Clinical Investigation of a Personalized Decision Support System for Insulin Injections in Adults with Type 1 Diabetes

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I humbly dedicate this thesis to…

My parents for their endless support throughout my life

&

My partner in life, Jonathan, for sharing this journey with me

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Throughout my fast-tracked PhD studies, I have had the privilege of collaborating with an interdisciplinary team of remarkable individuals.

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Abstract

Type 1 diabetes is a chronic condition resulting from the immune-mediated destruction of insulin-producing pancreatic beta cells. Consequently, lifelong insulin replacement therapy is required to manage the disease via multiple daily injections, most commonly using insulin pens, or continuous subcutaneous insulin infusion with an insulin pump.

The recent advent of continuous glucose monitoring with glucose sensors has augmented both insulin delivery methods, transforming the standard of care for type 1 diabetes. Despite this, attaining optimal glycemic targets is still challenging for most people and carries the risk of long-term complications.

In 2024, we have a variety of technological innovations that are commercially available, ranging from advanced glucose sensors to hybrid closed-loop systems to connected insulin pens. Since their introduction, insulin pens have dominated the global market and have gradually evolved over time. However, it was not until recently that smart pens and attachments began integrating continuous glucose monitoring coupled to digital platforms for combined real-time tracking. Yet, these devices still lack an adaptive decision component for unsupervised use.

The concept of personalized decision support systems is an emerging avenue marked by a growing interest in addressing this unmet need for individuals with type 1 diabetes using multiple daily injections. While a limited number of systems were investigated in large clinical trials, none have demonstrated glycemic improvement to date. Nevertheless, an effective automated approach could offer value to this underserved population, given the infrequent clinical monitoring in practice despite evolving insulin needs, partly due to restricted resources.

The core objectives of my thesis were to investigate the clinical outcomes and practical use of the McGill decision support system, integrating a novel optimization algorithm designed to

titrate insulin injection parameters, in hopes to bridge the gap. My primary work involved conducting a 12-week randomized controlled trial in 84 adults using multiple daily injections with type 1 diabetes and suboptimal glycemic control. This trial aimed to assess the effectiveness of the McGill decision support system in improving glycemia compared to a smartphone application with a non-adaptive insulin dose calculator. The primary outcome demonstrated a statistically significant and clinically meaningful improvement in glycated hemoglobin levels (gold standard assessment of glycemic control) with the system compared to the standalone application.

Notably, this trial is the first to demonstrate glycemic improvement with algorithm-guided insulin adjustments in adults on multiple daily injections. It is also the first to include a mixed methods approach, encompassing qualitative outcomes that shed light on unique patient perspectives regarding the use of this system.

The second part of my thesis entailed a three-part sub-study to evaluate the practical utility of this algorithm. This was accomplished through non-inferiority comparisons of weekly (Part A) and biweekly (Part C) adjustments made by the algorithm, benchmarked against those made by various endocrinologists. A novel assessment of intra-physician variability compared each endocrinologist's adjustments made in Part A to those made 12 weeks later (Part B), using the same dataset.

The main findings revealed comparable proportions of full agreement and full disagreement in the direction of insulin dose adjustments made by the algorithm to those made by endocrinologists. Interestingly, on average, physicians only fully agreed with themselves on the direction of insulin change about two-thirds of the time. Furthermore, the same physician even occasionally disagreed with themselves, reinforcing the subjective and complex nature of human decision making. Moreover, the average absolute percentage of change made by physicians was

higher than that of the algorithm, underscoring the algorithm's conservative approach. Overall, this study highlights the algorithm's potential utility in practice while also conceivably alleviating concerns about inadequate medical oversight.

Collectively, my thesis work demonstrated the clinical effectiveness and practical utility of the McGill decision support system, paving the way for clinical translation.

Résumé

Le diabète de type 1 est une condition chronique résultant de la destruction par médiation immunitaire des cellules bêta du pancréas qui produisent de l'insuline. Par conséquent, l'insulinothérapie est nécessaire pour toute la vie afin de gérer la condition par des injections quotidiennes, à l'aide de stylos à insuline, ou par l'infusion sous-cutanée continue d'insuline avec une pompe à insuline.

Le développement récent de la surveillance continue du glucose à l'aide de capteurs a amélioré les deux méthodes d'administration de l'insuline, ce qui a transformé la norme de soins pour le diabète de type 1. Malgré cela, l'atteinte des cibles glycémiques recommandées demeure un défi pour la plupart des personnes, avec le risque de complications à long terme.

En 2024, il y a plusieurs innovations technologiques disponibles sur le marché, comprenant des capteurs de glucose avancés, des systèmes semi-automatisés en boucle fermée, et des stylos à insuline connectés. Depuis leur introduction, les stylos à insuline ont dominé le marché global et ont progressivement évolué. Toutefois, ce n'est que récemment que les stylos et les accessoires intelligents ont commencé à intégrer la surveillance continue du glucose couplée à des plateformes électroniques, pour permettre un suivi en temps réel. Cependant, ces appareils ne sont toujours pas accompagnés d'un élément adaptatif pour une utilisation non supervisée.

Le concept de systèmes d'aide à la décision pour les injections d'insuline personnalisées est une voie émergente intéressante pour répondre à ce besoin méconnu des personnes atteintes de diabète de type 1 qui utilisent des injections quotidiennes. Bien que plusieurs systèmes aient été évalués dans le cadre d'essais cliniques, aucun d'entre eux n'a montré d'amélioration de la glycémie à ce jour. Néanmoins, une approche automatisée efficace pourrait être avantageuse pour

cette population mal desservie, compte tenu du suivi clinique peu fréquent dans la pratique malgré l'évolution des besoins d'insuline qui sont dus en partie aux ressources limitées.

Les principaux objectifs de ma thèse étaient d'évaluer les effets cliniques et l'utilisation pratique du système d'aide à la décision de McGill, incorporant un nouvel algorithme d'optimisation conçu pour ajuster les paramètres d'injection d'insuline. Mon travail principal a consisté à mener un essai contrôlé randomisé de 12 semaines chez 84 adultes atteints de diabète de type 1 utilisant des injections quotidiennes et ayant un contrôle glycémique sous-optimal. Cet essai visait à évaluer l'efficacité du système d'aide à la décision de McGill dans l'amélioration de la glycémie par rapport à une application mobile avec un calculateur de dose d'insuline non adaptatif. Le résultat principal a démontré une amélioration statistiquement significative et cliniquement importante des niveaux d'hémoglobine glyquée (évaluation de référence du contrôle de la glycémie) avec le système par rapport à l'application.

Cette étude est notamment la première à démontrer une amélioration de la glycémie grâce à des ajustements d'insuline guidés par l'algorithme chez les adultes utilisant des injections d'insuline. C'est également la première à inclure une approche de méthodes mixtes, comprenant des données qualitatives qui mettent en lumière les perspectives uniques des patients concernant l'utilisation de ce système.

La deuxième partie de ma thèse comprenait une sous-étude en trois parties pour évaluer l'utilité pratique de cet algorithme. Ceci a été réalisé par des comparaisons de non-infériorité des ajustements hebdomadaires (partie A) et bihebdomadaires (partie C) effectués par l'algorithme par rapport à ceux effectués par différents endocrinologues. Une nouvelle évaluation de la variabilité intra médecin a comparé les ajustements effectués par chaque endocrinologue dans la partie A à ceux effectués 12 semaines plus tard (partie B), en utilisant la même base de données.

Les principaux résultats ont indiqué des proportions comparables entre les endocrinologues et l'algorithme quant aux décisions en parfaite concordance ou discordance concernant la direction des ajustements d'insuline. Notamment, les médecins n'étaient en concordance avec eux-mêmes sur la direction du changement d'insuline que dans environ deux tiers des cas. Du plus, ils étaient même parfois en parfaite discordance avec eux-mêmes, ce qui renforce la nature subjective et complexe de la gestion de l'insuline. En outre, le pourcentage moyen de changement effectué par les médecins était plus élevé que celui de l'algorithme, ce qui souligne l'approche conservatrice de l'algorithme. Dans l'ensemble, cette étude démontre l'utilité pratique de cet algorithme, tout en atténuant potentiellement les inquiétudes liées à une surveillance médicale inadéquate.

Collectivement, mon travail de thèse a démontré l'efficacité clinique et l'utilité pratique du système d'aide à la décision de McGill, ouvrant la voie à une future intégration en clinique.

Contribution to Original Knowledge

Here, I outline my thesis contributions to original knowledge. A key point to note is that the engineering development of the algorithm (which was used in my clinical thesis work) formed the basis of Dr. Anas El Fathi's former PhD work under the supervision of Professor Ahmad Haidar. Building on that, my original contributions presented in this thesis pertain to the clinical conduct and evaluation of the algorithm, which we integrated with our novel smartphone application to form the McGill decision support system (DSS).

In Chapter 3, I present a manuscript that was recently submitted to a journal for peer review. This manuscript uncovers robust outcomes from a large clinical trial that investigated the effectiveness of the McGill DSS, which optimizes weekly insulin injection parameters. This study was the first non-pilot clinical work to demonstrate superior glycemic benefit in adults with type 1 diabetes (T1D) using multiple daily injections (MDI) with suboptimal baseline glycemic control, making a positive impact on the field with important future clinical implications.

Before this work, there was a gap to address the unmet need of adaptive MDI therapy for T1D. The interventional evidence is limited to only a few DSSs, all of which were ineffective at improving glycemic control. In addition, none of the prior work included qualitative assessments to provide insights on patient experiences and viewpoints, which is an increasingly valuable measure in clinical trials. For this reason, I added a qualitative sub-study to incorporate a mixed methods approach, strengthening the quality of the overall outcomes.

Furthermore, in light of recent research revealing variability in glucose values between different sensor types, I conducted a sub-analysis in a subset of re-consented participants who simultaneously wore their personal sensor alongside the study sensor during their participation.

The purpose was to explore any meaningful differences in sensor glucose metrics, in attempt to better understand some of the secondary glucose outcomes in the study.

In Chapter 4, I present another manuscript that was recently submitted to a journal for peer review. The manuscript describes a sub-study in which I compared the insulin dose adjustments made by the algorithm in the parent trial to mock adjustments made prospectively by a group of physician collaborators on identical retrospective datasets. Inspired by another group who conducted a survey study comparing their DSS to physicians, I designed this sub-study with a similar purpose and methodology to assess the practical use of the McGill DSS while introducing a unique study design with additional, novel objectives. In a structured three-part design, facilitated by our new physician platform, I captured inter-physician variability for both weekly and biweekly insulin adjustments. I also captured intra-physician variability by strategically designing the platform for repeated physician assessments on identical datasets in the second part without prior access to former assessments collected in the first part.

The findings indicated comparable recommendations made by the algorithm to those made by physicians, highlighting the potential of utilizing the McGill DSS in practice. Moreover, the intra-physician variability observed in this study further reinforces the inherent subjectivity involved in expert decision making surrounding insulin adjustments.

Finally, considering that our new physician platform enabled the successful execution of this sub-study, it could have broader applications. In the future, this platform could potentially be utilized by other researchers to test their algorithms in simulation studies.

Contribution of Authors

As the primary author, I (Alessandra Kobayati) was responsible for conducting a literature review and writing this entire thesis, including both manuscripts. Professor Ahmad Haidar provided high-level editorial feedback on all non-manuscript based sections of this thesis and offered general guidance on my thesis outline.

For both manuscripts, my initial and revised versions were all thoroughly reviewed by Professor Haidar. The manuscripts presented in Chapter 3 and Chapter 4 both underwent a final review and approval by all co-authors prior to journal submission.

Regarding clinical operations, I led the conduct of both studies under the supervision of Dr. Michael Tsoukas and Professor Haidar. Some of my main responsibilities included essential document development, liaising with key stakeholders, managing regulatory and ethics submissions, recruiting participants and physician collaborators, coordinating study procedures, and data management and handling. A more detailed summary of my contributions, along with those of my co-authors, is included after the preface section of each corresponding manuscript-based chapter.

Chapter 1. Introduction

1.1 Rationale

T1D is a chronic condition wherein little to no physiological insulin is produced as a result of immune-mediated destruction of pancreatic β-cells. Consequently, standard management of T1D involves exogenous intensive insulin therapy on a daily basis for survival. There are two main insulin delivery methods: MDI via insulin syringes or pens and continuous subcutaneous insulin infusion via a portable insulin pump. Both regimens have been enhanced with the adjunctive use of continuous glucose monitoring (CGM) using glucose sensors, providing similar improvements in glycemic control, irrespective of the delivery method. However, most adults with T1D still struggle to achieve recommended glycemic targets despite this groundbreaking advancement.

Nevertheless, over the past decade, we have seen an array of innovative diabetes technologies enter the market, chiefly toward the development of an artificial pancreas. More specifically, the advent of CGM set the stage for the era of hybrid closed-loop systems for semi-automated insulin delivery, which has proven to be superior to both sensor-augmented pump and MDI.

Recently, the field of DSSs has gained momentum with increasing interest to fulfill the leading yet underserved global market of MDI users. However, there is limited robust evidence in the literature to date.

1.2 Objectives

The McGill Diabetes Technology Lab has previously developed an optimization algorithm and tested its safety and feasibility against physician adjustments in a pilot study. Therefore, the unmet

need for adaptive MDI therapy, together with these preliminary findings, prompted further investigation of this technology in a larger and longer, properly-powered trial.

The primary objective of my thesis was to investigate the effectiveness of this algorithm, integrated with our novel smartphone application, forming the McGill DSS, in an outpatient clinical trial. I led a 12-week randomized controlled parallel trial comparing the McGill DSS to the standalone application in 84 MDI-treated adults with T1D and suboptimal glycemic control under free-living settings. This study primarily assessed glycemic measures while also assessing qualitative outcomes through semi-structured interviews to gain insights into patient perspectives concerning their experience using the study software.

The second objective of my thesis was to evaluate the practical utility of the algorithm by comparing its insulin adjustments to those made by a group of endocrinologists. Accordingly, I conducted a sub-study surveying 13 physician collaborators in three separate parts. Part A captured inter-physician variability, Part B captured intra-physician variability, both for weekly mock adjustments, and Part C captured inter-physician variability for biweekly mock adjustments. This study compared the direction of insulin dosing and the magnitude of change between the algorithm and physicians compared to those among physicians.

1.3 Outline

This is a manuscript-based thesis that consists of an introduction with an extensive background (Chapter 1), a detailed literature review on the specific area of research related to my core thesis work (Chapter 2), the body of the thesis including two manuscripts (Chapter 3 and Chapter 4), a comprehensive discussion (Chapter 5), and a conclusion (Chapter 6). Each manuscript-based chapter includes a brief preface followed by a dedicated section detailing the corresponding contributions of authors.

In Chapter 1, the rationale and objectives were discussed, followed by the outline of this thesis. This chapter continues on to provide a summary of the normal physiology of glucose homeostasis, followed by the pathophysiology, epidemiology, and short- and long-term complications of T1D. Subsequently, a general overview of the history and evolution of insulin is provided, in terms of formulations and delivery modes that led to the current standard of care, with a focus on commercial insulin delivery systems in their basic, advanced, and future forms.

Chapter 2 presents a literature review on bolus calculators and DSSs designed for MDI users with T1D. I discuss the current evidence while offering a critical appraisal that might explain some of the shortcomings. Finally, I touch on the unmet need for adaptive MDI support tools to transition to my first manuscript.

Chapter 3 integrates my manuscript describing the randomized controlled trial, which was submitted to a peer-reviewed journal. The manuscript presents the study design and methodology, an overview of the McGill DSS, the results and discussion, the strengths and limitations, as well as the complete list of figures, tables, and references.

Chapter 4 incorporates my manuscript describing the physician comparative sub-study. It includes the methodology employed, an overview of our newly developed physician platform, the study results and discussion, the strengths and limitations, as well as all tables, graphs, and references. This manuscript was also submitted to a peer-reviewed journal.

Chapter 5 presents a discussion encompassing all chapters while elaborating on certain aspects of the studies, including exploratory data. Moreover, this chapter addresses anticipated future directions for advanced MDI therapy. To end, a brief conclusion (Chapter 6) summarizes how the objectives were met as well as the practical implications of the research for potential clinical translation.

1.4 Background

1.4.1 Normal Physiology: Glucose Homeostasis

Under physiological conditions, glucose homeostasis is tightly controlled by counter-regulatory hormones, primarily insulin and glucagon from the endocrine pancreatic Islets of Langerhans. These hormones behave in a reciprocal manner in response to changes in plasma glucose levels to maintain normal glycemia (Figure 1.1).

In the absorptive state, the rise in plasma glucose concentration triggers the secretion of insulin from pancreatic β-cells, which enters the circulation to then act on several target organs to decrease glycemia while concurrently suppressing glucagon secretion. Insulin stimulates the hepatic storage of glucose into glycogen via glycogenesis (1). Furthermore, muscle and adipose tissue undergo glucose uptake in an insulin-dependent manner, with the latter promoting the production of triglycerides via lipogenesis. In addition, insulin stimulates amino acid uptake for protein synthesis in the muscle.

In contrast, during the fasting state, glucagon is secreted from pancreatic α-cells into circulation to ultimately increase blood glucose levels, predominantly by hepatic glucose production. The processes involved entail the breakdown of glycogen into glucose via glycogenolysis and the synthesis of new glucose via gluconeogenesis (2).

