-up appointments and the majority of children in this study attended their final appointment date
permitting the collection of data related to the child’s metabolic control and study participation. However, evaluating long-term use of continuous glucose monitoring is necessary and future research may look at increasing study duration to six months, or even one year.

**Implications for Practice**

The findings from this pilot trial provide preliminary evidence to suggest that continuous glucose monitoring has a positive effect on metabolic control by leading to a reduction in HbA1c levels. In addition, there was no evidence of harm and perhaps most notably children in the experimental group and their families were very satisfied with the use of the continuous glucose monitoring device. This indicates that continuous glucose monitoring could be offered in conjunction with a child’s current form of insulin administration.

The time required by clinicians to introduce the technology and provide follow-up care for continuous glucose monitoring use appears to be reasonable and acceptable as the information session and self-monitoring review only required approximately 30 minutes. In addition, interest in use of the device was very high in both groups; however, the actual use of the continuous glucose monitoring device was not. Many children (n=14; 63.6%) and their families (n=17; 85.0%) expressed significant interest in continuing to use the device following the conclusion of the study and ethics approval to return the devices to these families was sought. The continuous glucose monitors were returned to those in the experimental group who expressed such a desire.

However, there are several barriers which must be overcome in order to help realize the full potential clinical impact that continuous glucose monitoring has to offer. A major obstacle for patients is that frequent use of the continuous glucose monitoring system is required in order to attain the benefits of the device. Studies have shown that both adults and children only benefit
significantly if continuous glucose monitoring is used more than 70% of the time, which equates to more than five days per week (Raccah et al., 2009). Studies have also found that clinicians who do not routinely use continuous glucose monitoring in their practice may not feel that they have enough knowledge to educate their patients properly on the use of the device (Francescato, Geat, Stel, & Cauci, 2012; Larson & Pinsker, 2013). Thus, further education related to the use of continuous glucose monitoring for healthcare providers would need to be provided in order to improve their ability to recommend and explain the appropriate use of the device in diabetes management.

In addition, the costs associated with the technology are also a significant barrier. Currently, the Canadian government helps subsidize the costs associated with diabetes management, but the financial coverage and requirements to maintain this coverage vary from province to province, and the majority of the fees associated with continuous glucose monitoring go above and beyond what is provided and family members without private insurance must pay out of pocket. These factors may influence the low level of compliance identified in this study. Despite the continuous glucose monitoring device and sufficient sensors being provided free of charge to each participant, the cost of the tape to ensure adherence to the skin, as well as blood glucose test strips and the blood glucose meters were not provided in the study protocol. Future studies may wish to provide all diabetes management materials, including continuous glucose monitors, sensors, tape, blood glucose test strips, and blood glucose meters free of charge to all participants. This may contribute to higher rates of compliance because participants and their families do not have to pay out of pocket for any supplies while participating in research studies and will also help to ensure consistency in the technology being used by participants. Lastly, there is also a considerable commitment required from the child and their family when deciding
to add this technology to their diabetes management regimen. Taken together, these findings suggest that continuous glucose monitoring could be introduced into clinical practice at pediatric diabetes clinics with additional education, the provision of all diabetes management supplies free of charge to each participant, interest from children and their families, as well as commitment to the time and effort required from healthcare providers, children, and their families, but may not be currently feasible.

**Conclusions**

Continuous glucose monitoring is one of the newest forms of technology that is being used by children in the management of T1D. The evidence from the CHILD pilot trial suggests that continuous glucose monitoring may help to improve overall metabolic control by reducing HbA1c levels and may contribute to reduced fear of hypoglycemia through the availability of increased information related to both current and future blood glucose values and trends. However, this study also clearly demonstrates that there are difficulties in terms of ensuring compliance with using continuous monitoring and self-monitoring and that children need assistance, perhaps in the form of new technologies which prompt and reward children for acting on continuous glucose monitoring information. Continuous glucose monitoring is relatively easy to use and can be implemented by clinicians working with children living with T1D in pediatric diabetes clinics. The evidence from this CHILD pilot trial suggests that the use of continuous glucose monitoring for diabetes management in children is valuable in helping to improve metabolic control by reducing HbA1c levels which is critical to prevent and reduce the effects of long-term diabetes complications. However, a larger randomized controlled trial may not be feasible until further studies are carried out which evaluate methods to ensure compliance with use of the continuous glucose monitoring as well as self-monitoring of blood glucose. In
addition, more information about the underlying mechanisms leading to changes in diabetes management behaviours are necessary to determine what can be done to ensure action is taken to either increase or decrease blood glucose levels depending on what is warranted at this time. Research into compliance with continuous and self-monitoring as well as acting upon information provided by continuous glucose monitoring need to be carried out in order to help children with Type 1 diabetes strive to achieve CDA recommended HbA1c targets.
References