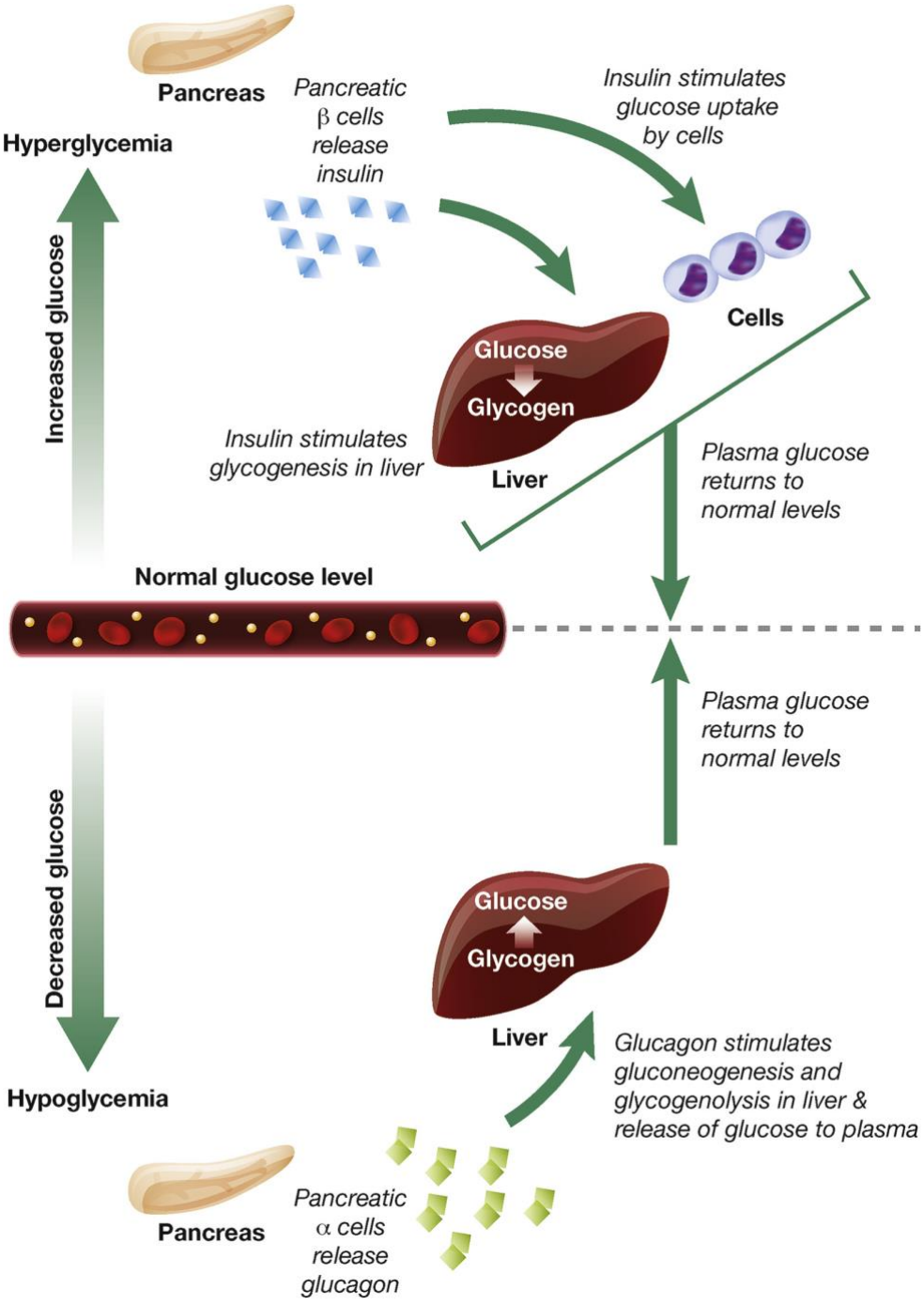

Figure 1.1 Glucose regulation with insulin and glucagon under physiological conditions. Permission for content use granted from (3).

1.4.2 Type 1 Diabetes

1.4.2.1 Pathophysiology

T1D is a chronic life-altering condition marked by the autoimmune destruction of pancreatic β-cells, causing dysregulation in glucose homeostasis resulting from the scarcity in insulin production. Consequently, exogenous insulin replacement therapy is essential for life, and this was made possible following the discovery of insulin in 1921, which transformed T1D from a fatal disease to a manageable condition (4).

In 1975, Unger and Orci coined T1D as a "bi-hormonal" disease with both insulin deficiency and glucagon dysregulation (5), altering the paracrine cross-talk leading to glucagon hypersecretion postprandially and a defective counterregulatory response to low blood glucose (6,7). The latter includes exercise-induced reductions in plasma glucose concentration (8).

The exact underpinnings of the faulty compensatory mechanisms are still not fully understood. Moreover, although the direct cause of T1D also remains to be elucidated, it is believed to be influenced by family history through genetic predisposition and an evolving landscape of environmental triggers that can induce autoimmunity (4,9). In fact, recent literature has underscored unhealthy eating and obesity (traditionally linked to type 2 diabetes (T2D)), pollutant exposure, insufficient infant microbial exposure, excessive antibiotic use, and dysregulated microbiota as lifestyle and environmental risk factors associated with the initiation of immune-mediated β-cell apoptosis. Nevertheless, the underlying pathophysiology of the disease remains obscure (9).

1.4.2.2 Prevalence

According to the 2022 International Diabetes Federation Atlas report, nearly 9 million people around the world are living with T1D, with an estimated 17% of that accounting for people younger

than 20 years of age. Although formerly regarded as juvenile diabetes, the onset of T1D can affect all ages. In fact, more than 60% of new global cases of T1D reported in 2022 were in adults (10). However, the 10th Edition Diabetes Atlas reported epidemiological gaps in incidence rate data on adult-onset T1D.

This Diabetes Atlas revealed that the African country, Eritrea, had the highest incidence rate of adult-onset T1D, with 46.2 per 100,000 population, followed by Sweden and Ireland. Moreover, the United States nearly tied with Australia in seventh and eighth place at roughly 16.5 per 100,000 (Figure 1.2). There is a similar trend in the T1D incidence rate in children under 15 years of age as that in adults, with Finland and Sweden being the highest at 52.2 and 44.1 per 100,000 population, respectively, and Canada ranking fifth at 37.9 per100,000 (Figure 1.3) (11).

The country with the highest prevalent case numbers across all ages is the United States. Canada is also among the top ten countries with the highest prevalent cases, with roughly 285,000 Canadians diagnosed with T1D (10). Collectively, Northern Europe and North America are among the leading regions with growing T1D incidence rates and prevalence cases (11). Nevertheless, the projected number of worldwide cases of T1D is expected to nearly double by 2040 (12).

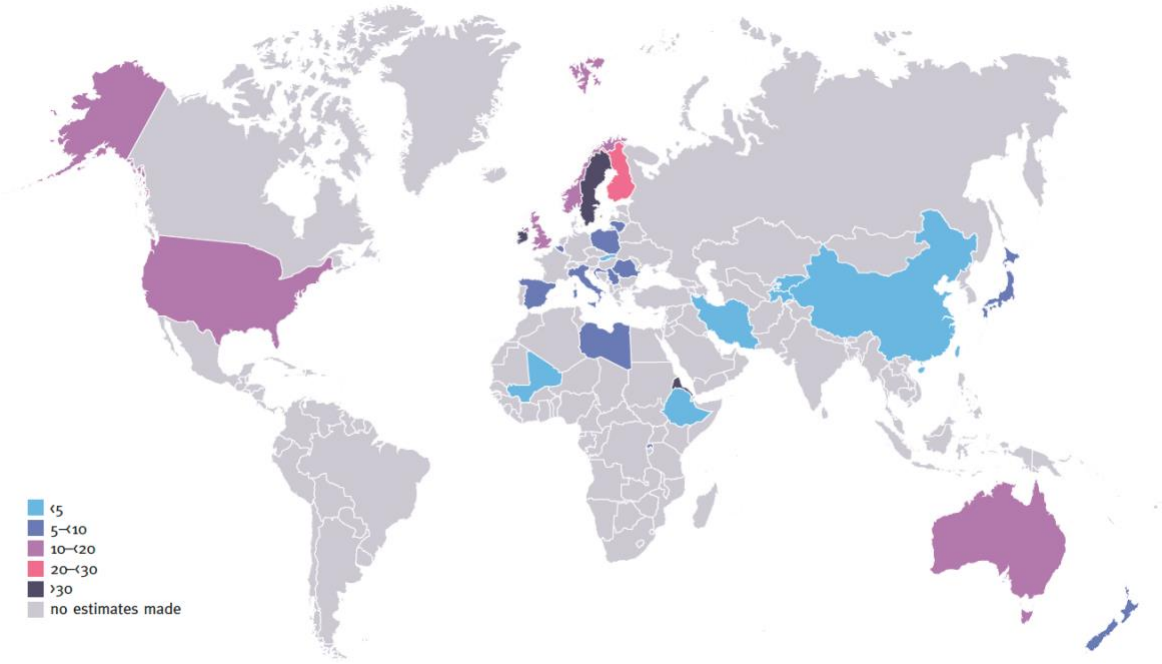

Figure 1.2 Estimated incidence rates per 100,000 population per year of T1D in adults aged 20-40 years. Copyright permission granted from (11)

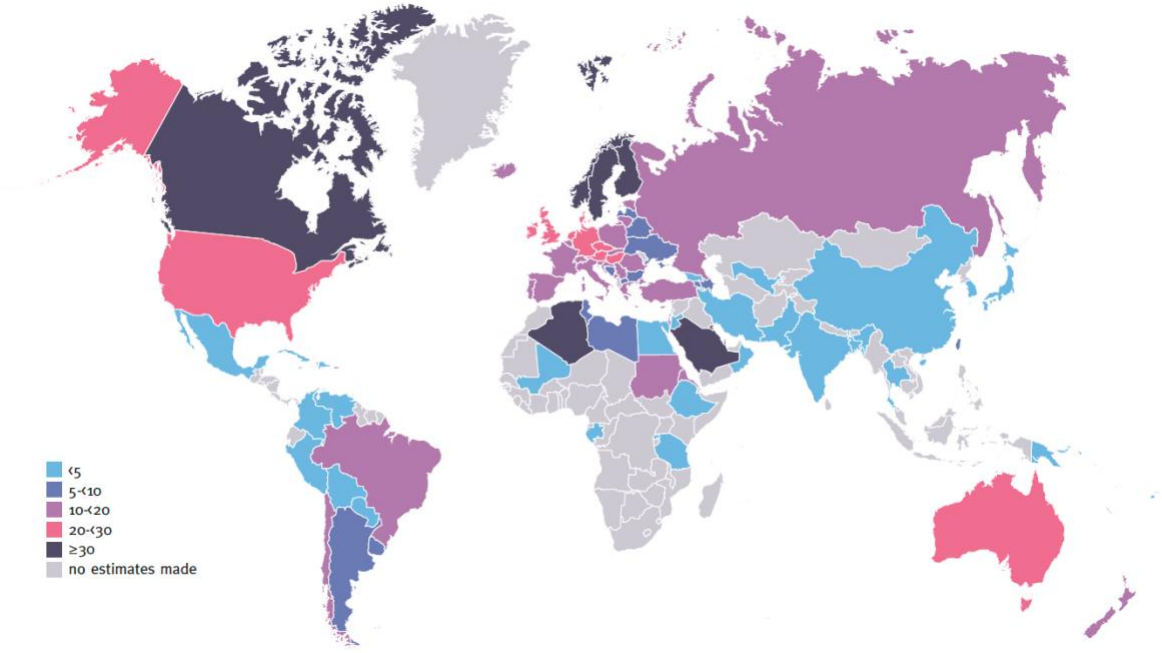

Figure 1.3 Estimated incidence rates per 100,000 population per year of T1D in youth under 15 years of age. Copyright permission granted from (11)

1.4.3 Complications of Type 1 Diabetes

1.4.3.1 Acute Complications

Hypoglycemia, defined as blood glucose levels less than 3.9 mmol/L, is a prevailing acute complication of T1D. Hypoglycemia involves acute symptoms that commonly include tremors, cardiac palpitations, sweating, hunger, irritability, confusion, blurred vision, and temporary cognitive impairment. People with T1D receive instructions from their healthcare team on how to manage hypoglycemia with rescue treatment.

Recurring hypoglycemia can eventually blunt the sympathetic response, causing impaired awareness of hypoglycemia from the hampered ability to self-recognize symptoms. Hypoglycemia that is left untreated can lead to severe hypoglycemia, defined as the need for third party assistance to receive treatment, which can result in serious short-term consequences, including seizures, coma, and even death (7,13,14). In fact, people with impaired awareness of hypoglycemia have a higher incidence of severe hypoglycemia (15).

Diabetic ketoacidosis is the other major acute complication that is potentially life-threatening if untreated in time. Diabetic ketoacidosis most commonly occurs when there is hyperglycemia from insufficient insulin, preventing glucose uptake. This state causes the body to undergo the ketogenic pathway, notably breaking down adipose tissue to generate ketone bodies as an alternative energy source. Elevated levels of plasma ketones cause the blood to become acidic, disrupting the pH and electrolyte balance, which can potentially lead to death (16,17).

1.4.3.2 Long-term Complications

Long-term complications, typically caused by persistent hyperglycemia, include the slow progression of microvascular and macrovascular comorbidities. Microvascular complications involve consequences affecting the eyes (retinopathy), kidneys (nephropathy), and nerves

(neuropathy). Macrovascular complications involve damage caused to large blood vessels that affect the heart (coronary artery disease), arteries (peripheral artery disease), and brain blood supply (cerebrovascular disease) (14).

1.4.4 Standard Treatments for Type 1 Diabetes

1.4.4.1 Evolution of Insulin

Insulin was discovered by Frederick Banting and Charles Best at the University of Toronto in 1921, which led to a Nobel Prize and eventually became recognized as one of the greatest breakthroughs in medicine of the 20th century. First-generation insulins were derived from the pancreas of pigs and cows; however, animal insulin was difficult to produce, lacked consistency between batches, and was linked to immunogenicity concerns.

In the early 1980s, animal insulin was replaced with synthetic human insulin made by recombinant DNA technology, which solved the shortcomings of insulin manufacturing while improving the safety profile. Human insulins include short-acting regular insulin, such as Humulin® R, which start working in 30 minutes, peak around two-three hours, and last between six-ten hours. Another type is intermediate-acting insulin, like Humulin® N also known as neutral protamine Hagedorn (NPH), with delayed onset of action (~two hours) and peak (~six hours), as well as variable duration of action (12-20 hours). Human insulins, however, still lacked sufficient resemblance to the endogenous profile of insulin secretion, causing hypoglycemia concerns.

Roughly a decade later, genetically modified insulin analogs leaped in development with altered pharmacological action for improved absorption, quicker onset, and more predictable duration of action. Insulin analogs mimic the profile of physiological basal and bolus (prandial) insulin release more closely, diminishing the major hypoglycemia concerns from previous forms of insulin (Figure 1.4) (18–20).

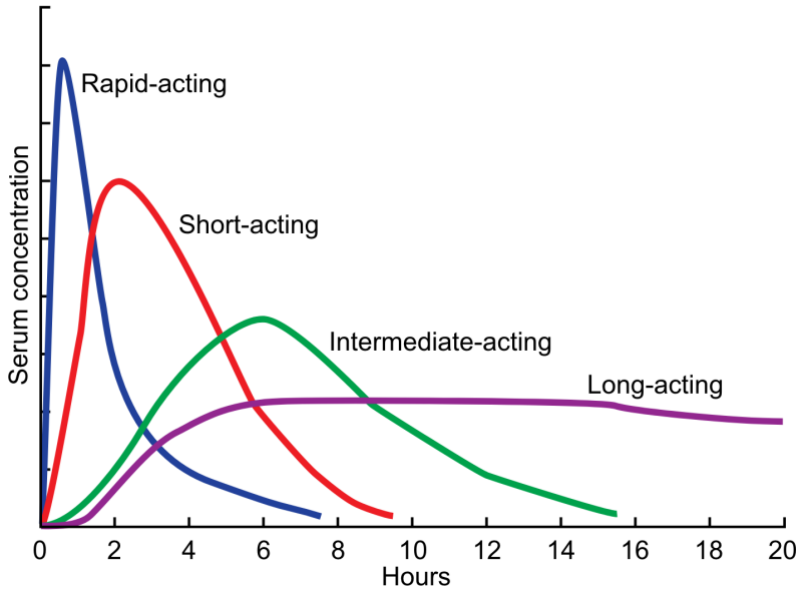

Figure 1.4 Pharmacokinetic profiles of human insulin and first-generation insulin analogs. Adapted version from (21), based on the original figure which was reproduced with permission from (18). Copyright Massachusetts Medical Society.

1.4.4.2 Insulin Analogs

First-generation long-acting insulin analogs, glargine and detemir U-100 (100 units in one millilitre of fluid) became commercially available in the early 2000s. Long-acting analogs overcame the peak effect of intermediate-acting NPH, courtesy of a low peak:trough ratio, allowing for a flatter profile with a longer duration of action lasting up to 24 hours. Consequently, long-acting analogs more closely simulate the background secretion of physiological insulin.

Second-generation basal analogs, known as ultra long-acting insulins, were subsequently developed with a much longer duration of action, such as degludec U-100 (up to 42 hours) and stronger concentration, such as glargine U-300 (three-fold stronger concentration than the U-100 formulation). Compared to intermediate-acting NPH requiring twice-daily dosing, long-acting and ultra long-acting analogs allow for once-daily dosing, with the latter enabling greater flexibility in between doses.

Similarly, first-generation rapid-acting insulin analogs overcame the pharmacokinetic challenges and atypical profile of short-acting human insulin, namely, the slow onset, delayed peak, and prolonged duration of action. Conversely, lispro and aspart insulin analogs begin working in just 10-15 minutes, have a peak effect within two hours, and last up to five hours. Therefore, insulin analogs offer a more accurate representation of physiological prandial insulin secretion while improving patient adherence and hypoglycemia risk.

Second-generation rapid-acting analogs include faster-acting aspart and ultra-rapid lispro, which offer an even quicker onset of action, permitting bolus injections to be given at meal time up to 20 minutes post-initiation. These analogs also have a slightly faster peak and duration of action (Table 1.1) (20,22,23).

Table 1.1 Pharmacokinetic properties of human insulin and insulin analogs. Open access permission from (23).

Insulin type	Onset time	Peak effect	Duration of action
Ultra-rapid-acting			
Faster insulin aspart	4 min	1–3 h	3–5 h
Ultra-rapid insulin lispro	2 min	1–2 h	4.5 h
Rapid-acting			
Insulin lispro	10–15 min	1–2 h	3–5 h
Insulin aspart	10–15 min	1–3 h	3–5 h
Insulin glulisine	10–15 min	1–2 h	2–4 h
Short-acting			
Regular human insulin	30 min	2–3 h	6.5 h
Intermediate-acting			
NPH insulin	1–3 h	5–8 h	18 h
Long-acting			
Insulin Glargine U100	1.5 h	None	24 h
Insulin Glargine U300	6 h	None	24–36 h
Insulin Detemir U100	3–4 h	6–8 h	24 h
Insulin Degludec U100+U200	30–90 min	None	42 h

1.4.4.3 Intensive Insulin Therapy

Conventional insulin therapy is the traditional delivery method involving the administration of one or two daily injections of intermediate-acting insulin with or without short-acting insulin. This regimen, however, is limiting as it requires rigid lifestyle planning around the atypical time-action insulin profile. In contrast, intensive insulin therapy refers to the basal-bolus regimen. For MDI users, this typically consists of three or more rapid-acting bolus insulin injections and one or two long-acting basal insulin injections per day, providing greater lifestyle flexibility. For pump users, this involves the continuous infusion (basal) with additional boosts of infusion (bolus) of rapid-acting insulin. This regimen aims to mimic the physiological patterns of insulin secretion (24).