Appendices
Appendix A. Eligibility Screening Form

Eligibility Screening Form  

Date: __________________

If a Child with T1D you are caring for is using an Insulin Pump, PLEASE SCREEN THEM for eligibility for the Continuous Glucose Monitoring and HbA1c (CHILD) Pilot Trial (MUST BE YES TO BE ELIGIBLE)

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is this child aged 6 – 18?</td>
<td></td>
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</tr>
<tr>
<td>2. Has the child been diagnosed with T1D &gt; 1 year?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Is the child willing to perform at least 3 blood glucose checks per day?</td>
<td></td>
<td></td>
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<tr>
<td>4. Has the child been using CSII &gt; 1 month?</td>
<td></td>
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<tr>
<td>5. Does the child’s family/caregiver appear to be competent to give informed consent?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Is the child and family/caregiver English speaking?</td>
<td></td>
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</tr>
</tbody>
</table>

(ALL ANSWERS IN THIS SECTION MUST BE NO TO BE ELIGIBLE)

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does this child have documented celiac disease?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Does the child use corticosteroids that have systemic effects?</td>
<td></td>
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</tr>
<tr>
<td>3. If the child is a girl, has she achieved menarche?</td>
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<td></td>
</tr>
<tr>
<td>4. Is the child currently using continuous glucose monitoring?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Is the child unable to cognitively self-manage, based on parent or caregiver opinion?</td>
<td></td>
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</tr>
</tbody>
</table>

On the basis of the above criteria, is this child eligible for the CHILD Pilot Trial?

NO   YES   . . . If yes, please now assess their willingness to have someone from the study tell them about it, using the Introduction to Prospective Participants form.

Is the family interested in hearing more about the CHILD Pilot Trial?

YES   NO   . . . if no, why not?

After hearing about the CHILD Pilot Trial did the family consent to participate?

YES   NO   . . . if no, why not?

Thank you, Krystie Robinson-Vincent  RN, PhD candidate
Appendix B. Introduction to Prospective Participants Form

Introduction to Prospective Participants

Clinic Staff Member: Krystie is a PhD student at the Lawrence S. Bloomberg Faculty of Nursing. If you are interested, she will explain a study investigating children with type 1 diabetes using insulin pumps and two types of glucose monitoring. The study will compare continuous and self-monitoring of glucose to find out if the type of glucose monitoring will affect glucose control in children with Type 1 diabetes and to find out how children feel about the type of glucose monitoring they are asked to use. You are not under any obligation to participate. Are you interested in hearing more about this study?
Appendix C. Sample Consent Form
Information and Consent Form for Parent

Title of Research Project: The Continuous Glucose Monitoring and HbA1c In Children for Long-term Diabetes Management (CHILD) Pilot Trial

Investigator: Krystie A. Robinson-Vincent RN, PhD Candidate, Lawrence S. Bloomberg Faculty of Nursing, University of Toronto.

Krystie Robinson-Vincent is doing the study while she is a PhD student at the University of Toronto, as part of her PhD degree. She is being supervised by Professor Ellen Hodnett.

Purpose of Study:
Frequent checking of blood sugar levels is an important part of taking care of diabetes. Insulin pumps with a continuous glucose monitor give many blood sugar numbers each day and may give you and your child important facts about blood sugar levels. The study will look at two types of blood sugar checks: (1) continuous glucose monitoring and (2) self-monitoring. This study is being done to find out if the type of checking will affect blood sugar control in children with Type 1 diabetes. As well, we want to find out how children feel about the type of checking they are asked to use.

Study Design:
If you and your child agree to be in the study, we will ask you to answer a few questions about your child’s diabetes and ask your child about his or her diabetes. This will take about 20 minutes. After this, your child will be randomly assigned to one of two groups: (1) continuous glucose monitoring or (2) self-monitoring for 3 months.

“Random assignment” means that whichever group your child will be in is by chance. You, your doctor, and the researcher will not get to choose the group. This means that if you and your child agree to be in the study, your child will have a fifty-fifty chance of being in one group or the other. This way of putting children in groups is very important to be able to find out how helpful the two types of blood sugar checking are in making blood sugar control better in children with Type 1 diabetes. The nursing and medical care you and your child get at the clinic will not change because you are in this study.

Self-Monitoring Group
If your child is in the self-monitoring group, we will ask your child to check their blood sugar using their home blood sugar meter 3 times each day (before meals). We will also ask you and your child to check blood sugars before bedtime if sugars are high or low (part of normal diabetes care). At your child’s regular 3-month follow-up appointment, a small amount of blood will be taken from your child using a finger prick to see what your child’s average blood sugar is. You will also be asked some questions about your child’s diabetes. This will take about 20 minutes.

Continuous Glucose Monitoring Group
If your child is in the continuous glucose monitoring group, the diabetes nurse will teach you and your child how to use the monitor. Your child will be asked to use the monitor for 3 days each week (your child may use it more than this). This means your child will wear a sensor under their skin that will check blood sugar levels and send the numbers to your child’s insulin pump. After 3 days (or more if it still works), the sensors are thrown in the garbage and a new one is used. Your child will also be asked to check his or her blood sugar 3 times each day using their home blood sugar meter. At your child’s regular 3-month follow-up appointment, a small amount of blood will be taken from your child using a finger prick to see what your child’s average blood sugar is. You will also be asked some questions about your child’s diabetes. This will take about 20 minutes. Because this is a pilot study, all parts of the continuous glucose monitor must be returned after the study is over.
Information and Consent Form for Parent

Potential Harms: Using a continuous glucose monitor is thought to be safe. It is possible that your child may have skin problems from the monitor. If your child has really low or really high blood sugar levels and they need you or someone else to help them, then you and your child will be asked to call your doctor. Your child’s doctor may want to see them that day. Or, if your child is not feeling well and you think your doctor should know, then you are also asked to call his or her doctor. You and your child do not give up any rights by being in this study.

Potential Benefits: Your child being in the study may help give information to nurses and doctors about whether continuous glucose monitoring can make blood sugar levels better in children with Type 1 diabetes. Many children in other studies have said that they are not as scared of low blood sugar levels, but your child may or may not feel the same way.

Confidentiality: We will respect your privacy. Your names will not be given to anyone. The information from this study will be kept in a locked place. Only people from the study will be able to look at this information. After the study is over, the information will still be kept in a locked place. The results from the study will not use your names.

Compensation of Participants: You and your child will not get money for being in the study. But, at the end of the study, as a way to thank you for being in the study, your child will receive a gift card.

Participation: If you decide to let your child be in this study you can take them out of the study at any time. The care you and your child receive from the doctors, nurses and other caregivers will not change in any way.

Contact Person: You have a right to ask questions about this study at any time. If you have any questions about the study or about your being in the study, please call me at any time at 416-710-0595. My PhD supervisor, Professor Ellen Hodnett, can be reached at (416) 946-8676.

Communication of Results: If you want a copy of the results from this study (written in lay language) sent to you when it is over, please tell us below. If you say no to having the results at first, but then change your mind and would like to see them, please contact the researcher, Krystie Robinson-Vincent at 416-710-0595 or by email at krystie.vincent@utoronto.ca

☐ I would like to receive a summary of the study results (written in lay language)
(If YES, please make a tick mark in the box, and write your address below).

Mailing Address: ____________________________________________________________
__________________________________________________________________________
__________________________________________________________________________

Krystie A. Robinson-Vincent
RN, PhD Candidate, University of Toronto
Information and Consent Form for Parent

Study Title: The Continuous Glucose Monitoring and HbA1c In Children Long-term Diabetes Management (CHILD) Pilot Study

Participant ID: ________________________  Participant Initials: ________________

PARTICIPANT CONSENT

By signing this form, I agree that:

1. You have explained this study to me. You have answered all my questions.
2. You have explained the possible harms and benefits (if any) of this study.
3. I know what I could do instead of having my child take part in this study. I understand that I have the right not to let my child take part in the study. I also have the right to take my child out of the study at any time. My decision about my child taking part in the study will not affect my child’s health care.
4. I am free now, and in the future, to ask questions about the study.
5. I have been told that my child’s medical records will be kept private except as described to me.
6. I understand that no information about my child will be given to anyone or be published without first asking my permission.
7. I have read and understood pages 1 to 3 of this consent form. I agree, or consent, that my child _____________ take part in this study.
8 I have received a copy of this Information and Consent form.