The Diabetes Control and Complications Trial (DCCT) was a landmark study that demonstrated the long-term benefits of intensive insulin therapy over conventional therapy. The findings revealed that a mean reduction in hemoglobin A1c (HbA1c) below 7.0% in the intensive insulin group was associated with delayed and attenuated progression of retinopathy, neuropathy, and nephropathy (25). Accordingly, tight glycemic control is linked with reduced risk of long-term complications. Furthermore, the observational Epidemiology of Diabetes Interventions and Complications follow-up study demonstrated sustained benefits in microvascular protection. This study also reported reductions in macrovascular complications from the group that had early implementation of intensive insulin therapy in the initial DCCT (26). Accordingly, intensive insulin therapy is the mainstay treatment for T1D (27).

1.4.4.4 Target Recommended Guidelines

Following the DCCT outcomes, an HbA1c target below 7.0% became the gold-standard glycemic target in attenuating long-term diabetes complications for adults with T1D. HbA1c is a blood marker that represents an individual's average glucose control over the past 90-120 days, in

accordance with the average lifespan of erythrocytes (red blood cells). However, there is wide variability in the lifespan duration of erythrocytes among individuals. Furthermore, HbA1c measurements tend to be more influenced by the glycosylation of younger red blood cells in the last 30 days over older ones.

In addition, there are numerous conditions that alter the turnover rate of erythrocytes, rendering HbA1c measurements less accurate. For example, iron deficiency and vitamin B12 deficiency result in reduced erythrocyte destruction, thus prolonging their lifespan, which can falsely increase an HbA1c value. Conversely, anemias caused by blood loss result in the destruction of younger red blood cells, increasing their turnover rate, and in turn, falsely lowering HbA1c. Nevertheless, HbA1c remains the primary biomarker used in clinical practice (28).

Of note, the HbA1c metric falls short in providing information about daily glycemic excursions. Alternatively, the increasing adoption and reliance on CGM reports has permitted a more comprehensive understanding of day-to-day glucose profiles, including visual patterns of daily and weekly trends for more precise management. In fact, according to an international consensus report, 14 days of CGM data for mean glucose and time in and above range, and at least 30 days of time below range and glycemic variability are correlated with 90 days of data. CGM metrics are now complementing HbA1c in the overall assessment of glycemic control, both in clinical practice and in trials.

The consensus statement put forward recommended targets for the following CGM metrics in adults with T1D: more than 70% time between 3.9-10 mmol/L, less than 4% time below 3.9 mmol/L, less than 1% time below 3.0 mmol/L, less than 25% time above 10 mmol/L, and less than 5% time above 13.9 mmol/L. Importantly, every 5% increase in time in range is linked with clinically meaningful benefits. Table 1.2 displays the recommended daily target thresholds for

most adults with T1D. Notably, higher-risk, elders, and youth under 25 years of age have less stringent CGM targets (29,30).

Table 1.2 International consensus for CGM targets for T1D. Adapted and reproduced with permission from (29)

	TIR		TBR		TAR	
Diabetes group	% of readings; time per day	Target range	% of readings; time per day	Below target level	% of readings; time per day	Above target level
Type 1*/type 2	>70%; >16 h, 48 min	70–180 mg/dL (3.9–10.0 mmol/L)	<4%; <1 h <1%; <15 min	<70 mg/dL (<3.9 mmol/L) <54 mg/dL (<3.0 mmol/L)	<25%; <6 h <5%; <1 h, 12 min	>180 mg/dL (>10.0 mmol/L) >250 mg/dL (>13.9 mmol/L)

There are varying relationships between CGM metrics and HbA1c outcomes. A comparison across large CGM trials revealed that a 10% improvement in time in range in individuals with baseline HbA1c of 8.0% or higher is correlated with an HbA1c reduction of about -1.0%. On the other hand, the same 10% improvement in time in range in those with baseline HbA1c between 7-7.9% is correlated with a much lower HbA1c improvement of about -0.4%. Furthermore, time in range and mean glucose have both been found to be moderately correlated with HbA1c (31).

1.4.4.5 Multiple Daily Injections

MDI typically involves one or two long-acting insulin injections intended to mimic the slow secretion of endogenous basal insulin to cover background needs. This regimen also requires multiple rapid-acting insulin (bolus) injections to control postprandial glucose excursions.

Prandial bolus delivery is characterized by two main dosing strategies: fixed-dose and carbohydrate counting. The original fixed-dose method continues to be used by some individuals with T1D, involving a set amount of bolus insulin for each meal type based on the assumption that the pre-calculated portion of carbohydrates remains constant. This approach offers less flexibility

for dietary and lifestyle changes. Alternatively, carbohydrate counting is the more advanced and precise method involving the use of insulin-to-carbohydrate ratios (ICRs). ICRs are used to determine how many carbohydrates are covered by one unit of insulin for a given meal and time of day. Carbohydrate counting offers dietary freedom with unrestricted carbohydrate intake. Typically, people with T1D have three or four mealtime ICRs according to varying sensitivity patterns throughout the day that require stronger or weaker ratios at different timepoints (32,33).

Traditionally, MDI involved the use of a vial and syringe. Today, disposable and refillable basal and bolus insulin pens are now the leading devices used for this regimen (Figure 1.5) (34). Furthermore, MDI remains the predominant insulin delivery method used by people with T1D worldwide (35).

Figure 1.5 Insulin delivery via MDI. Adapted and reproduced with permission from (36), Copyright Massachusetts Medical Society.

1.4.4.6 Continuous Subcutaneous Insulin Infusion

The alternative insulin delivery technique involves a portable insulin pump. This method has the advantage of mimicking physiological insulin secretion more closely due to the continuous nature

of insulin delivery throughout the day at adjustable programmed basal infusion rates, along with manual bolus input at meal times.

A traditional insulin pump is a battery-operated device that comprises an insulin reservoir (cartridge of rapid-acting insulin) that is connected to an infusion set comprising tubing and a cannula that is inserted under the skin (Figure 1.6). A patch pump differs by eliminating the need for tubing, connecting the pump directly on the skin via an integrated cannula. Infusion sites include the abdomen, thighs, arms, and buttocks (27,36).

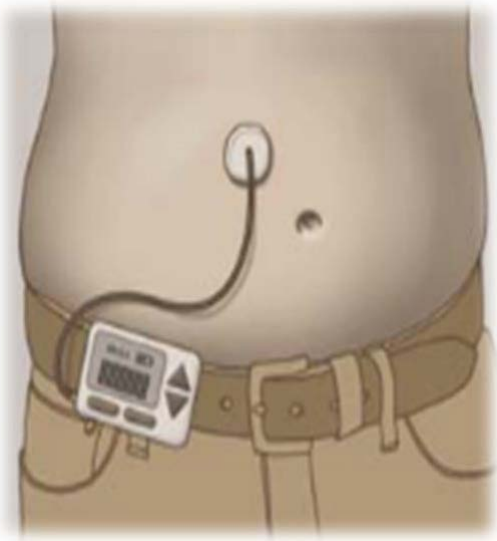

Figure 1.6 Continuous insulin infusion via insulin pump. Adapted and reproduced with permission from (36), Copyright Massachusetts Medical Society.

1.4.4.7 Glucose Monitoring

In earlier times, individuals with T1D had to rely on urine sticks to get an indirect measurement of their blood glucose level. Urine glucose testing was used for over 50 years, albeit limited by the hours of wait time before high glucose levels were approximately detected in urine, resulting in delayed and inaccurate measurements via a color-based dipstick system.

In the early 1970s, urine glucose testing was replaced by self-monitoring of blood glucose (SMBG) with capillary blood measurements using a lancet to prick the finger and a glucometer device to obtain a direct blood glucose reading. SMBG is a direct method to obtain accurate and real-time readings of one's blood glucose levels. In fact, this approach paved the way for intensive insulin therapy by virtue of implementing timely hyperglycemia and hypoglycemia corrections, enabling the conduct of the landmark DCCT, which in turn, transformed the standard of care for T1D (37). However, despite the inverse relationship between the frequency of SMBG measurements and HbA1c (38), this method has several drawbacks. These limitations include multiple daily finger-pricks, adherence problems, and the absence of feedback regarding glucose excursions between measurements (39).

Fortunately, the adoption of CGM in the early 2000s overcame these issues, simplifying glucose monitoring. CGM comprises a sensor containing an electrode that is inserted under the skin and continuously measures the interstitial fluid to wirelessly relay estimated glucose readings to a receiver or application over 5-15-minute intervals. There are two main types of personal CGM systems used in unsupervised settings, namely, real-time CGM (rtCGM) and intermittently scanned CGM (isCGM).

The first commercially available personal rtCGM was the Guardian® system (Medtronic, United States) developed in 2004. This system integrated alarms and had a lifespan of three days, but it required daily calibrations and the margin of error was high. However, the Guardian system evolved over time, doubling in sensor wear duration and nearly cutting the margin of error in half.

The personal Dexcom rtCGM (Dexcom Inc., United States) evolved within the G-series generations every few years with lower error and increased lifespan, starting with the Dexcom G4® Platinum to G5®, both having a sensor wear up to seven days with optional alarms. The

Dexcom G6® was subsequently developed with extended sensor wear up to 10 days while being the first rtCGM to spare calibrations. The G7® is currently the latest version that was approved for commercial use, with the same lifespan but is over 50% smaller in size. It also combines the transmitter and sensor into one device and requires a warm-up period of under 30 minutes (40).

Several landmark trials have confirmed the benefit of rtCGM over SMBG in adults. The JDRF study reported a significant HbA1c reduction of -0.5% in adults aged 25 years and older with T1D on MDI and pump after six months of using rtCGM compared to SMBG (41). Similarly, two other 6-month trials (GOLD and DIAMOND) demonstrated a significant HbA1c reduction of -0.4% and -0.6%, respectively, with rtCGM compared to SMBG in MDI-treated adults with T1D and suboptimal glycemic control (42,43). Another 6-month trial (HypoDe) reported improvements in hypoglycemic events with rtCGM in near-optimally controlled MDI-treated adults with T1D and impaired awareness of hypoglycemia or history of severe hypoglycemia (44).

In 2018, the first-generation Freestyle Libre™ system (Abbott Diabetes Care, United States) became commercially available as the first isCGM requiring users to scan the sensor to obtain readings, with at least one scan every eight hours to capture continuous data. It was also the first factory-calibrated sensor with the longest lifespan (14 days) to reach the market. The commercialization of the Freestyle Libre system was supported by the 6-month IMPACT safety trial, which demonstrated a significant reduction in hypoglycemia without degradation of HbA1c compared to SMBG in a large cohort of well-controlled adults with T1D on MDI and pump (45). Of note, another 6-month trial conducted in youth with T1D and suboptimal glycemic control reported no HbA1c improvement with isCGM compared to SMBG (46). Conversely, the 6-month FLASH-UK trial, conducted in an adult population, demonstrated a significant HbA1c reduction of -0.5% with isCGM compared to SMBG (47).

The original Freestyle Libre system evolved into the second-generation Freestyle Libre 2®, equipped with optional alarms. Recently, this system was converted into an rtCGM, eliminating the need for scanning. Currently, the third-generation Freestyle Libre 3® is the latest rtCGM that is smallest in size and will soon become commercially available (48).

All CGM systems have an inherent lag of roughly 15 minutes between the interstitial fluid and plasma glucose, which is exacerbated during rapid changes in glycemia. Nevertheless, they provide a reliable approximation of one's current glucose levels in a less invasive and more convenient way than finger-pricking with SMBG. Furthermore, all forms of CGM technology continue to evolve toward smaller sensor size, longer duration, and reduced margin of error (49,50). CGM technology has revolutionized diabetes care, improving glycemic control similarly in both MDI and pump users (51). CGM is now considered part of the standard of care and is recommended at the outset of diagnosis (35).

1.4.5 Advanced and Emerging Insulin Delivery Technologies for Type 1 Diabetes

1.4.5.1 Hybrid Closed-Loop Systems

Over the past two decades, research on advanced insulin pump technology has progressed significantly from sensor-augmented pump therapy to the world's first commercially available hybrid closed-loop system (MiniMed™ 670G (Medtronic, United States)), with continually evolving technology. Hybrid closed-loop is now commonly referred to as automated insulin delivery (AID). AID technology involves the integration of a control algorithm in a pump or hosted on a portable device that wirelessly receives CGM input for continuous feedback to automatically adjust basal insulin delivery rates every 5-10 minutes in response to changing needs (Figure 1.7). Currently, there are several commercially available AID systems, namely, MiniMed™ 780G (Medtronic, United States), CamAPS® FX (CamDiab, United Kingdom), Control-IQ™ (Tandem

Diabetes Care, United States), Omnipod® 5 (Insulet, United States), DBLG1™ (Diabeloop, France), and iLet® Bionic Pancreas (Beta Bionics, United States) (52,53).

AID has proven to improve both glycemic control and quality of life in youth (54) and adults (55). Nevertheless, all systems still require manual user announcement of prandial boluses, hence "hybrid" closed-loop. While AID can more closely imitate endogenous insulin secretion than MDI, it is associated with known issues surrounding cost, visibility, discomfort, and device failures, making it undesirable for some to adopt (52,53).

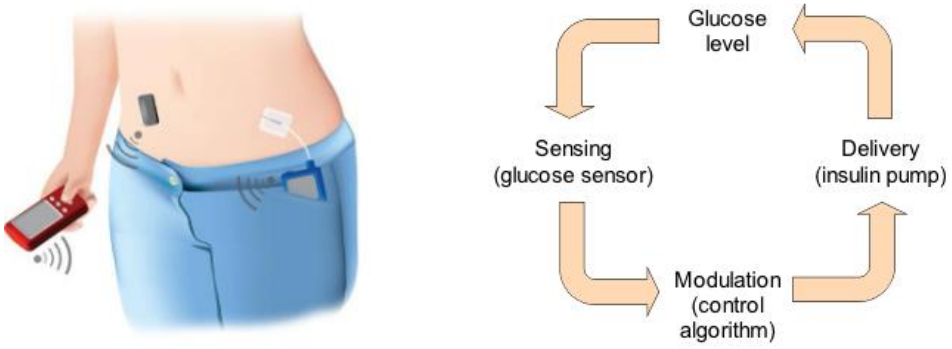

Figure 1.7 Overview of a hybrid closed-loop system. Open access permission from (53)

1.4.5.2 Decision Support Systems for Multiple Daily Injections

Since their introduction, insulin pens have gradually evolved over time, albeit with minimal enhancements, including built-in or add-on memory features. However, there has been a shift in focus toward advancing MDI therapy in recent years, given the underserved yet dominating market.

In 2017, the InPen™ (Companion Medical Inc., United States) entered the American market as the first FDA-cleared reusable smart pen. It incorporates wireless Bluetooth technology that communicates with a smartphone application equipped with a bolus calculator and active insulin tracking, offering a new approach to MDI therapy. Subsequently, Bigfoot Unity™ (Bigfoot

Biomedical Inc., United States) was launched as the first FDA-cleared smart pen cap system in 2021. This system is compatible with most basal and bolus disposable pens and wirelessly transmits data to a smartphone application (56). However, both commercial systems lack an adaptive decision support tool guided by an algorithm.

The principal concept behind a DSS entails the same core idea of AID for insulin pumps, which is to utilize digital platforms and algorithms to optimize insulin injections. A DSS would integrate CGM with smart pen devices and an algorithm that recommends tailored insulin adjustments on a regular basis (Figure 1.8). Although research on DSSs has increasingly gained popularity in recent years, there is limited robust evidence (57). To this end, my thesis is focused on the clinical impact of a novel DSS.

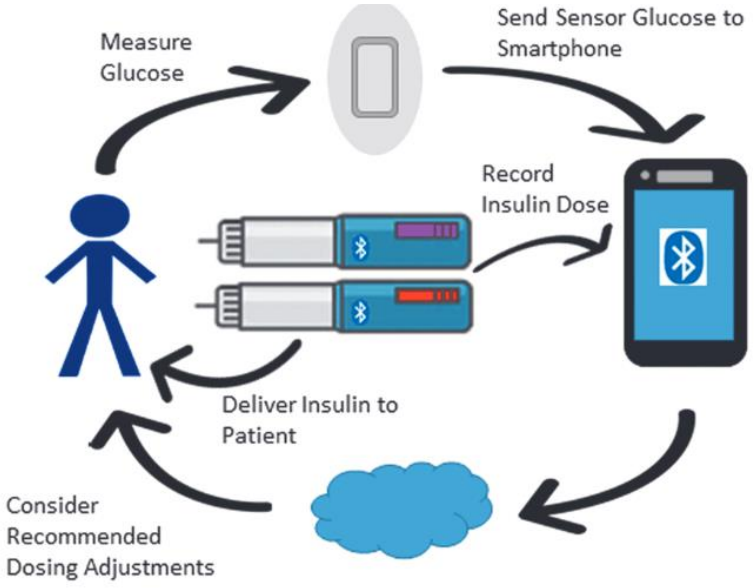

Figure 1.8 Concept overview of a DSS for MDI therapy. Open access permission from (57)

In the next chapter, I present an appraisal of the clinical evidence of relevant research. I begin with a literature review on standalone automated bolus calculators and then on adaptive DSSs, providing a comprehensive background to orient my core thesis work in the field.

Chapter 2. Literature Review

The literature review below summarizes and critically appraises the current interventional evidence, starting with non-adaptive bolus calculators and then adaptive DSSs. The appraisal focuses on studies involving populations that consisted either partially or entirely of MDI-treated individuals with T1D, in keeping with the relevance of this thesis. The ensuing bolus calculator section is organized by hardware and software sub-sections, which are each further sub-categorized by trial.

2.1 Bolus Calculators

An automated bolus calculator was initially introduced as an insulin pump feature. Bolus calculators are designed to facilitate mealtime and correction bolus calculations using one's programmed parameters and current glucose level while accounting for real-time residual active insulin, abating the risk of insulin stacking (58).

The use of automated bolus calculators was later extended to MDI users as an embedded feature in glucose meters and subsequently incorporated in smartphone applications. The intended purpose is to simplify MDI therapy, alleviating the need for numeracy skills that are otherwise required for manual dose calculations, which are currently associated with poorer glycemic outcomes (59,60).

2.1.1 Handheld Bolus Calculator for Multiple Daily Injections

Maurizi et al. (2011) ran a 6-month, pilot, randomized, controlled, parallel trial with Calsulin (Thorpe Products Ltd., United Kingdom), a pocket-size bolus calculator device. A total of 40 adults on MDI therapy with T1D (mean baseline HbA1c: 7.9%) were randomized to either continue with manual bolus estimations (control) or receive automated bolus calculations from Calsulin

(experimental). After 6 months, there was a substantial between-group reduction in HbA1c of -0.78% ($p<0.05$) (61).

2.1.2 Glucose Meter with a Built-In Bolus Calculator

Several randomized controlled studies have investigated the Accu-Check® Aviva Expert (Roche Diagnostics, Germany) combined with carbohydrate counting in MDI-treated adults with and without previous carbohydrate counting practice. The Aviva Expert is a glucose meter equipped with an integrated bolus calculator that computes prandial and correction bolus doses. The calculations are based on one's capillary blood glucose reading, remaining active insulin from the previous dose, target glucose level, anticipated carbohydrate intake, meal-specific ICR, insulin sensitivity factor (ISF), and exercise (62).

2.1.2.1 Schmidt et al. (2012)

The BolusCal trial employed a 16-week, open-label, randomized, controlled, three-arm parallel design, conducted in 51 MDI-treated adults with T1D (mean baseline HbA1c: 9.0%) on fixed-dose basal-bolus regimen. This pilot study assessed the feasibility of an intensive three-hour structured diabetes management course with and without the added use of the Aviva Expert. Participants were randomized in a 1:3:3 ratio to either: control (fixed-dose per usual care), carbohydrate counting, or carbohydrate counting plus the Aviva Expert. Only the latter two groups received additional baseline training on carbohydrate counting.

After 16 weeks, there was a large between-group improvement in HbA1c of -0.8% ($p=0.017$) with the combined use of carbohydrate counting with the automated bolus calculator compared to control. However, no difference was found between the two carbohydrate counting groups, suggesting no added glycemic benefit from the bolus calculator. Nevertheless, the group

with the Aviva Expert reported significantly higher treatment satisfaction scores from baseline compared to the carbohydrate counting-only group (62).

2.1.2.2 Hommel et al. (2017)

The same group as (62) subsequently conducted the StenoABC study. This was a 12-month, open-label, randomized, controlled, two-way parallel trial. It was designed to assess the long-term impact of their combined intensive structured diabetes and carbohydrate counting training course (provided to both groups) with and without the Aviva Expert bolus calculator in 168 carbohydrate counting-naïve adults with T1D on MDI (mean baseline HbA1c: 9.0%) (59). In contrast to their pilot findings (62), this study demonstrated a small but significant difference between both carbohydrate counting groups of -0.2% ($p=0.033$) in favor of the intensive training combined with long-term automated bolus calculations (-0.5%) over manual bolus calculations (-0.3%) (59).

2.1.2.3 Ziegler et al. (2013)

The ABACUS study entailed a 6-month, open-label, randomized, controlled trial in 218 MDI-treated adults already practicing carbohydrate counting with inadequate glycemic control (mean baseline HbA1c: 8.8%). Participants were randomized 1:1 to receive the Aviva Expert or to continue with their usual care involving a standard glucose meter. Both groups received baseline carbohydrate counting refresher training.

Despite a small mean reduction in the average daily bolus calculator use from start to end (2.9/day to 2.7/day; $p<0.01$), the experimental group still achieved a robust improvement in HbA1c from baseline (-0.7%). The control group also achieved a meaningful improvement (-0.5%), resulting in a modest but significant between-group difference of -0.2% ($p<0.05$) (63), which is consistent with the findings from the StenoABC trial (59). The large improvements found in both groups may have been attributed to frequent insulin adjustments made throughout the study.

Importantly, however, significantly more participants in the bolus calculator group achieved an HbA1c improvement greater than 0.5% compared to the control group (56% versus 34%, respectively; $p<0.01$) (63).

2.1.2.4 Gonzalez et al. (2016)

The Expert study was the first randomized controlled trial using a crossover design to compare automated bolus calculations with the Aviva Expert versus manual calculations with a standard glucose meter. Overall, 51 MDI-treated adults with T1D and suboptimal glycemic control (mean baseline HbA1c: 8.1%) completed the study. All participants were acquainted with carbohydrate counting but still received a two-hour diabetes management refresher training at baseline.

Both the traditional and Aviva Expert meters were used for 12 weeks by all participants in random sequence order with a 12-week washout period in between (64). Contrary to the aforementioned findings from the StenoABC (59) and ABACUS (63) trials, this study found no difference in HbA1c between the meters when participants served as their own control (64).

2.1.2.5 Vallejo Mora et al. (2017)

The CBMDI study was a 16-week, open-label, randomized, controlled, parallel trial, conducted in 70 adults with T1D on MDI therapy with suboptimal glycemic control (mean baseline HbA1c: 8.4%). All participants were required to perform carbohydrate counting for the study. The participants were randomly assigned to either the Aviva Expert for automated calculations or a traditional meter for manual estimations, both in addition to intensive baseline training (65). Similarly to the ABACUS trial (63), this study involved intensified insulin adjustments during the intervention period for both groups.

However, the authors reported a between-group difference in HbA1c of -0.3% that was not statistically significant (65). Furthermore, in their 4-month extension study, both groups used the

automated bolus calculator, but there were no between- or within-group changes from baseline, suggesting no additional glycemic benefit with prolonged use of automated bolus calculations. Nevertheless, significantly greater treatment satisfaction and reduced fear of hypoglycemia were reported after eight months of using the bolus calculator (66).

Collectively, these studies revealed conflicting findings regarding the Aviva Expert's impact on glycemia. Some studies that did not reach statistical significance may have been underpowered or affected by design flaws. Nevertheless, overall positive findings tend to suggest only modest improvements in HbA1c when carbohydrate counting was augmented with automated bolus calculations guided by the Aviva Expert glucose meter.

2.1.3 Smartphone Application-based Bolus Calculators

2.1.3.1 Charpentier et al. (2011)

The TeleDiab 1 study was a 6-month, open-label, multicenter, randomized, controlled, parallel trial that investigated the efficacy and safety of DIABEO, a smartphone application integrating a formula-based, non-adaptive bolus calculator, with and without telemedicine. This study included 180 adults on MDI (63%) and pump (37%) with T1D and a mean baseline HbA1c of 9%.

Participants were randomized 1:1:1 into three groups: paper logbooks on top of quarterly in-person follow-ups (group 1), DIABEO in addition to quarterly in-person follow-ups (group 2), and DIABEO combined with biweekly teleconsultations with physicians. After six months, the DIABEO application coupled with either in-person visits (per standard of care) or frequent teleconsultations both resulted in a statistically significant and substantial HbA1c reduction of -0.7% and -0.9% compared to usual care, respectively (both $p<0.001$) (67).

2.1.3.2 Franc et al. (2020)

Almost a decade later, the same group as (67) conducted the TELESAGE trial to assess the DIABEO system with a similar three-arm design but over a 12-month duration. Moreover, this study involved biweekly teleconsultations provided by trained delegated nurses instead of physicians. In addition, the sample size was over 3.5-fold larger (665 adults) with a similar mean baseline HbA1c (9.1%). This cohort also consisted of MDI (47%) and pump (53%) users, albeit more balanced, but additionally included a small proportion of individuals with T2D (8%) (68). Although less profound than their previous findings (67), these results consistently demonstrated a meaningful HbA1c improvement with the DIABEO software plus quarterly monitoring (-0.41%), with further benefit obtained when combining the system with biweekly nurse-led teleconsultations (-0.51%), both compared to control ($p<0.001$) (68).

2.1.3.3 Secher et al. (2021)

A 26-week, open-label, multicenter, randomized, controlled, parallel trial investigated isCGM with and without the mySugr smartphone application (mySugr, Austria) equipped with a built-in bolus calculator. A total of 170 adults with T1D using fixed-dose MDI therapy who were naïve to both CGM and carbohydrate counting (mean baseline HbA1c: 8.1%) were randomized in a 1:1:1:1 ratio to either: usual care (fixed-dose), isCGM alone, isCGM plus mySugr, or mySugr alone. All participants received basic diabetes education at baseline, but training on carbohydrate counting was restricted to the groups involving the bolus calculator application.

In this study, the primary endpoint was the change from baseline in the percentage of CGM time in range between carbohydrate counting plus isCGM versus usual care. However, there was no statistically significant difference between those groups. Moreover, no difference was found between the groups that used the application alone or in conjunction with isCGM compared to

usual care. Interestingly, while neither the standalone application or isCGM groups had improvements in HbA1c, there was a trending improvement observed in the combined group (isCGM plus mySugr). Furthermore, the authors observed significantly improved patient-reported diabetes treatment satisfaction scores in both isCGM groups (with and without mySugr) compared to control (69).

Taken together, the large-scale evidence involving application-based bolus calculators is mixed. The DIABEO system resulted in robust glycemic improvements compared to usual care, although the software notably consisted of a more advanced bolus calculator based on non-learning algorithms. In contrast, the study involving the mySugr application reported no difference in the main CGM outcome but found a trending reduction in the HbA1c outcome, which might point to a study design flaw.

In all, while some studies suggest mild glycemic improvement with an automated bolus calculator among MDI users, the collective interventional evidence is ambivalent. Regardless, standard bolus calculators do not optimize insulin parameters over time, precluding them from adapting to changes in insulin requirements, hence limiting their clinical utility and benefit (70). Furthermore, it is important that the insulin parameters used by bolus calculators represent an individual's actual needs to ensure accurate calculations (58). Yet, a common challenge in clinical practice is the limited follow-up frequency with healthcare professionals. People with T1D can be monitored quarterly if glycemic targets are not met or have comorbidities but are otherwise typically monitored on an annual basis (71), in part due to restricted resources and access (72).

Additionally, qualitative evidence has revealed that some individuals avoid making self-initiated adjustments and continue with their prescribed regimen until the next follow-up appointment due to a lack of confidence or competency (73), resulting in long periods of using

potentially insufficient parameters. Consequently, a DSS encompassing an adaptive bolus calculator that regularly adjusts insulin parameters could alleviate some of these constraints in between medical appointments.

2.2 Decision Support Systems for Multiple Daily Injections

To date, there are few large-scale randomized controlled trials that have investigated the efficacy of DSSs to optimize insulin injection parameters. Below is a detailed appraisal of the clinical evidence on feasibility, safety, and efficacy of DSSs that were designed either partially or exclusively for MDI adjustments and T1D. The following sub-sections are organized by DSS, each beginning with a brief overview of the system, followed by the corresponding preliminary and advanced (if applicable) clinical work, leading up to the manuscripts (Chapters 3 and 4) from my core thesis work.

2.2.1 The Diabetes Insulin Guidance System

The Diabetes Insulin Guidance System (DIGS) (Hygieia, Inc., United States) consists of adaptive algorithms that use glucose readings to adjust meal-specific insulin doses, with varying aggressiveness in recommendations depending on how close one's glucose levels are to optimal targets (74).

2.2.1.1 Bergenstal et al. (2012)

A 12-week, feasibility, uncontrolled study assessed the safety of the DIGS in refining insulin doses. There were three unrelated groups that were independently analyzed: 20 MDI-treated adults using carbohydrate counting with T1D and suboptimal glycemic control (group 1), and MDI-treated adults with T2D and suboptimal glycemic control while on fixed-dose basal-bolus regimen (group 2, n=20) or twice-daily intermediate-acting insulin (group 3, n=6). Each group of participants were

asked to record time-stamped SMBG readings and meal-specific insulin information in paper diaries, which were used by the DIGS to generate weekly insulin adjustments. The recommendations were reviewed and approved by the medical team, who then conveyed the changes to participants.

Overall, 99.8% of all DIGS-made recommendations received physician approval without being overridden. Although a trend was observed in mean glucose and HbA1c, this was only applicable to the groups including individuals with T2D. The group that consisted of people with T1D had no change in glycemic outcomes (74).

2.2.2 The Adaptive Bolus Calculator for Type 1 Diabetes System

The Adaptive Bolus Calculator for Type 1 Diabetes (ABC4D) DSS was developed at Imperial College London. The ABC4D system consists of a smartphone application that features an adaptive bolus calculator mode comprising an algorithm that combines a run-2-run (R2R) framework with case-based reasoning (CBR), and an online clinical portal. R2R is a model-based approach that uses CGM data and postprandial glycemic outcomes from the previous run to modify meal bolus parameters toward optimal glycemic targets. CBR is an artificial intelligence tool that involves a problem-solving approach that adapts meal bolus parameters by retrieving a similar case from the previously solved case database and re-using that solution or creating a new solution. Cases are revised with the R2R control if the selected solution led to an off-target postprandial glycemic outcome (75,76).

2.2.2.1 Reddy et al. (2016)

The ABC4D DSS was initially clinically tested in a 6-week, single-arm, feasibility study in 10 MDI-treated adults with T1D and suboptimal baseline control (mean HbA1c: 8.4%). At the end of each week, participants visited the research facility to download their CGM data and ABC4D

application data required to run the algorithm in the clinical platform and generate meal bolus parameter adjustments. All recommendations were reviewed and approved by the medical team prior to updating each participant's application.

The authors observed a downward trend in the number of postprandial hypoglycemic events in the last week (1 event) compared to the first week (3.5 events). Although this study was not powered, had a small sample size, and lacked a control group, it was considered feasible and safe to investigate further in a controlled trial (76).

2.2.2.2 Unsworth et al. (2023)

The refined ABC4D DSS was investigated in a 12-week, blinded, randomized, controlled, crossover trial in 37 MDI-treated adults with T1D (mean baseline HbA1c: 7.7%). In this version, the meal bolus parameter adaptations were performed locally in the participants' application when the adaptive mode was enabled. All participants received structured refresher training on diabetes management prior to the 2-week run-in period. Thereafter, participants were stratified by HbA1c and randomized 1:1 to receive the adaptive application or the non-adaptive version (comprising only the standard bolus calculator) for 12 weeks, followed by a 6-week washout period before switching over to the alternate group.

During the adaptive intervention, the case database was updated every day, influencing each participant's daily bolus calculations in the application without their awareness, which allowed for a blinded design. The application data was automatically transferred to the clinical platform and reviewed for safety by the research team every two weeks, although no interfering changes were made. The primary endpoint was the change in daytime percent time in range with the Dexcom G6® rtCGM.

There were marginal changes in time in range for both the ABC4D DSS (0.1%) and the non-adaptive application (1.9%), both of which are not clinically meaningful. There was also no significant difference in HbA1c between the periods. Furthermore, post-hoc analyses revealed a significantly higher proportion of accepted meal bolus calculations in the last two weeks when using the non-adaptive application compared to the adaptive version (94% versus 79%, respectively; p=0.009). The diminished acceptance rate observed in the DSS group may suggest suboptimal performance of the adaptive component (77).

2.2.3 The Patient Empowerment through Predictive Personalized System

The Patient Empowerment through Predictive Personalized (PEPPER) DSS was developed by the same group that created the ABC4D system but designed this one for both pump and MDI users. PEPPER utilizes CBR technology as the basis of their adaptive bolus calculator to adjust ICR and ISF parameters. However, it also couples a safety system comprising 1) predictive glucose threshold alerts, 2) a rescue carbohydrate recommender for hypoglycemia treatment, 3) a dynamic bolus insulin constraint to avoid insulin stacking, and 4) a 30-minute glucose forecasting algorithm (exclusively for pump users).

PEPPER is hosted on a smartphone application that features the standard bolus calculator with real-time graphics in the non-adaptive mode and the CBR-based insulin recommender and safety system in the adaptive mode. The application data is automatically transferred to a clinical platform for remote clinical monitoring and review of CBR-made revisions to manually reject the ones excluded from the adjustment criteria (78,79).

2.2.3.1 Liu et al. (2020)

An 8-week, single-arm, feasibility study was conducted to initially assess the PEPPER safety system (excluding the pump-specific module) without the CBR component in six MDI-treated

adults with T1D and suboptimal baseline glycemic control (mean HbA1c: 7.9%). The primary endpoint assessed the percentage of time below 3.9 mmol/L from the standard bolus calculator (safety system disabled) during a 2-week run-in period compared to the last two weeks of the intervention with the safety system enabled. The authors observed a downward trend in the time below 3.9 mmol/L and an upward trend in time in range in favor of the safety system (78).

2.2.3.2 Avari et al. (2021)

A 12-week, open-label, randomized, controlled, crossover trial investigated the complete PEPPER DSS (CBR-based insulin recommender and safety system enabled). Overall, 54 adults with T1D (mean baseline HbA1c: 7.7%) on pump (52%) and MDI (48%) who were already practicing carbohydrate counting completed a 4-week run-in period with the non-adaptive bolus calculator. All participants were provided with Dexcom G5® sensors, and the pump users received the Cellnovo pump (Cellnovo Ltd., United Kingdom). They all received refresher training and applicable device training. Thereafter, participants were randomized to receive the PEPPER DSS or the standard application (CBR-algorithm and safety system disabled) in the first period.

In the PEPPER intervention, each participant's case-base was reviewed in the clinical platform twice per week by the medical team to reject revised case solutions according to exclusion criteria prior to releasing the updates. After a 3-4-week washout period, pump users were withdrawn following the Cellnovo manufacturer-initiated market withdrawal, precluding their participation in the second period.

Overall, the percentage of CGM time in range between the use of the adaptive system and non-adaptive calculator was not significantly different (63% versus 58%, respectively; p=0.27). It is noteworthy that this study may have been underpowered. Nevertheless, there were also no between-group differences in postprandial glucose, HbA1c, and insulin outcomes. Patient-reported

outcomes similarly revealed no differences, except for a significantly higher perceived frequency of hypoglycemia while using the PEPPER DSS, albeit likely caused from the hypoglycemic alerts as part of the safety system (80).