________________________________________  __________________________________
Name of Parent/Legal Guardian (Please print)  Signature of Parent/Legal Guardian

Date: ____________________  Time: ____________________

________________________________________  __________________________________
Name of Person Who Explained Consent (Please print)  Signature of Person Who Explained Consent

Date: ____________________  Time: ____________________

If you have any questions about this study, please call _________________________ at ____________________

If you have any questions about your rights as a participant in a study, please call the Office of Research Ethics at the University of Toronto at 416-946-3273.
Appendix D. Sample Assent Form

Information and Assent Form for Child

Title of Research Project: The Continuous Glucose Monitoring and HbA1c In Children for Long-term Diabetes Management (CHILD) Pilot Trial

Investigator: Krystie A. Robinson-Vincent RN, PhD Candidate, Lawrence S. Bloomberg Faculty of Nursing, University of Toronto.

Krystie Robinson-Vincent is doing a study while she is a student at the University of Toronto. Her supervisor is Professor Ellen Hodnett.

My name is [identify yourself to the child by name].

Why Are We Doing This Study?:
We are doing this study to look at two kinds of blood sugar checking: (1) using a sensor worn on your belly and (2) using your home blood sugar meter. We want to try and find out what way of checking blood sugars will make your blood sugar better. We also want to try and find out how it feels to use these ways of checking blood sugars.

What Will Happen During the Study?:
We will ask you a few questions about your diabetes. This will only take a couple of minutes. After this you will be put in a group. One group of children will use a sensor on their bellies and the other will use a home blood sugar meter, for 3 months.

You, your doctor, and the people doing the study do not get to pick which group you are in. The decision will be made by a computer program, randomly. “Random” means it is like flipping a coin to decide which group you are in. This way of choosing groups is the best way to find out how helpful the two ways of checking blood sugars are for children like you.

Self-Monitoring Group
If you are in the group where you keep using your home blood sugar meter, we will ask you to check your blood sugar 3 times each day, like you do now. After 3 months, you will come back to the clinic and a nurse will take a little bit of your blood, about three or four drops, from your finger, with a finger prick. You will also be asked some questions about your diabetes. This will only take a few minutes.
Information and Assent Form for Child

Continuous Glucose Monitoring Group
If you are in the group where you will use a sensor worn on your belly, a nurse will teach you and your family how to use it. You will wear the sensor on your belly for 3 days each week (or more if it still works). After 3 days (or more), you need to throw the sensor in the garbage and put a new one in. This sensor will give you a lot of blood sugar numbers every day. You will also need to check your blood sugars 3 times each day using your home blood sugar meter. After 3 months, you will come back to the clinic and a nurse will take a little bit of your blood, about three or four drops, from your finger, with a finger prick. You will also be asked some questions about your diabetes. This will only take a few minutes. You will need to give the continuous glucose monitor back after the study is over.

Are There Good Things and Bad Things About the Study?:
We think using sensors on your belly are safe. It is possible that you may feel sore skin on your belly. If you have really low or really high blood sugars and you need someone to help you, you will be asked to tell your parents and they will phone your doctor, because they may want to see you right away.

Being in this study may help nurses and doctors find out about these sensors. Many children have said that they were less scared of having really low blood sugars, but you may or may not feel this way.

Who Will Know About What I Did in the Study?:
If we think you are not feeling well, we may have to talk to your doctor about your blood sugars.

Can I Decide If I Want to Be in the Study?:
Nobody will be angry or upset if you do not want to be in the study. We are talking to your parents about the study and you should talk to them about it too.

Krystie A. Robinson-Vincent
RN, PhD Candidate, University of Toronto
Information and Assent Form for Child

Study Title: The Continuous Glucose Monitoring and HbA1c In Children Long-term Diabetes Management (CHILD) Pilot Study

Participant ID: ________________________  Participant Initials: ________________

ASSENT

I was present when _______________________________ read this form and said that he or she agreed, or assented, to take part in this study.

________________________________________
Name of Person Who Obtained Assent (Please print)  Signature of Person Who Obtained Assent

Date: ________________  Time: ________________

If you have any questions about this study, please call _________________________ at __________________

If you have any questions about your rights as a participant in a study, please call the Office of Research Ethics at the University of Toronto at 416-946-3273.
Appendix E. Data Entry Forms

ENTRY FORM

Participant Study Number

Child’s Date of Birth

Date This Form Completed

Section A: Baseline Characteristics (complete immediately before randomization)

1. Sex:
   - Male
   - Female

2. Race:
   - White
   - Black
   - Asian
   - South Asian
   - First Nation/Aboriginal
   - Other/Unknown
   - More than one racial background