2.2.4 The InControl Advice System

The InControl Advice DSS, developed at the University of Virginia, involves model-based insulin optimization for both basal and bolus parameters. The adaptive application also integrates an rtCGM-guided bolus calculator and incorporates predictive modeling of early hypoglycemia with rescue carbohydrate advise upon exercise announcement (81,82).

2.2.4.1 Breton et al. (2018)

An early iteration of this system was assessed in a pilot, randomized, controlled, crossover trial in 24 adults with T1D on a carbohydrate counting regimen using either MDI (n=8) or pump (n=16) with near-optimal glycemic control (mean baseline HbA1c: 7.2%). This study involved two standardized interventions with identical schedules of meal contents and exercise while following standard therapy (control) or DSS advice (experimental) over 48 hours with remote monitoring.

This was preceded by a 4-week data collection period to obtain optimized baseline treatment parameters from the DSS to be used in the intervention period. The input data was based on Dexcom G4® rtCGM and personal pump downloads (for pump users) or data from the mySugr application (for MDI users).

Preliminary findings of this acute study under controlled settings revealed trends in favor of the DSS in reducing both glycemic variability and percentage of CGM time in hypoglycemia. Consequently, this suggested that the system was safe and feasible (81).

2.2.4.2 Bisio et al. (2022)

This DSS subsequently developed into the InControl Advice system (TypeZero Technologies, United States). This refined version was investigated in a 12-week, open-label, randomized, controlled, parallel trial in MDI-treated adolescents and adults with a mean baseline HbA1c of 7.5%. Following a 2-week run-in period with blinded rtCGM, 80 participants were randomized in a 2:1 ratio to either receive the InControl Advice DSS plus Dexcom G5® (experimental, n=57) or the Dexcom G5® alone (control, n=23). All participants were provided with the NovoPen 6® and NovoPen Echo® Plus connected insulin pens for automatic dose and time recording. Additionally, those who were not already using degludec and aspart switched to these formulations for the study.

During the intervention, there were biweekly remote visits for CGM downloads to generate optimized parameters by the DSS (experimental) or manual adjustments by the research team in cases of alarming hypoglycemia and hyperglycemia or upon request (control). The primary outcome, which was based on the percentage of CGM time in range, did not differ significantly after 12 weeks compared to baseline between the groups (3.3% for control versus 4.4% for experimental; p=0.86). There were also no between-group differences for other glycemic metrics, including HbA1c, nor for patient-reported outcomes (82). Overall, the InControl Advice DSS seemed feasible and safe but did not demonstrate efficacy in glycemic outcomes, which is consistent with the results reported from the ABC4D and PEPPER DSSs.

2.2.5 The DailyDose System

The DailyDose DSS, developed at the Oregon Health & Science University, comprises a smartphone application integrated with a bolus calculator and real-time insulin tracking while providing carbohydrate advice for announced exercises. The adaptive application also integrates simple machine learning tools to predict hypoglycemia (via forecasting algorithms) and to match

specific glycemic outcomes with desirable outcome variables (via case-based reasoning algorithms). The latter is carried out in the form of recommended adjustments for basal doses, ICRs or fixed-doses, ISFs, and adherence dosing behavior (83,84).

2.2.5.1 Tyler et al. (2020)

The preliminary system was tested in a small, 4-week, single-arm, feasibility study to assess the safety of weekly adjustments made by this DSS, which were pre-reviewed and approved by the medical team. Overall, 15 adults with T1D on MDI therapy completed the study and were provided with Dexcom G6® rtCGM. The participants also received a food and exercise tracking application, as well as data capturing pen devices for automatic insulin dose collection.

This pilot study found trending reductions in both overnight time in range and hypoglycemia in the last week compared to the first week. When they compared the weekly recommendations made by the DSS to those made by three endocrinologists, there was a 68% overall agreement rate between them (83).

2.2.5.2 Castle et al. (2022)

The refined version of this DSS, known as DailyDose, was assessed in a proof-of-concept, single-arm study in 24 MDI-treated adults with T1D and suboptimal glycemic control (mean baseline HbA1c: 8.2%). This study entailed a 2-week baseline period with unblinded Dexcom G6® rtCGM use as an informal comparator. This period was followed by an 8-week intervention period whereby all participants received devices to capture insulin doses and an iPhone running the DailyDose application for weekly insulin and behavioral adjustment recommendations.

The pre-defined primary endpoint was the percentage of CGM time in range. This outcome was found to be no different in the last two weeks with DailyDose compared to the 2-week baseline period with CGM alone (51% versus 50%, respectively; p=0.25). Furthermore, the other secondary

CGM outcomes were also not different compared to the baseline period, except for time above 13.9 mmol/L, which increased by 5.4% (p=0.025) in the final two weeks (84). Although this study lacked a dedicated control group, it was powered a priori, and the authors surpassed their target recruitment goal, which may suggest suboptimal algorithm performance. Nevertheless, a randomized controlled trial would be required to provide definitive conclusions.

Collectively, the ABC4D, PEPPER, and DailyDose DSSs, based on machine learning algorithms, have all demonstrated no glycemic improvement in large-scale trials. Moreover, the InControl Advice DSS, which is based on model algorithms, also did not improve glycemia. The main commonality across all studies was the selection of CGM time in range as the primary endpoint, which was consistently found to have no statistically significant difference between the respective DSS and control. Furthermore, none of the DSSs led to an improvement in HbA1c in the studies that were long enough to report it.

One plausible elucidation, particularly for the InControl Advice and DailyDose DSSs that included basal adaptation, is that MDI users typically have more glycemic variability from once-daily basal dosing. This infrequent dosing results in less retrospective data for an algorithm to analyze and optimize compared to a closed-loop algorithm in an AID system that receives continuous feedback. Consequently, the CGM glycemic metric might require bigger sample sizes or longer durations to detect meaningful differences. Alternatively, it is possible that the types of algorithms used in these DSSs, although designed for MDI users, may have not been optimal in their current version, requiring further work.

2.2.6 The Endo.Digital System

The Endo.Digital DSS (ED-DSS) (version 2, DreaMed Diabetes Ltd., Israel) recently obtained FDA clearance to assist healthcare providers with insulin management for individuals over the age

of 6 years with T1D and T2D on MDI or pump. The DSS comprises a physician platform hosting an algorithm that analyzes and recommends insulin dosing and behavioural adjustments. The recommendations are based on CGM or SMBG data and information from the affiliated smartphone application equipped with a bolus calculator (85).

2.2.6.1 Nimri et al. (2022)

Nimri and colleagues conducted a survey study to compare MDI adjustment decisions made by the ED-DSS to those made by 20 experienced secondary care physicians across multinational centers. The outcomes were based on 3-week retrospective real-world data from 17 anonymized adults with T1D on MDI either on CGM or SMBG (mean HbA1c: 7.4%). The ED-DSS and all physicians independently analyzed each case in the dataset and proposed hypothetical recommendations of modified dosing parameters (for once-daily basal dose, ICRs, and ISFs), as well as behavioral suggestions associated with insulin administration.

The primary endpoint was the proportion of overall agreement and disagreement rates (each combining full and partial) between the physicians compared to physicians and the ED-DSS. Full agreement was defined as a suggested change of the same parameter in the same direction by both parties. Partial agreement was defined as a change in one parameter by one party and a change to a different parameter or time period but in the same direction by the other party. Full disagreement was recorded when both parties recommended a change in the opposite direction for the same parameter. Partial disagreement was described as a change to a parameter in a specific direction by one and a change to a different parameter or time period in the opposite direction by the other.

The overall average proportion of directional agreement was 68% for basal, 55% for ICRs, and 58% for ISFs between physicians and the ED-DSS. These proportion outcomes were

statistically non-inferior to the average thresholds between the physicians (62% for basal, 49% for ICRs, and 50% for ISFs). Non-inferior proportions were similarly found for the disagreement rates between the pairs. Furthermore, the mean absolute percentage of change from the average physician (13%, 33%, and 54%) was higher than that recommended by the ED-DSS (8%, 14%, 12%) for basal, ICRs, and ISFs, respectively (85).

2.2.7 The McGill System

The McGill Diabetes Technology Lab previously developed a model-based optimization algorithm specifically for MDI therapy. This system employs a Bayesian approach that estimates optimized basal and meal bolus parameters based on retrospective meal, insulin, and sensor glucose data. The algorithm was initially designed for daily adjustments, using the past 24-hour data while indirectly accounting for previously learned adjustments from preceding days, combined with optimal target values to estimate new parameter recommendations for the subsequent day (86).

2.2.7.1 Fathi et al. (2020)

The earlier iteration of this algorithm was tested for safety and feasibility in a pilot, non-inferiority, randomized, controlled, parallel trial involving 21 adolescents (mean baseline HbA1c: 8.6%) at a diabetes camp over 11 days. The participants were randomized to receive daily parameter adjustments either from one of six camp physicians or by the algorithm (pre-approved by a physician). All participants wore the first-generation Freestyle Libre™ isCGM for the entire study and followed standardized meals during the intervention. The primary endpoint was the percentage of CGM time in range in the last seven days of the intervention.

Although the average percent time in range for participants in the algorithm group was similar to that in the physician group, it was not statistically significant (40% versus 38%, respectively; p=0.89). Due to recruitment challenges, the sample size was nearly 60% under the

powered target, rendering the findings exploratory. Nevertheless, when comparing the first few days to the last few days of the intervention, both had significantly less within-group daily hypoglycemic events.

Safety was established on the basis that 92% of algorithm-made recommendations were approved by physicians, and only 8% were modified prior to implementation. Furthermore, a retrospective execution of the algorithm was conducted on the physicians' dataset to compare directional insulin adjustments, which revealed 54% concordance with the physicians' recommendations. Overall, this study demonstrated acute safety and feasibility, albeit under supervised and controlled settings over a short duration (86).

This pilot study was the stepping stone toward a larger and longer randomized controlled trial under free-living settings, which forms the basis of my core clinical thesis work. I investigated the effectiveness of the McGill DSS comprising a refined version of this algorithm that generated weekly adjustments, incorporated with our novel smartphone application equipped with a bolus calculator. The second part of my thesis work evaluated the directional and magnitude of change of insulin adjustments made from the McGill DSS algorithm in the parent trial compared to mock adjustments made by a group of endocrinologists based on identical datasets.

Chapter 3. A Novel Bayesian Decision Support System for Automated Insulin Doses in Adults with Type 1 Diabetes on Multiple Daily Injections: A Randomized Controlled Trial

3.1 Preface

The manuscript presented in this chapter describes the clinical trial that investigated the McGill DSS. This outpatient study consisted of a two-arm design with a 1:1 randomization ratio. This chapter reveals the clinical outcomes from the use of the McGill DSS compared to the standalone iBolus application among 84 MDI-treated adults with T1D and suboptimal glycemic control. Additionally, a qualitative thematic analysis from 24 semi-structured interviews is included, shedding light on the commonly shared views and perspectives from a sub-group of participants who used the study software for 12 weeks. The importance of incorporating a qualitative component in a clinical trial, as well as the rationale behind the selected methodology are explained in more detail in Chapter 5 (Discussion).

3.2 Contribution of Authors

Alessandra Kobayati, Ahmad Haidar, and Anas El Fathi conceptualized the design of the trial. Dr. Michael A. Tsoukas, Dr. Jean-François Yale, and Dr. Laurent Legault contributed feedback in the early planning stages. Alessandra Kobayati contributed to the conceptual design of the iBolus application and performed quarterly software testing throughout the trial.

Alessandra Kobayati led the conduct of the trial, which entailed the development of essential documents and participant-facing tools, the recruitment of participants, the handling of regulatory and ethics submissions and correspondence, the coordination of study procedures, and

the management of data and study documentation. Anas El Fathi provided technical support in the early stages of the trial. Adnan Jafar processed the raw data needed for the analyses and created three supplementary graphs included in the appendix. Alessandra Kobayati and Ahmad Haidar carried out the statistical analyses and interpreted the results.

Alessandra Kobayati designed the qualitative sub-study, developed the interview guide, conducted the semi-structured interviews, and served as the primary coder responsible for the thematic analysis. Alessandra Kobayati developed the sensor comparison sub-study, developed the optional consent form, re-consented a subset of participants, and performed the analysis.

Ahmad Haidar was responsible for the general oversight of the trial conduct as the sponsor. Dr. Michael Tsoukas was responsible for the medical oversight of the trial as the principal investigator. Dr. Natasha Garfield (co-investigator) and Dr. Tsoukas conducted the majority of clinical assessments to confirm eligibility during admission visits. Dr. Laurent Legault (co-investigator) carried out the remaining clinical assessments. Dr. Garfield and Dr. Jean-François Yale (co-investigator) helped with the recruitment process.

Alessandra Kobayati drafted the original manuscript and appendix, generated all tables and figures (except for Supplementary Figures 3.5-3.7), and revised the manuscript in accordance with Ahmad Haidar's editorial input. The other co-authors reviewed and approved the final manuscript prior to journal submission.

A Novel Bayesian Decision Support System for Automated Insulin Doses in Adults with Type 1 Diabetes on Multiple Daily Injections: A Randomized Controlled Trial

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3.3 Abstract

We developed a decision support system (DSS), composed of a mobile app and a dose titration algorithm, to provide weekly basal and bolus recommendations for people with type 1 diabetes on multiple daily injections. We assessed our system in a 12-week randomized trial in 84 adults with suboptimal glucose control. Participants were randomized to either use the DSS or a non-adaptive bolus calculator app (control) for 12 weeks. Participants used the Freestyle Libre sensor. The DSS reduced mean HbA1c from 8.6% to 8.1% while the control reduced HbA1c from 8.6% to 8.5%; a treatment effect of -0.40% (95% CI: -0.75 to -0.051; p=0.025). The proportion of participants with improvements in HbA1c of ≥0.5%, ≥1.0%, and ≥1.5% were almost doubled in the DSS arm compared to control. There were no severe hypoglycemia or diabetic ketoacidosis. We conclude that our DSS improves HbA1c in adults with suboptimal control.

Clinical trial registration number: NCT04123054

3.4 Introduction

Type 1 diabetes is characterized by the destruction of pancreatic β cells, requiring lifelong insulin replacement therapy (1). Intensive insulin therapy, through multiple daily injections (MDI) or an insulin pump, with a target glycated hemoglobin (HbA1c) <7%, reduces microvascular and macrovascular complications (2,3). MDI therapy is used by the majority of individuals with type 1 diabetes worldwide, but it is associated with frequent glycemic fluctuations, primarily due to variability in subcutaneous insulin absorption (4), insulin sensitivity, physical activities (5), different food composition (6), and stress, among other factors. Furthermore, infrequent clinical follow-ups impede timely adjustments of insulin doses, further exacerbating the challenges with

MDI therapy (7). Most people with type 1 diabetes on MDI therapy do not achieve glycemic targets (8).

The introduction of continuous glucose monitoring (CGM) systems has revolutionized type 1 diabetes care. In the case of insulin pumps, algorithm-guided titrations of insulin doses based on real-time CGM readings are now commercially available and improve glycemic outcomes and quality of life compared to conventional pump therapy (9). For MDI therapy, the recent availability of smart insulin pens and caps (10), which track insulin doses and communicate wirelessly with smartphones, have paved the way for the development of decision support systems (DSSs) that enable algorithm-guided automatic titrations of insulin doses based on retrospective analysis of CGM readings (11). No such DSS is commercially available.

Several feasibility studies have assessed DSSs for MDI therapy (12–16), but only three randomized controlled trials have been reported so far. The InControl Advice system was tested in a 12-week parallel trial in 80 adolescents and adults (17), the ABC4D system was tested in a 12-week crossover trial in 37 adults (18), and the PEPPER system was tested in a 12-week crossover trial in 54 adults (19). None of the studies demonstrated improvements in glycemic outcomes with their DSS.

Here, we present the results of a 12-week randomized parallel controlled study that assessed the effectiveness of our McGill DSS based on a novel Bayesian optimization algorithm in 84 adults on MDI therapy with suboptimal baseline glycemic control.

3.5 Results

Between March 05, 2020, and September 27, 2023, 179 individuals were pre-screened for interest and basic eligibility. A total of 94 adults on MDI therapy were officially screened; 9 were ineligible and one withdrew prior to randomization due to commitment concerns. Consequently, 84

participants with a suboptimal baseline HbA1c of 7.5% or higher were enrolled in the study. Participants were randomized in a 1:1 ratio and stratified according to previous sensor use to either the McGill DSS (iBolus app with the optimization algorithm; experimental arm) or the non-adaptive iBolus app (control arm). The recruitment flow of participants is presented in Figure 3.1. Baseline characteristics were comparable across both groups (Table 3.1). The overall mean age was 38 (12) years, diabetes duration was 22 (12) years, HbA1c was 8.6% (1.1), 44% were female, and 76% were regular sensor users (defined as at least three consecutive months of sensor wear prior to enrolment).