3. Date of Diabetes Diagnosis:
   - Year
   - Month
   - Day

4. HbA1c
   - %

5. Aspects of Hypoglycemia
   a. Number of hypoglycemic episodes

6. Aspects of Hyperglycemia
   a. Number of hyperglycemic episodes

7. Aspects of Diabetic Ketoacidosis
   a. Number of Diabetic Ketoacidosis episodes

Please turn the page for more questions ....
Section B: Randomization Instructions

1. Complete Entry Form, Section A. questions 1 to 4 and Section B. questions 1 to 5
2. Call the Randomized Controlled Trials Unit at the Lawrence S. Bloomberg Faculty of Nursing 416-978-2392
   You will be provided with the group assignment
3. Follow the instructions to enter the answers to Section B. questions 1 and 2, which will identify the child.
4. Mark the study group assigned by the Online Randomization Service under Section B question 4 below.
5. Complete Section B. question 5

1. Study Identifying Code 001#
2. Study Code Number
3. Child’s Date of Birth Year Month Day
4. Allocated Study Group
   - CONTINUOUS GLUCOSE MONITORING
   - SELF-MONITORING OF BLOOD GLUCOSE
5. Date and Time of Randomization Year Month Day 24 Hour Clock
Section C: Baseline Self-Evaluation Questionnaire

DIRECTIONS: We would like to know how you feel about low blood sugar in different situations or about things that may happen because of low blood sugar. Even if you have not been in every situation, please answer the question as you think it might make you feel. Please circle one answer for each sentence.

<table>
<thead>
<tr>
<th>Question</th>
<th>Not Afraid</th>
<th>A Little Afraid</th>
<th>Afraid</th>
<th>Very Afraid</th>
<th>Extremely Afraid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Having low blood sugar when I am home with my parents makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. Having low blood sugar when I am asleep at night makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. Having low blood sugar when I am at school makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. Having low blood sugar when I am out with a group of friends makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5. Having low blood sugar when I am alone makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6. Having low blood sugar when I am at diabetes summer camp makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>7. Having low blood sugar when I am at a camp that is not for kids with diabetes makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>8. Acting silly when my blood sugar gets low makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9. Passing out from low blood sugar makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>10. Being alone when my blood sugar is low and having no one to help me makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>11. Having a seizure when my blood sugar is low makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>12. Not realizing when my blood sugar gets low makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>13. Making a mistake at school because my blood sugar is low makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>14. Embarrassing myself when my blood sugar is low makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>15. Asking for help when my blood sugar is low makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
**Section C: Baseline Self-Evaluation Questionnaire (continued)**

**DIRECTIONS:** We would like to know how you feel about low blood sugar in different situations or about things that may happen because of low blood sugar. Even if you have not been in every situation, please answer the question as you think it might make you feel. Please circle one answer for each sentence.

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Hardly Ever</th>
<th>Sometimes</th>
<th>Most of the Time</th>
<th>All of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. I worry about having low blood sugars even when my blood sugar range has been ok.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>17. I keep my blood sugar high when I am with friends so I won’t have to worry about it going low.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>18. I don’t like to be alone because I am worried that my blood sugar might get low.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>19. I take less insulin than I should because I don’t want my blood sugar to get low.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>20. I keep my blood sugar higher than it should be so I won’t have to worry about it getting low.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>21. I check my blood sugar often because I am afraid it might get low.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>22. I want to go to the doctor more often than I do now because I am worried about my blood sugar being low.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>23. I eat more food than I should because I don’t want my blood sugar to get low.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>24. I eat a bigger snack at bedtime than I should so I can be sure my blood sugar won’t get low in the middle of the night.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

**Total Score**
OUTCOMES FORM

Participant Study Number

Child’s Date of Birth

Date this Form Completed

1. HbA1c

2. Aspects of Hypoglycemia
   a. Number of hypoglycemic episodes

3. Aspects of Hyperglycemia
   a. Number of hyperglycemic episodes

4. Aspects of Diabetic Ketoacidosis
   a. Number of Diabetic Ketoacidosis episodes

Please turn page for more questions...
5. Aspects of Skin Reactions

a. Number of adverse skin reactions at finger prick sites

b. Number of adverse skin reactions at site of infusion set insertion

For those in the continuous glucose monitoring group:

c. Number of adverse skin reactions at site of continuous glucose monitoring insertion

Type: Minor (e.g. irritation, inflammation, dry skin)

Please describe:

_____________________________________________________________________________________________________________________

Type: More than minor (e.g. suspected local infection, lipoatrophy)

Please describe:

_____________________________________________________________________________________________________________________
ADVERSE EVENT FORM

Participant Study Number

Child’s Date of Birth
Year / Month / Day

Date this Form Completed
Year / Month / Day

Serious or unexpected adverse reactions or injuries experienced by participants from their participation in the CHILD pilot study should be reported to the Charles H. Best diabetes Centre within 48 hours.

Description of Adverse Event (please provide a detailed description).
_____________________________________________________________________________________________________________________
_____________________________________________________________________________________________________________________

1. Date of the adverse event:
   Year / Month / Day

2. Hypoglycemic Episode Requiring Intervention
   ○ Yes  ○ No

   a. Severity:
      ○ Moderate (required minimal assistance)  ○ Severe (required significant assistance)

   b. Action Taken
      ○ Consumed Carbohydrate  ○ Reduced insulin dose  ○ Delayed insulin dose
      ○ Discontinued CGM temporarily  ○ Discontinued CGM permanently

   c. Outcome
      ○ Resolved  ○ Adverse event still present (no treatment)  ○ Adverse event still present (being treated)
      ○ Unknown  ○ Residual effects present (not treated)  ○ Residual effects present (treated)

Please turn the page for more questions...
Page 1 of 3
3. Diabetic Ketoacidosis Episode Requiring Intervention

- Yes ☐ No ☐

a. Severity:

- Moderate (required minimal assistance) ☐ Severe (required significant assistance) ☐

b. Action Taken

- Increased insulin dose ☐ Delayed insulin dose CGM ☐ Discontinued CGM temporarily ☐
- Discontinued CGM permanently ☐

c. Outcome

- Resolved ☐ Adverse event still present (no treatment) ☐ Adverse event still present (being treated) ☐
- Unknown ☐ Residual effects present (not treated) ☐ Residual effects present (treated) ☐

4. Skin Reaction Requiring Intervention

- Yes ☐ No ☐

a. Severity:

- Moderate (required minimal assistance) ☐ Severe (required significant assistance) ☐

b. Type:

- Scabbing ☐ Lipoatrophy ☐ Localized skin infection ☐
- Other __________________________________________________________

Please turn the page for more questions...
Participant Study Number

Child's Date of Birth

Date this Form Completed

- c. Action Taken
  - Insertion Site Changed
  - Discontinued CGM temporarily
  - Discontinued CGM permanently

- d. Outcome
  - Resolved
  - Adverse event still present (no treatment)
  - Adverse event still present (being treated)
  - Unknown
  - Residual effects present (not treated)
  - Residual effects present (treated)

5. Moderate Severe Psychological Distress Reported by Clinical Staff, Parent, or Child, Requiring Intervention

- a. Action Taken
  - Referral for counselling
  - Discontinued CGM temporarily
  - Discontinued CGM permanently

- b. Outcome
  - Resolved
  - Adverse event still present (no treatment)
  - Adverse event still present (being treated)
  - Unknown
  - Residual effects present (not treated)
  - Residual effects present (treated)
  - Attended Counselling
### Section A: Self-Evaluation Questionnaire

**DIRECTIONS:** We would like to know how you feel about low blood sugar in different situations or about things that may happen because of low blood sugar. Even if you have not been in every situation, please answer the question as you think it might make you feel. Please circle one answer for each sentence.

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<td>5. Having low blood sugar when I am alone makes me feel...</td>
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<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
**Section A: Self-Evaluation Questionnaire (continued)**

**DIRECTIONS:** We would like to know how you feel about low blood sugar in different situations or about things that may happen because of low blood sugar. Even if you have not been in every situation, please answer the question as you think it might make you feel. Please circle one answer for each sentence.

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</tr>
</tbody>
</table>

Total Score

Please turn the page for more questions...
Section B: Participant Satisfaction

Your opinions about your study participation are very important. The first three questions are about your experiences as a participant in the CHILD Study.