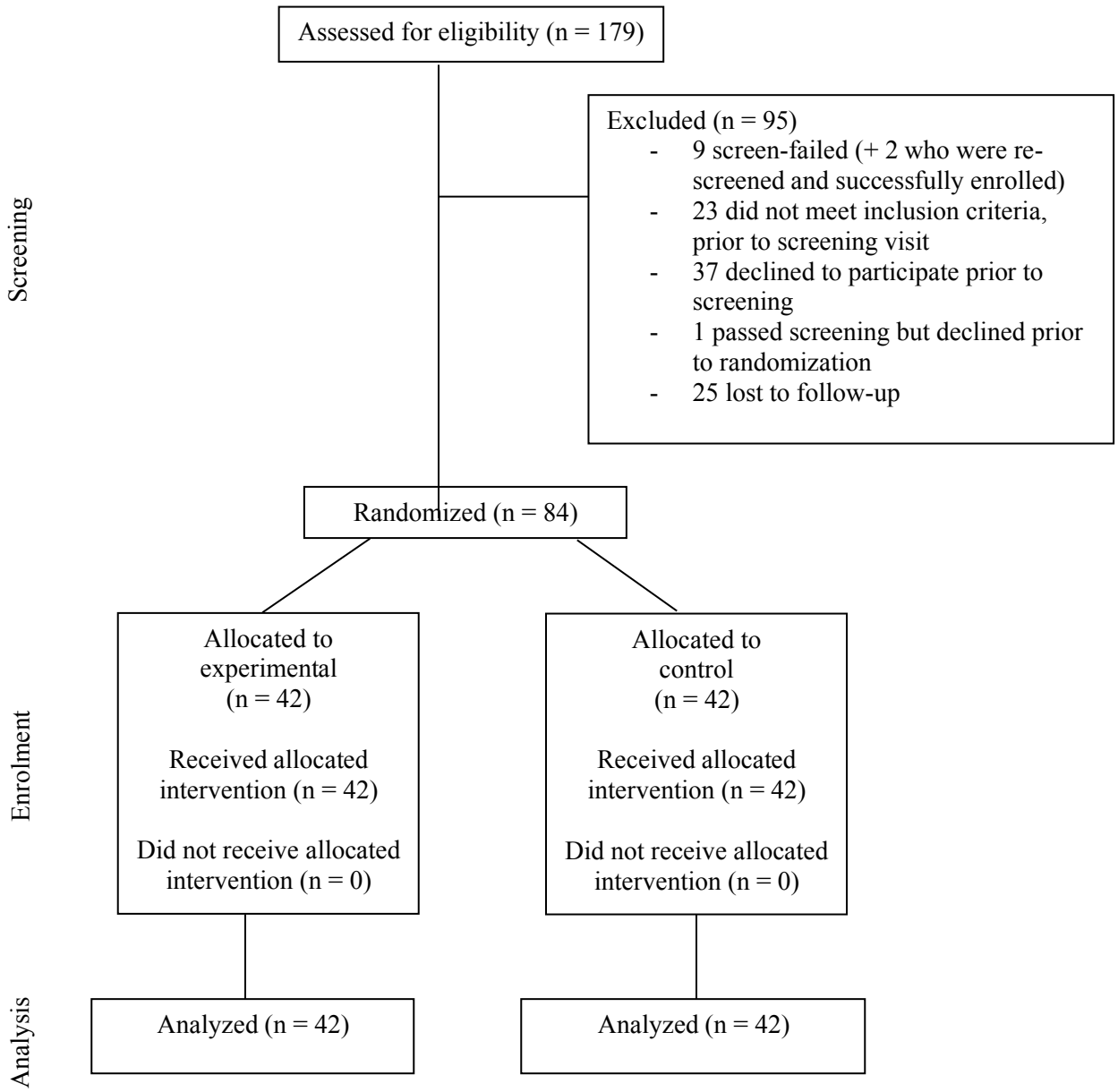

Figure 3.1 Participants flowchart diagram.

Table 3.1 Baseline characteristics of participants (n=84).

	Overall (N=84)	Experimental arm (n=42)	Control arm (n=42)
Age (years)	38 (12)	39 (12)	38 (12)
Female sex, n (%)	37 (44)	20 (48)	17 (40)
Weight (kg)	78 (14)	77 (13)	79 (14)
BMI (kg/m^2)	26 [23–29]	26 [23–29]	26 [24–29]
Duration of diabetes (years)	22 (12)	21 (11)	23 (13)
HbA1c (%)	8.6 (1.1)	8.6 (1.1)	8.6 (1.0)
Prior rt/isCGM use*, n (%)	64 (76)	32 (76)	32 (76)
Ethnic origin, n (%)			
Caucasian	60 (71)	29 (69)	31 (74)
Black	7 (8.3)	3 (7.1)	4 (10)
Asian	5 (6.0)	3 (7.1)	2 (4.8)
Hispanic	5 (6.0)	4 (10)	1 (2.4)
Arab	4 (4.8)	2 (4.8)	2 (4.8)
Other	3 (3.6)	1 (2.4)	2 (4.8)
Geography, n (%)			
Urban	73 (87)	38(90)	35(83)
Rural	11 (13)	4 (10)	7 (17)
Meal strategy regimen, n (%)			
Carb-counting	51 (61)	27 (64)	24 (57)
Fixed-dose	33 (39)	15 (36)	18 (43)
Basal pen increment, n (%)			
2.0U	4 (4.8)	2 (4.8)	2 (4.8)
1.0U	75 (89)	38 (90)	37 (88)
0.5U	5 (6.0)	2 (4.8)	3 (7.1)
Bolus pen increment, n (%)			
1.0U	66 (79)	32 (76)	34 (81)
0.5U	18 (21)	10 (24)	8 (19)
Basal insulin types, n (%)			
Degludec	47 (56)	22 (52)	25 (60)
Glargine U-300	8 (9.5)	3 (7.1)	5 (11)
Glargine U-100	18 (21)	12 (29)	6 (14)
Basaglar	6 (7.1)	2 (4.8)	4 (9.5)
Determir	5 (6.0)	3 (7.1)	2 (4.8)
Bolus insulin types, n (%)			
Aspart	34 (40)	16 (38)	18 (43)
Trurapi	4 (4.8)	1 (2.4)	3 (7.1)
Lispro	26 (31)	14 (33)	12 (29)
Admelog	3 (3.6)	3 (7.1)	0 (0.0)
Fast-acting aspart	14 (17)	7 (17)	7 (17)
Glulisine	3 (3.6)	1 (2.4)	2 (4.8)

Data are presented as mean (SD) or median [IQR] unless stated otherwise.

*Legend: rt: real-time, is: intermittently scanned; new user was defined as <3months of uninterrupted use prior to study enrolment, and regular user was defined as ≥3months.

3.5.1 User-App Interactions

Participants in the experimental and control groups used the app to determine meal boluses 2.7 [2.4–3.1] and 2.5 [1.9–3.0] times per day (p=0.11), respectively, and to determine correction boluses 0.56 [0.17–1.3] and 0.46 [0.21–1.2] times per day (p=0.93), respectively (Supplementary Table 3.4). Participants also used the app to log basal insulin dose 0.92 [0.82–0.98] and 0.86 [0.67–0.94] times per day (p=0.0078), respectively. App usage to determine boluses as well as log basal doses were stable throughout the study (Supplementary Figure 3.5).

In the experimental group, there were 50 instances of large accumulative changes (more than 30% from baseline or a previously approved parameter) in therapy parameters that required approval from a member of the study's clinical team before the new parameters were transmitted to participants. All reviewed parameters were approved without any modification to the algorithm recommendations.

3.5.2 HbA1c Outcomes

The McGill DSS reduced mean HbA1c from 8.6% at baseline to 8.1% at end-of-study, while the standalone app reduced mean HbA1c from 8.6% to 8.5% (Figure 3.2; Supplementary Figure 3.4). The within-group change in HbA1c from baseline at end-of-study was greater for the experimental group (-0.55% (0.87%)) compared to the control group (-0.14% (0.74%); Table 3.2) with a between-group difference of -0.40% (95% CI -0.75 to -0.051; p=0.025; Figure 3.2).

Table 3.2 Primary Outcome.

	Experimental (n=42)	Control (n=42)	Difference [95% CI]	p value
HbA1c, change from baseline (%)	-0.55 (0.87)	-0.14 (0.74)	-0.40 [-0.75 to -0.051]	0.025

Data presented as mean (SD) unless otherwise indicated.

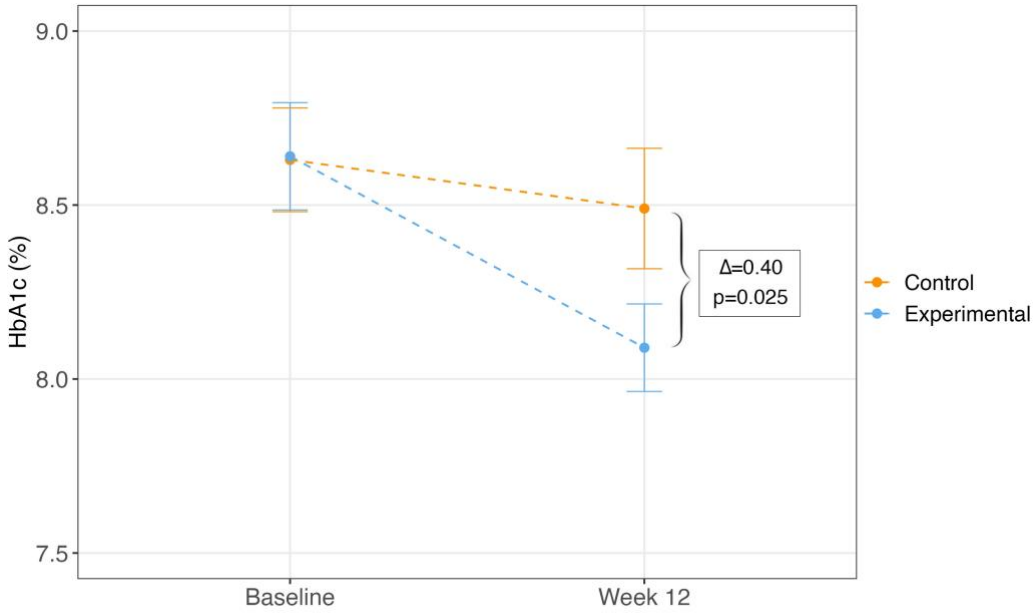

Figure 3.2 Change in HbA1c from baseline to Week 12 from 42 experimental and 42 control participants. Values are mean (standard error).

The proportion of participants who achieved an end-of-study HbA1c of ≤7.5% and ≤ 7.0% was 19% (experimental group) compared to 17% (control group) (p=1.0) and 12% (experimental group) compared to 0% (control group) (p=0.055), respectively. The proportions of participants with improvements in HbA1c from baseline of ≥0.5%, ≥1.0%, and ≥1.5% were almost doubled in the experimental group compared to control (52%, 19%, and 12% vs. 31%, 9.5%, and 4.8%, respectively; Figure 3.3). The proportions of participants with worsening in HbA1c of ≥0.5%, ≥1.0%, and ≥1.5% were substantially reduced in the experimental group compared to the control group (2.4%, 2.4%, and 0.0% vs. 21%, 7.1%, and 2.4%, respectively; Figure 3.3)

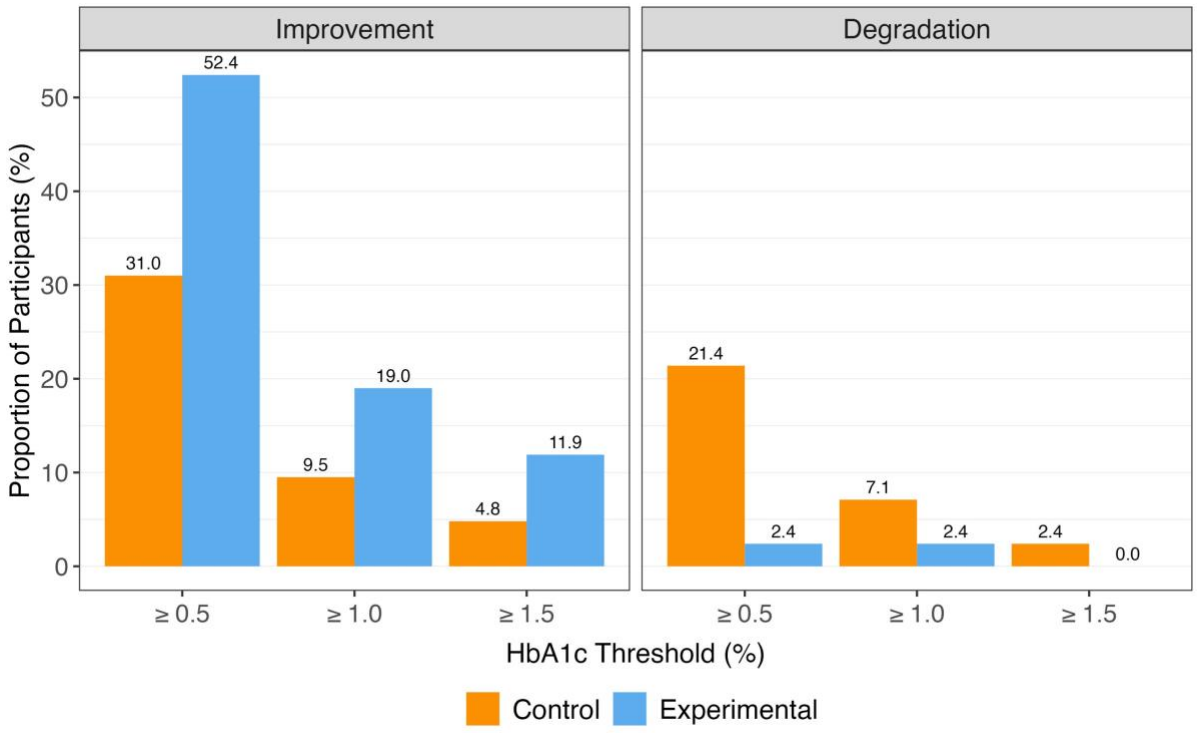

Figure 3.3 Proportion of participants with improvements and degradations in HbA1c by ≥0.5%, ≥1.0%, ≥1.5% compared to baseline.

3.5.3 CGM Outcomes

There were no differences between the groups in any of the percentages of time spent in, below, and above target ranges, as well as glycemic variability (Supplementary Table 3.5). CGM outcomes were not different between groups whether the comparison was carried out for the entire 12-week period or only the last 4-week period.

During the study, eight participants (three experimental and five control) who wore their personal real-time CGM (Dexcom G6) simultaneously with the study intermittently-scanned CGM consented and granted sharing access to their personal sensor data. We obtained 47±29 days of overlapping sensor data. We observed discrepancies between the sensor types. The intermittently-

scanned study sensor had more readings in the hypoglycemic ranges and less readings in the hyperglycemic ranges compared to real-time CGM, all $p<0.05$ (Supplementary Table 3.6).

3.5.4 Insulin Dosing Parameters and Algorithm Recommendations

There were no differences in the mean changes (from baseline to end-of-study) in insulin dose parameters (basal and bolus) between the two groups (Supplementary Table 3.7). However, the algorithm made substantially larger individual changes (increasing and decreasing) in the insulin dose parameters in the experimental group compared to the changes observed, as per standard of care, in the control group (Supplementary Figure 3.6; Supplementary Figure 3.7). 15 (36%) and 9 (21%) participants underwent >20% and >30% changes in basal insulin doses in the experimental group compared to only 2 (4.8%) and 2 (4.8%) in the control group, respectively. Similarly, 19 (45%) and 13 (31%) participants in the experimental group underwent >20% and >30% changes in prandial insulin doses, compared to only 3 (7.1%) and 1 (2.4%) in the control group, respectively (Supplementary Table 3.8).

Even though the algorithm made large individual changes to insulin dose parameters, the directional changes (increasing vs decreasing) were comparable, underscoring the importance of personalized changes. 12 (29%) participants had both their basal and bolus insulin parameters increased, 11 (26%) participants had both parameters decreased, 9 (21%) participants had their basal parameter increased and bolus parameter decreased, and 10 (24%) participants had their basal parameter decreased and bolus parameter increased (Supplementary Table 3.9).

3.5.5 Safety

There were no episodes of severe hypoglycemia or diabetes ketoacidosis throughout the study (Table 3.3). There were three serious adverse events in the experimental group, none of which were deemed related to the study. One involved hip surgery following a ski accident, another

involved overnight hospital admission due to gastrointestinal issues, and the other was a bone fracture caused by an accidental misstep at home that required a medical intervention and evaluation for surgery. There was also one serious adverse event in the control group, comprising a bone fracture caused by an accidental stumble at home that required a medical intervention and evaluation for surgery. Overall, there were more adverse events in the experimental group (n=22) compared to control (n=4), with upper respiratory illness covering the majority of events (n=12; Table 3.3).

Table 3.3 Adverse events.

Outcome	Experimental arm (n=42)	Control arm (n=42)
No. of severe hypoglycemia events	0	0
No. of diabetic ketoacidosis events	0	0
Total no. (%) of adverse events	***22***	***4***
Acute relapse of neuropathic pain	1	0
Prolonged hyperglycemia (due to spoiled insulin)	1	0
Positive COVID-19 infection	3	1
Other upper respiratory infection	9	2
Bacterial throat infection	1	0
Allergic reaction to insect bite	1	0
Bone fracture	3	1
Diarrhea (led to hospitalization)	1	0
Acute relapse of vertigo	1	0
Vomiting	1	0

Participant did not test for ketones and only notified the research team of the hyperglycemia upon resolution with insulin replacement.

3.5.6 Exploratory Patient-Reported Outcomes

As part of an exploratory sub-study, 11 participants in each group completed the modified Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the modified mHealth App Usability Questionnaire (MAUQ).

There were no between-group differences for any of the questionnaire items of either instrument. For the DTSQ, both groups consistently scored high and had higher monthly scores compared to baseline for: convenience, understanding of diabetes, willingness to continue current treatment, and overall treatment satisfaction (Supplementary Figure 3.8). For the MAUQ, both groups also scored very high in all items, suggesting a favourable experience with the standalone iBolus app (Supplementary Figure 3.9).

3.5.7 Qualitative Outcomes

24 one-on-one semi-structured interviews were conducted in a sub-sample of participants (12 experimental and 12 control). Three broad themes emerged from the analysis: 1) enhanced glycemia due to personalized dose recommendations (algorithm), 2) advantage of digital solutions over traditional standard of care (standalone iBolus app), and 3) desire for advanced MDI technologies in practice (future directions). 8 sub-themes were further identified, with selected ones reported below. The complete list of themes and sub-themes are listed in Supplementary Table 3.10. The interview topic guide is provided in Supplementary Table 3.11. Quotations from participants were included to illustrate lived experiences in their own voice (20).

One major sub-theme related to the algorithm was streamlined access to timely decision support. All 12 (100%) participants in the experimental sub-sample expressed a sense of gratitude for receiving frequent insulin adjustments compared to long wait times in traditional settings.

> "*The 6-month patient visit in the hospital, um, to let that go for such a long period of time could have negative consequences to one's health. This [algorithm], at least gives, you know, a guidance immediately in real-time, and again, it does give the patient the option to override." (P116, experimental)*

Another recurring algorithm-related sub-theme was an appreciation for the conservative (gradual and incremental) nature of dose adjustments, expressed by half (50%) of the experimental sub-sample.

"It's not a crazy jump week over week when there are changes…I was happy to see that…sometimes there's only one adjustment… it's gradual, it slowly adjusts to the required dosage" (P126, experimental)

Another sub-theme that was identified was trust in technology, whereby ten (83%) experimental participants expressed a strong feeling of trust with the algorithm.