1. What I liked about being in the study (mark all that apply)
   - Meetings with research staff at the pediatric diabetes centre
   - Put into the group I wanted
   - Being in this study helped me feel less afraid
   - There was nothing extra I had to do
   - Helped find the answer to important questions
   - Liked nothing
   - Other ______________________________________________________________________________

2. What I disliked about being in the study (mark all that apply)
   - Meetings with research staff at the pediatric diabetes centre
   - Not put into the group I wanted
   - Being in this study caused me to feel afraid
   - Didn’t like the extra things I had to do
   - Disliked nothing
   - Other ______________________________________________________________________________

3. If you had the decision to make again, would you choose to be in the study? (choose only one)
   - Definitely yes
   - Probably yes
   - Probably not
   - Definitely not
   - Not sure

4. If you had a choice in the future, what would you prefer to use for glucose monitoring? (choose only one)
   - Self-monitoring of blood glucose
   - Continuous glucose monitoring

Please turn the page for more questions...
Section C: Experience of Using the Continuous Glucose Monitoring Device

The next questions are about your experiences with the Continuous Glucose Monitoring device. Based on the use of the continuous glucose monitoring device for three days per week for the time you were in this study, please rate each of these statements on a scale of 0 to 5, if “0” is “not at all” and “5” is “very much so.”

1. Instructions about the monitor were easy to follow

   not at all  0  1  2  3  4  5  very much so

2. The monitor caused me discomfort

   not at all  0  1  2  3  4  5  very much so

3. Wearing the monitor interfered with my activities

   not at all  0  1  2  3  4  5  very much so

4. Wearing the monitor caused me to worry

   not at all  0  1  2  3  4  5  very much so

5. I had problems with the machine not working properly

   not at all  0  1  2  3  4  5  very much so

6. I disliked having to wear two machines

   not at all  0  1  2  3  4  5  very much so

Please turn the page for more questions...
Section D: Parent Satisfaction

Your opinions about the study participation are very important. The first three questions are about your experiences as a parent of a participant in the CHILD Study.

1. What I liked about having my child in the study (mark all that apply)
   - Meetings with research staff at the pediatric diabetes centre
   - Child was put into the group I wanted
   - Having my child being in this study helped me feel less afraid
   - There was nothing extra I/my child had to do
   - Helped find the answer to important questions
   - Liked nothing
   - Other _____________________________________________________________________________

2. What I disliked about having my child in the study (mark all that apply)
   - Meetings with research staff at the pediatric diabetes centre
   - Child was not put into the group I wanted
   - Having my child being in this study caused me to feel afraid
   - Didn’t like the extra things I/my child had to do
   - Disliked nothing
   - Other _____________________________________________________________________________

3. If you had the decision to make again, would you agree to have your child participate in the study? (choose only one)
   - Definitely yes
   - Probably yes
   - Probably not
   - Definitely not
   - Not sure

4. If you had a choice in the future, what would you prefer your child use for glucose monitoring? (choose only one)
   - Self-monitoring of blood glucose
   - Continuous glucose monitoring
Section E: Experience of Your Child Using the Continuous Glucose Monitoring Device

The next questions are about your child’s experiences with the Continuous Glucose Monitoring device. Based on the use of the continuous glucose monitoring device for three days per week for the time your child was in this study, please rate each of these statements on a scale of 0 to 5, if “0” is “not at all” and “5” is “very much so”

1. Instructions about the monitor were easy to follow
   not at all 0 1 2 3 4 5 very much so

2. The monitor caused my child discomfort
   not at all 0 1 2 3 4 5 very much so

3. Wearing the monitor interfered with my child’s activities
   not at all 0 1 2 3 4 5 very much so

4. Wearing the monitor caused me to worry about my child
   not at all 0 1 2 3 4 5 very much so

5. My child had problems with the machine not working properly
   not at all 0 1 2 3 4 5 very much so

6. My child disliked having to wear two machines
   not at all 0 1 2 3 4 5 very much so

Please turn the page for more questions...
Section F: Illness

The next questions are about any episodes of being sick you experienced during your time in the study.

1. Number of times you were sick: [ ]

For each episode of feeling sick you experienced during your time in the study, please provide the following details:

2. Date of being sick: [ ]  [ ]  [ ]
   Year    Month    Day

3. Sickness experienced:
   - Cold, cough
   - Flu
   - Strep throat, tonsillitis
   - Ear infection
   - Urinary tract infection
   - Other ________________
POST-STUDY QUESTIONNAIRE
SELF-MONITORING GROUP

Participant Study Number

Child's Date of Birth

Date this Form Completed

Section A: Self-Evaluation Questionnaire

DIRECTIONS: We would like to know how you feel about low blood sugar in different situations or about things that may happen because of low blood sugar. Even if you have not been in every situation, please answer the question as you think it might make you feel. Please circle one answer for each sentence.