"I had complete confidence in the recommendations, it was going really well, you could really see that there was a good change." (P115, experimental)

Several sub-themes also emerged from the standalone bolus calculator. A noted one was enhanced dosing regimen from real-time insulin-on-board tracking and insulin delivery history. Nine (75%) and six (50%) of the control and experimental sub-samples, respectively, stated that the real-time tracking of active insulin was a critical feature in facilitating their daily insulin management.

"*What I liked the most was being able to know how many units of insulin were onboarding, so you know, not to like stack my insulin doses, that, by far was my favorite thing of the entire app." (P025, control)*

Seven (29%) of the interviewed participants stated that they used the app experientially to enhance their diabetes management.

"I was using the app in ways where if I had a low blood sugar, I would kind of see where I can get some free carbs…putting in 15 or putting in 20 grams and seeing how high [in carbs] I can go before it tells me I need one unit [of insulin]." (P124, experimental)

3.6 Discussion

We conducted a randomized controlled trial comparing a novel DSS for weekly insulin adjustments compared to a standalone app with a bolus calculator in adults with type 1 diabetes and suboptimal control. The DSS reduced mean HbA1c significantly compared to the standalone bolus calculator. Moreover, it doubled the proportion of participants with improvements of HbA1c and substantially decreased the proportion of participants with worsening of HbA1c at different thresholds. These improvements in glycemic outcomes were preceded by large and individualized changes to the insulin parameters by the DSS. Other randomized trials have assessed DSSs in adults with type 1 diabetes on MDI therapy (17–19), but this is the first trial to demonstrate a meaningful improvement in glycemia, in the form of -0.4% control-adjusted HbA1c reduction.

In our study, HbA1c reductions were not accompanied by improved CGM outcomes, which contradicts studies of closed-loop insulin pumps (21,22). This might be due to the inherent glycemic variability in MDI users caused by the low frequency in which they dose basal insulin (once per day). Our algorithm analyzes glucose data from the past seven days before recommending insulin changes, which subsequently leads to fluctuations between weekly adjustments as a result of less control. In contrast, closed-loop insulin pumps adjust insulin every 5–10 minutes based on real-time CGM readings, resulting in more control and thus less daily glycemic variability. It is, therefore, possible that our sample size was not large enough to detect statistical differences in CGM outcomes for an MDI population. Moreover, we used first-generation intermittently scanned sensors, which has been reported to be less accurate than real-time sensors (23), and that may have further increased glycemic variability as measured by the sensor.

The percentage of time below 3.9 mmol/L observed in our entire study cohort was higher than the recommended target of <4% (24). However, these higher values were observed in both groups, and thus does not indicate a safety signal with our DSS. This is further supported by the lack of increased perceived hypoglycemia collected from our PRO data. Moreover, the first-generation intermittently scanned sensor has been reported to be less accurate in the hypoglycemic range (23). Our exploratory sensor comparison with real-time CGM showed that the intermittently-scanned CGM had more readings in the hypoglycemic range, thus suggesting that they may have overestimated hypoglycemia in our study. Others have confirmed large differences between sensor types too (25).

Strengths of our study include the use of a randomized controlled design and the inclusion of participants with high baseline HbA1c, which is representative of the general MDI population. Furthermore, participants entered the study with their personal long-acting and rapid-acting insulins and insulin pens (with various increments) without changing to any uniform insulin type or pen, further increasing the generalizability of our findings. Another strength is the diversity of our study cohort, with one third being non-Caucasian and a little over one third used fixed prandial boluses. Finally, we stratified participants according to previous sensor use to ensure balance between groups, given that glycemic improvements can be obtained from initiating CGM (26–28).

Our study has several limitations. One limitation was the lack of a pre-randomization run-in period to assess and compare baseline CGM metrics with the last few weeks of the study. The control group also lacked baseline optimization; although, neither group received insulin titrations at baseline. Additionally, control participants were permitted to have their parameters modified by their health care providers without restrictions per their usual standard of care. Another limitation was the lack of insulin correction factor optimization by the DSS, but participants were free to

manually adjust this parameter during the intervention as needed (carried out by seven participants). Finally, insulin dosing details were recorded by users through the app rather than being automatically captured by a smart pen or cap device. However, all participants received baseline training and understood the importance of accurate and timely reporting, with additional support by automated compliance reminders in the app.

In conclusion, our DSS significantly improved HbA1c in adults with suboptimal glucose control on MDI therapy. Randomized controlled trials in pediatrics are warranted.

3.7 Methods

3.7.1 Trial Design

This was an open-label, randomized, controlled, parallel trial over 12 weeks. The objective was to compare the McGill DSS that provides weekly adaptations to basal and prandial doses with a non-adaptive bolus calculator. All participants were supplied with first-generation Abbott's Freestyle Libre sensors. Participants were allowed to simultaneously wear their personal real-time CGM, if applicable.

The trial protocol was approved by the Research Ethics Board of the McGill University Health Center. Health Canada granted Investigational Testing Authorization to conduct the trial with the McGill DSS and iBolus app (entire system regulated as a class II investigational medical device). Written informed consent was obtained from all participants prior to commencement.

3.7.2 Participants

Inclusion criteria included adults (≥18 years old) with a diagnosis of type 1 diabetes for at least one year, using multiple daily injections, and with a baseline HbA1c of ≥7.5%. Exclusion criteria comprised the use of intermediate-acting insulin, pregnancy or breastfeeding, use of non-insulin

antihyperglycemic agents within one month, severe hypoglycemia or diabetic ketoacidosis within one month, significant nephropathy, neuropathy, or retinopathy (per the investigator's judgement), recent blood transfusion, hemoglobinopathy, anemia, or other conditions likely to interfere with the study procedures per the investigator's judgment.

Most participants were recruited at the endocrinology clinic of the McGill University Health Center. If the participant had an eligible HbA1c level collected within one week of the screening visit, it was used as the baseline measurement; otherwise, a new baseline HbA1c measurement was taken.

3.7.3 Randomization

We utilized a computer-generated permuted-block 1:1 randomization, stratified according to regular sensor use (≥3 months) or new sensor use by using different blocks (sizes 10 and 4, respectively) for each strata. A member of the research team who was not involved in the study prepared digitally sealed envelopes with the randomization sequence, which were revealed after enrolment was confirmed.

3.7.4 Procedures and Interventions

Following randomization, participants received refresher training on diabetes management that included a review on pharmacokinetic action of insulin analogs, insulin storage and care, injection techniques, carbohydrate counting (if applicable), and hypoglycemia and hyperglycemia management.

Study LibreLink app accounts were created for each participant using coded credentials, followed by training on the insertion, use, and disposal of the freestyle libre system. Participants were asked to scan their Freestyle libre sensor at least five times per day (upon waking, prior to

meals, and before bedtime). Sensor readings were automatically transferred to our LibreView Professional account and downloaded weekly into a secure drive and database.

Initial iBolus app programming involved either enabling the carbohydrate counting setting or keeping it disabled for fixed-dose users, along with their personal dosing parameters (basal dose, target glucose level, insulin sensitivity factor, active insulin time, basal and bolus pen increments, and carbohydrate ratios or fixed doses for each meal type). The app was designed to lock the meal strategy (carbohydrate counting or fixed-dose) selection upon initiation so participants were not able to switch to the opposite strategy after starting the study. Participants in both groups received training on the iBolus app and were instructed to use it daily and accurately for timely basal logging and real-time meal and correction bolus calculations. The control group used the non-adaptive iBolus app, which relied on their personal programmed parameters, and the experimental group used the adaptive version of the app.

3.7.5 iBolus app

The iBolus app was developed with the aim of facilitating bolus calculations for MDI therapy while simplifying remote data collection in the study. The app was designed with a focus on making the graphical user interface with simple icon-based features while limiting text (Supplementary Figure 3.10).

iBolus is equipped with a built-in bolus calculator that computes doses for meal and correction boluses in real-time based on programmed parameters (meal-specific carbohydrate ratio, glucose target, and insulin sensitivity factor) and current glucose level and its trend, while accounting for active insulin-on-board from previous rapid-acting insulin doses. The app also has a function to log basal doses, with an optional notification that could be enabled as a daily reminder at the regular time of administration. In the event of a mistake, there was a 30-minute window to

delete any log. Furthermore, automatic alert notifications were sent to participants in the event of three missing consecutive basal logs or insufficient use defined as three or less entries (e.g. meal bolus) within 36 hours. This served to increase adherence by reminding participants about app usage.

Upon requesting a meal bolus, the meal type (breakfast, lunch, dinner, or bedtime) was set by default depending on the time of day. Then, participants were prompted to enter their sensor glucose level and select its trend arrow and enter the amount of carbohydrates, if applicable. The calculated bolus was subsequently displayed along with its calculation details. Upon confirming a dose, the app automatically updated the real-time insulin-on-board on the home screen as well as the log history. Participants were permitted to override a calculated dose with the option to select one of the following reasons: dose is higher than usual, exercise, sick, stress, menstrual cycle, alcohol. However, the optional reason selection merely served as a note and did not change the bolus calculation. Upon requesting a correction bolus, participants were prompted to enter their sensor glucose level and its trend arrow to calculate the dose, which they could accept or override.

The non-adaptive iBolus app comprised all aforementioned features, which relied on the programmed personal parameters, which can be changed manually by the participants at any time. In contrast, the adaptive iBolus app entailed weekly notifications that displayed the previous week's basal and meal bolus parameters along with the new optimized parameters determined by the algorithm. Upon acknowledgement, the new parameters automatically updated the app settings to be used in the following week.

Logged data were automatically transferred to our secure cloud server upon internet connection. Missing data notifications and the weekly parameter notifications required internet

connection. Participants had the iBolus app installed on their personal phone, if compatible, or received a study phone with the app.

3.7.6 The McGill Decision Support System

Our algorithm employed a model-based Bayesian approach to estimate insulin dosing parameters (once-daily basal dose and fixed bolus doses or carbohydrate ratios) (29). Once a week, the algorithm was executed on the cloud (MATLAB R2018b running on a Google Cloud Virtual Machine) for all active experimental participants. The algorithm utilized the previous week's sensor data obtained by the Freestyle software and insulin and meal data obtained by the iBolus app as input to fit a glucoregulatory model using a Bayesian approach to estimate the therapy parameters that would have resulted in optimal control in the previous week. The recommendations for the following week were a mixture of these optimal parameters and the parameters used in the previous week depending on the ability of the model to explain the data and the statistical confidence in the optimal parameters' estimates. The algorithm recommendations were subsequently pushed to the participants in the form of an app notification, requiring acknowledgement to automatically populate their app settings.

The algorithm was executed weekly; however, all previous weeks were implicitly included in the algorithm recommendations. Each week, the algorithm used the Bayesian's prior probabilistic distributions to combine last week's data with the most recent therapy parameters (which were learned from previous weeks) to generate recommendations for the following week. This iterative process ensures that lessons from previous weeks are carried to future recommendations.

The app and the algorithm were accompanied by an online platform that was accessed by the research team only for data visualization. If there was more than a 30% cumulative change in

any therapy parameter from baseline or a previously approved parameter, then approval from a member of the study's clinical team was required in the platform before the new parameters were pushed to participants.

3.7.7 Patient-Reported Outcomes

As part of an exploratory psychosocial sub-study, participants were enrolled on the basis of convenience sampling, wherein any new participant who was enrolled in the main study was given the opportunity to participate in this sub-study with a target range of 20-25 individuals. Exploratory patient-reported outcomes entailed serial administration of a modified version of the Diabetes Treatment Satisfaction Questionnaire at baseline and every four weeks of the intervention. At the end of the 12-week intervention, these participants completed a modified version of the mHealth App Usability Questionnaire to gauge the usability of the standalone iBolus app.

The Diabetes Treatment Satisfaction Questionnaire is a validated instrument composed of eight questions, broken down into two measures, both scored on a 7-point Likert scale: 1) treatment satisfaction (questions 1, 4, 5, 6, 7, 8), with higher scores indicating greater satisfaction, and 2) perceived frequency of hyperglycemia and hypoglycemia (questions 2, 3), with lower scores representing better perceived glycemia (30). One of the questions was only asked to the experimental group as it pertained to the algorithm adjustments of their insulin doses. The latter question and the one about recommending the iBolus app to others were not asked at baseline.

The mHealth App Usability Questionnaire is a validated survey for a standalone mobile health application. This instrument is composed of 18 items, broken down into three factors: 1) ease of use, 2) interface and satisfaction, and 3) usefulness (31). All items are scored on a 7-point Likert scale ranging from 1 (disagree) to 7 (agree). One question from the ease of use factor and one from the usefulness factor were removed due to their irrelevance to the iBolus app.

3.7.8 Semi-structured Interviews

The sub-cohort of participants who completed questionnaires also took part in semi-structured one-on-one exit interviews led by a topic guide (Supplementary Table 3.11). The interviews were audio recorded, transcribed verbatim, and then underwent a thematic analysis by two coders via an inductive approach without predefined codes to better understand participants' experience and gauge usability of the study software.

3.7.9 Outcomes

The primary endpoint was the change from baseline in HbA1c at end-of-study. Secondary endpoints included the percentage of time for which sensor glucose levels were in the following ranges: between 3.9-10mmol/L, between 3.9-7.8mmol/L, <3.9mmol/L, <3mmol/L, >7.8mmol/L, >10mmol/L, >13.9mmol/L, and >16.7mmol/L, as well as standard deviation, mean sensor glucose, and insulin delivery. Data from CGM metrics were calculated for three periods: 1) overnight (23:00-7:00), daytime (7:00-23:00), and overall (24-hour).

3.7.10 Statistical Analysis

We assumed a 0.8% standard deviation of HbA1c, as previously reported in the literature (27), and we predicted an estimated difference of 0.5% between the two arms. We consequently calculated that 84 participants would provide 80% power at the 5% significance level.

The comparison of the primary endpoint was made using a linear mixed model accounting for baseline HbA1c. Hypothesis testing of between-group differences in other continuous outcomes were performed using the two-sample t-test or the non-parametric Wilcoxon rank sum (Mann-Whitney) test. The Shapiro-Wilk test was used to assess normality. Data were reported as mean (standard deviation) for normally distributed variables and median [interquartile range] for

non-normally distributed variables. The analysis was based on a modified intention-to-treat approach, which included data from all randomized participants for whom a final HbA1c measurement was collected after at least ten completed weeks of intervention.

Statistical analyses were performed using R v12.1 and MATLAB 2020. All p-values for the between-group comparisons were two-tailed. P-values <0.05 were considered as significant. No corrections for multiplicity were made for the secondary outcomes.

For the interview data, we adopted a qualitative descriptive methodology to explore and provide descriptions of participants' experiences and views with low inference from the data (32). We employed a thematic analysis to identify recurring patterns in thoughts and experiences shared by participants that can be grouped together into themes to more accurately summarize the data. Codes were developed inductively, not predefined, albeit through a deductive lens due to prior experience, knowledge, and preconceived notions. The NVivo 12 software was used to manage, store, and analyse the data.

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3.10 Appendix

Supplementary Table 3.4 Daily user interaction with the main app features throughout the study.

	Experimental arm (n=42)	Control arm (n=42)	p value
Meal bolus (/day)	2.7 [2.4–3.1]	2.5 [1.9–3.0]	0.11
Correction bolus (/day)	0.56 [0.17–1.3]	0.46 [0.21–1.2]	0.93
Basal log (/day)	0.92 [0.82–0.98]	0.86 [0.67–0.94]	0.0078

Data are presented as median [IQR].

Supplementary Table 3.5 Overall (24-hour), daytime (07:00-23:00), and nighttime (23:00-07:00) profiles for CGM outcomes.

	Experimental arm (n=42)	Control arm (n=42)	p value
Overall (24-hour)			
Percent time 3.9–10.0 mmol/L	48 (12)	45 (14)	0.47
Percent time 3.9–7.8 mmol/L	29 (9.4)	27 (11)	0.27
Percent time <3.9 mmol/L	5.9 [3.2–9.2]	4.3 [2.2–7.7]	0.16
Percent time <3.0 mmol/L	1.7 [0.67–3.4]	1.2 [0.57–2.8]	0.33
Percent time >7.8 mmol/L	65 (12)	69 (13)	0.22
Percent time >10.0 mmol/L	46 (14)	50 (16)	0.36
Percent time >13.9 mmol/L	18 [11–26]	20 [12–29]	0.57
Mean glucose (mmol/L)	10.0 [8.8–11]	10.5 [9.1–11]	0.33
SD glucose (mmol/L)	4.2 (0.78)	4.1 (0.80)	0.72
Daytime (07:00-23:00)			
Percent time 3.9–10.0 mmol/L	48 (13)	46 (15)	0.68
Percent time 3.9–7.8 mmol/L	29 (9.6)	28 (11)	10.48
Percent time <3.9 mmol/L	4.5 [1.8–7.0]	3.1 [1.6–7.2]	0.50
Percent time <3.0 mmol/L	1.1 [0.25–2.5]	0.68 [0.22–2.4]	0.55
Percent time >7.8 mmol/L	67 (12)	69 (14)	0.46
Percent time >10.0 mmol/L	48 (15)	49 (17)	0.63
Percent time >13.9 mmol/L	21 [12–27]	21 [11–30]	0.82
Mean glucose (mmol/L)	10.1 [9.1–11]	10.5 [8.9–12]	0.67
SD glucose (mmol/L)	4.2 (0.77)	4.1 (0.85)	0.67
Nighttime (23:00-07:00)			
Percent time 3.9–10.0 mmol/L	47 (14)	44 (14)	0.25
Percent time 3.9–7.8 mmol/L	30 [24–37]	25 [19–30]	0.067
Percent time <3.9 mmol/L	6.9 [4.2–11]	5.1 [2.1–8.9]	0.13
Percent time <3.0 mmol/L	2.2 [1.4–5.0]	1.8 [0.47–4.1]	0.31
Percent time >7.8 mmol/L	63 (15)	69 (15)	0.089
Percent time >10.0 mmol/L	45 (17)	50 (17)	0.15
Percent time >13.9 mmol/L	18 [9.4–24]	19 [12–25]	0.38
Mean glucose (mmol/L)	9.8 [8.4–11]	10.2 [9.3–11]	0.13
SD glucose (mmol/L)	4.0 [3.7–4.5]	4.0 [3.7–4.4]	0.90

Data are presented as mean (SD) or median [IQR].