<table>
<thead>
<tr>
<th>Question</th>
<th>Not Afraid</th>
<th>A Little Afraid</th>
<th>Afraid</th>
<th>Very Afraid</th>
<th>Extremely Afraid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Having low blood sugar when I am home with my parents makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. Having low blood sugar when I am asleep at night makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. Having low blood sugar when I am at school makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. Having low blood sugar when I am out with a group of friends makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5. Having low blood sugar when I am alone makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6. Having low blood sugar when I am at diabetes summer camp makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>7. Having low blood sugar when I am at a camp that is not for kids with diabetes makes me feel...</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>8. Acting silly when my blood sugar gets low makes me feel...</td>
<td>1</td>
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<td>9. Passing out from low blood sugar makes me feel...</td>
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<td>2</td>
<td>3</td>
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<td>10. Being alone when my blood sugar is low and having no one to help me makes me feel...</td>
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<tr>
<td>11. Having a seizure when my blood sugar is low makes me feel...</td>
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<td>12. Not realizing when my blood sugar gets low makes me feel...</td>
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<td>13. Making a mistake at school because my blood sugar is low makes me feel...</td>
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<td>14. Embarrassing myself when my blood sugar is low makes me feel...</td>
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1. What I liked about being in the study (mark all that apply)
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   - There was nothing extra I had to do
   - Helped find the answer to important questions
   - Liked nothing
   - Other

2. What I disliked about being in the study (mark all that apply)
   - Meetings with research staff at the pediatric diabetes centre
   - Not put into the group I wanted
   - Being in this study caused me to feel afraid
   - Didn’t like the extra things I had to do
   - Disliked nothing
   - Other

3. If you had the decision to make again, would you choose to be in the study? (choose only one)
   - Definitely yes
   - Probably yes
   - Probably not
   - Definitely not
   - Not sure

4. If you had a choice in the future, what would you prefer to use for glucose monitoring? (choose only one)
   - Self-monitoring of blood glucose
   - Continuous glucose monitoring

Please turn the page for more questions...
Section C: Parent Satisfaction

Your opinions about your study participation are very important. The first three questions are about your experiences as a parent of a participant in the CHILD Study.

1. What I liked about having my child in the study (mark all that apply)
   - Meetings with research staff at the pediatric diabetes centre
   - Child was put into the group I wanted
   - Having my child being in this study helped me feel less afraid
   - There was nothing extra I/my child had to do
   - Helped find the answer to important questions
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   - Other ____________________________

2. What I disliked about having my child in the study (mark all that apply)
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3. If you had the decision to make again, would you agree to have your child participate in the study? (choose only one)
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   - Definitely not
   - Not sure

4. If you had a choice in the future, what would you prefer your child use for glucose monitoring? (choose only one)
   - Self-monitoring of blood glucose
   - Continuous glucose monitoring
Section D: Illness

The next questions are about any episodes of illness you experienced during your time in the study.

1. Number of times you were ill: [ ]

For each episode of illness you experienced during your time in the study, please provide the following details:

2. Date of illness: [ ] / [ ] / [ ]
   Year       Month       Day

3. Illness experienced:
   - Cold, cough
   - Flu
   - Strep throat, tonsillitis
   - Ear infection
   - Urinary tract infection
   - Other ____________________
PARTICIPANT CONTACT SHEET

Participant Study Number

Child’s Date of Birth

Date this Form Completed

Year
Month
Day

CONFIDENTIAL: RETAIN IN PARTICIPANT FILE - DO NOT RETURN THIS FORM TO THE DATA COORDINATING CENTRE

Section A: Group Allocation Information

1. Allocated Study Group

   CONTINUOUS GLUCOSE MONITORING

   SELF-MONITORING OF BLOOD GLUCOSE

2. Date and Time of Randomization

   Year
Month
Day
24 Hour Clock

Section B: Contact Information

1. Child’s Contact Information:

   Name: ________________________

   Address: ________________________

   Telephone: ________________________

2. Secondary Contact Information:

   Name: ________________________

   Address: ________________________

   Telephone: ________________________

3. Family Doctor’s Contact Information

   Name: ________________________

   Address: ________________________

   Telephone: ________________________

Section C: Follow-Up Information

1. Date of 3-Month Follow Up Appointment and Planned Post-Study Questionnaire

   Year
Month
Day
24 Hour Clock

Section D: Forms Status

<table>
<thead>
<tr>
<th>Forms Status</th>
<th>Number of Forms</th>
<th>Participant Contacted</th>
<th>Data Entry Completed</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Entry</td>
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<tr>
<td>Outcomes</td>
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<td>Adverse Event (if necessary)</td>
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<tr>
<td>Post-Study Questionnaire - CGM Group</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Post-Study Questionnaire - SMBG Group</td>
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