Supplementary Table 3.6 Comparison of outcomes between real-time and intermittently scanned CGMs (n=8).

	Intermittently scanned CGM	Real-time CGM	p value
Hypoglycemic events, n	10 (9.8)	3.0 (2.6)	0.044
Percent time 3.9–10 mmol/L	47 (12)	41 (18)	0.083
Percent time <3.9 mmol/L	4.7 [1.4–7.7]	1.1 [0.40–2.6]	0.016
Percent time <3.0 mmol/L	1.5 [0.17–2.1]	0.10 [0.050–0.28]	0.016
Percent time >10 mmol/L	47 (16)	57 (20)	0.010
Percent time >13.9 mmol/L	18 (10)	26 (15)	0.053
Percent time >16.7 mmol/L	6.3 (6.6)	8.4 (9.4)	0.15
Mean glucose (mmol/L)	10.0 (1.6)	11.0 (1.9)	0.041

Data are presented as mean (SD) or median [IQR].

Supplementary Table 3.7 Changes from baseline to the last week in insulin dosing parameters.

	Experimental arm (n=42)	Control arm (n=42)	p value
Basal insulin (U/day)	0.5 (7.0)	0.2 (1.2)	0.80
Prandial insulin (%)	0.8 [-14.4–38.8]	0.0 [0.0–0.0]	0.27

Data are presented as mean (SD) or median [IQR].

Supplementary Table 3.8 Absolute relative change (%) in prandial and basal dose parameters from baseline to the last week.

	Experimental, n (%)		Control, n (%)	
Proportion of participants with changes:	Basal dose	Bolus dose*	Basal dose	Bolus dose*
>|10%|	25 (60)	29 (69)	4 (9.5)	7 (17)
>|20%|	15 (36)	19 (45)	2 (4.8)	3 (7.1)
>|30%|	9 (21)	13 (31)	2 (4.8)	1 (2.4)
>|40%|	1 (2.4)	10 (24)	1 (2.4)	0 (0)
>|50%|	0 (0)	5 (12)	0 (0)	0 (0)
>|60%|	0 (0)	4 (9.5)	0 (0)	0 (0)
>|70%|	0 (0)	3 (7.1)	0 (0)	0 (0)
>|80%|	0 (0)	1 (2.4)	0 (0)	0 (0)
>|90%|	0 (0)	1 (2.4)	0 (0)	0 (0)
>|100%|	0 (0)	1 (2.4)	0 (0)	0 (0)

*Bolus dose includes combined mean relative changes for breakfast, lunch, and dinner.

Supplementary Table 3.9 Proportions of experimental participants with changed basal and bolus insulin combinations from last week compared to baseline.

	Overall proportion of participants, n (%)
Basal and bolus insulin increased	12 (29)
Basal and bolus insulin decreased	11 (26)
Basal increased and bolus decreased	9 (21)
Basal decreased and bolus increased	10 (24)

Supplementary Table 3.10 Thematic analysis of exit interviews in 24 participants.

Themes	Sub-themes	Selected quotes
1) Enhanced glycemia due to personalized dose recommend-ations	1.1) Streamlined access to timely decision support	*"The 6-month patient visit in the hospital, um, to let that go for such a long period of time could have negative consequences to one's health. This [algorithm], at least gives, you know, a guidance immediately in real-time, and again, it does give the patient the option to override." (P116, experimental)* *"The adjustments made weekly was extremely helpful versus having to wait for your 4-month or 6-month meeting with a professional… changing the doses is something we rely on medical professionals to do, um, I've worked on changing them by myself at times, and there's always that fear, "have I gone too far"…if the application is as safe as professionals, then it's like having that contact but on a regular basis." (P119, experimental)* *"My ratios have changed in the past few months, and they haven't changed in 10 plus years. So I'm basing that off of there's been more data, more information given, so I think it's definitely beneficial…For the first time in years, I feel like [pause] I don't know how to explain it, but that I have direct feedback… It's a no brainer." (P124, experimental)* *"It's like having a real doctor with you 100% making adjustments every week...now in 2020, you need to have this in your phone, that makes it a lot better." (P122, experimental).*
	1.2) Appreciation for conservative (gradual and incremental)	*"The little changes made a difference in the long run, so for the week that a dose would increase by one unit…you do see that even if changes that were made seem insignificant, they were significant enough to make a difference." (P119, experimental)* *"When I see the numbers come in, they're very minimal in terms of change…but it ended up working out" (P124, experimental)*

	algorithm adjustments	*"It's not a crazy jump week over week when there are changes…I was happy to see that…sometimes there's only one adjustment… it's gradual, it slowly adjusts to the required dosage" (P126, experimental)*
	1.3) Trust in technology	*"I had complete confidence in the recommendations, it was going really well, you could really see that there was a good change." (P115, experimental)* *"I didn't pay attention to the recommendations, I trusted it 100%, I was very satisfied, and I'm sure that if I had paid attention, they would have been really good recommendations, but I had 100% confidence." (P122, experimental)* *"The fast acting insulin changes, I 100% trust those…I would say, overall, very trustworthy" (P124, experimental)* *"After a week I was pretty comfortable with it…I was giving [insulin] and I wasn't going low or anything…until basically you understand what the app is trying to do, and, uh basically, seeing that your sugar is in a normal range, you do get a trust…I would say it's easier as time progresses." (P126, experimental)*
2) Advantage of digital solutions over traditional standard of care	2.1) Enhanced dosing regimen from real-time insulin-on-board tracking and insulin delivery history	*"I like the fact that it [the app] kept track of how much insulin I had in my body at the time, so it won't overdose me, which I can't do on my own" (P017, control)* *"I could check for example the number of units that I had given myself the previous meal, which normally, I can't do…I can't remember what I gave myself, whereas here, I could check it if I wanted to. That's perhaps the most striking difference." (P018, control)* *"What I liked the most was being able to know how many units of insulin were onboarding, so you know, not to like stack my insulin*

		doses, that, by far was my favorite thing of the entire app." (P025, control) *"In the past, if I was high, I would take insulin over and over again, you know, over the period of half an hour realizing it's not changing, whereas now I just let it wait and it does come back down eventually…it tells me not to and basically just to be patient" (P124, experimental)*
	2.2) Experiential learning	*"There were a few times where I would think, "do I need to correct [with insulin for carb intake] or not", and if the calculated [insulin] dose [by the app] was zero, I wouldn't log it [the carbs]…I think for me, it was more of–or for anybody who's just checking on the basis of, "can I eat right now?" could be used in that sense" (P119, experimental)* *"I could learn to play the doctor, I could see what's going on at the back. Like I could see that because I did this, because I got that…I can see how effective it is…so it was great to see that at the same time" (P120, experimental)* *"I was using the app in ways where if I had a low blood sugar, I would kind of see where I can get some free carbs…putting in 15 or putting in 20 grams and seeing how high [in carbs] I can go before it tells me I need one unit [of insulin]." (P124, experimental)*
	2.3) Alleviation of mental burden associated with dose calculations	*"I don't even have to think about it, I just have to enter, I don't have to do any mental math…it takes most of the guesswork out of taking insulin…the iBolus app did the rest of the work for me, so it was very convenient." (P026, control)* *"…it calculated my insulin for me…I've been diabetic since I was 13 and I still can't stand doing the mental math 'cause it's just like–I just prefer that it does it for me." (P117, experimental)*

	2.4) User-friendliness	*"Easy to use, very visual. There were really only three dropdown menus, so very easy to follow...everything was necessary and easy to find" (P014, control)* *"I liked how easy it [iBolus app] is…what I need was there and easy to find, um, the interface itself was, like, perfect…there's no extra gibberish in it, you know, so I think that for any age group it's very straightforward and easy to use." (P025, control)* *"Very easy to use, simple, very concise, um, the information required is very clear. In terms of entering the data, notes, that was all–it was an easy interface, so user friendly and easy to understand as well." (P119, experimental)*
3) Desire for advanced MDI technologies in practice	3.1) Anticipated future adoption	*"I'd opt for it again… it helps you to have a better, uh, better follow-up of your diabetes, it helps you to improve…To have it directly in the phone, it's wonderful, you know every week, it's really better than waiting 3 to 6 months." (P115, experimental)* *"Sign me up for a rerun [laughing], I'm kind of sad of having to stop the treatment simply because it has been working well, so, um, I–I do see where potentially this could be life-changing for people, and I would like to see it continue forward…I absolutely think I would be gung ho for it." (P119, experimental)* *"It's way, way, much better just receiving the adjustment on the phone, uh, on the app. Oh yeah, it's very convenient…And if we could have the doctor also get involved and see the results, that would be a great advantage" (P120, experimental)* *"it's the new generation of diabetes apps. I think it would be a plus for everyone to have it because it definitely, uh, adjusts in real time…I'd definitely use it, that's for sure because I find–in fact, it makes my life a lot easier. It was more efficient" (P122, experimental)*

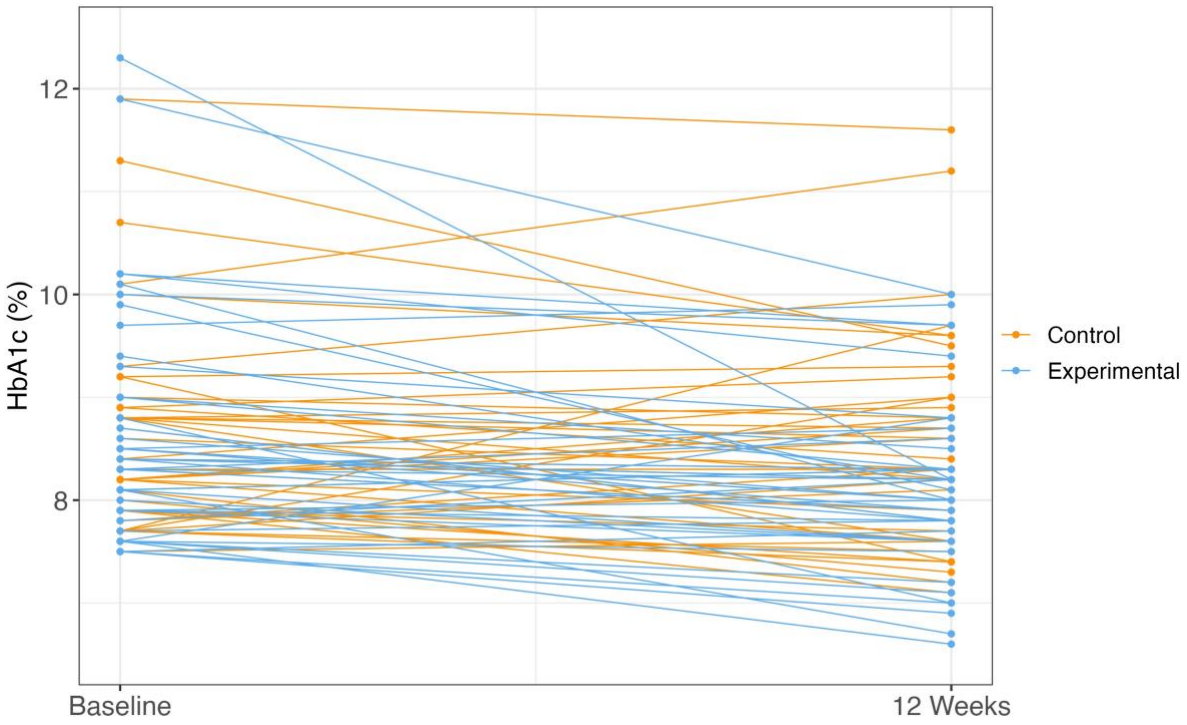
Supplementary Table 3.11 interview topic guide.

Initial questions	• Can you describe what your overall experience using multiple daily injections has been like throughout your participation in the study, in comparison to your usual management before you participated?

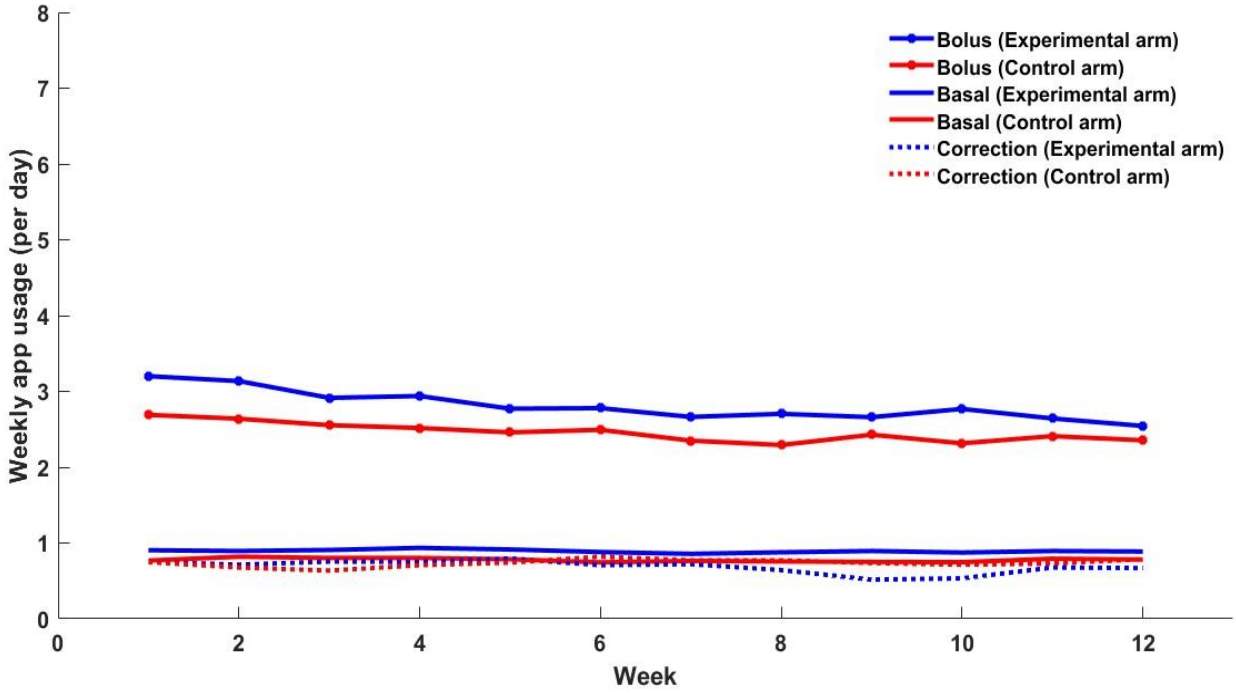
More specific questions	• Can you tell me about your experience using Freestyle Libre sensors throughout the study, in terms of convenience?
	• Can you describe your overall experience using the iBolus app?
	  ○ What specific features did you like the most from the iBolus app?
	  ○ What specific features did you like the least from the iBolus app?
	  ○ What features, if any, would you have liked to see?
	• If you could, would you incorporate the iBolus app into your daily insulin management?
	• How have your hypoglycemia concerns or fears changed since before the intervention began?
	• How have your hyperglycemia concerns or fears changed since before the intervention began?
	• Can you tell me about the personalized recommendations that you received, in terms of your overall treatment satisfaction?
	  ○ What about in terms of your overall glucose control?
	  ○ Can you describe your overall level of trust with the recommendations that you received?
	  ○ What did you think about the weekly frequency in which you received the recommendations?
	  ○ What are your thoughts on receiving insulin dose adjustments directly from the iBolus app, compared to traditional in-hospital follow-up visits?
	  ○ What were the advantages of receiving personalized recommendations?
	  ○ What were the disadvantages?

Final questions	• If the learning algorithm was integrated into the iBolus app, which would allow for regular dose adjustments, would you switch to this advanced form of therapy, and why? • Is there anything else that you would like to tell us about your experience with the software used in the study?

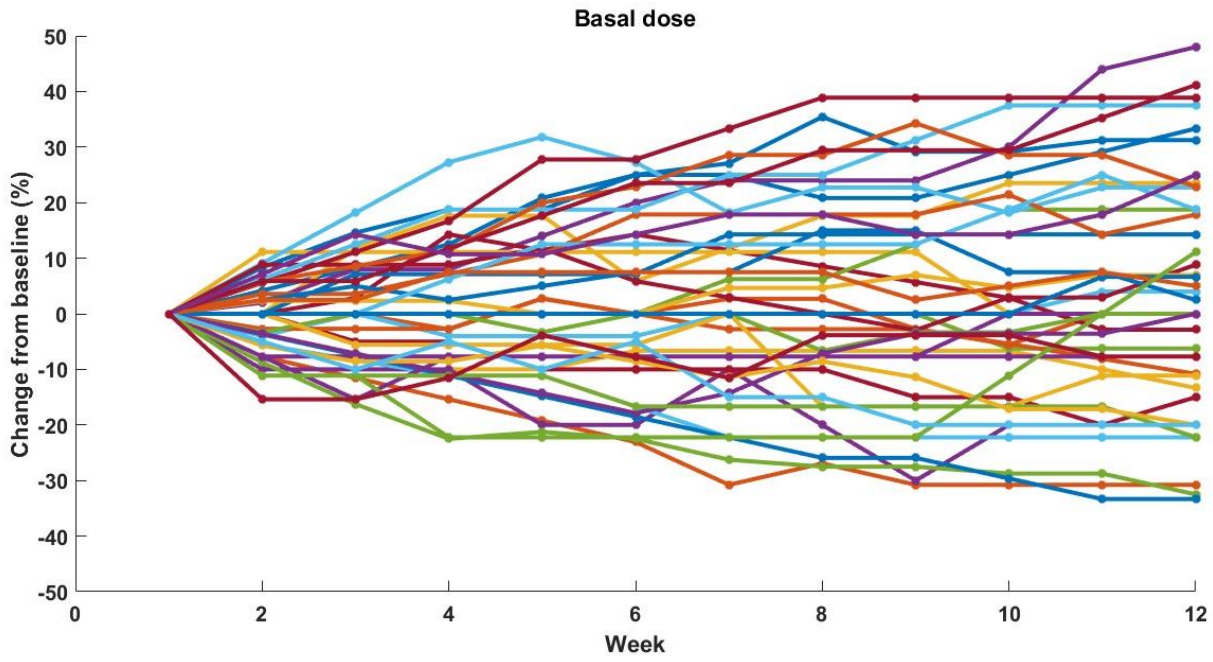
The topic guide represents the general flow of the interview (questions in red were only asked to participants in the experimental group).



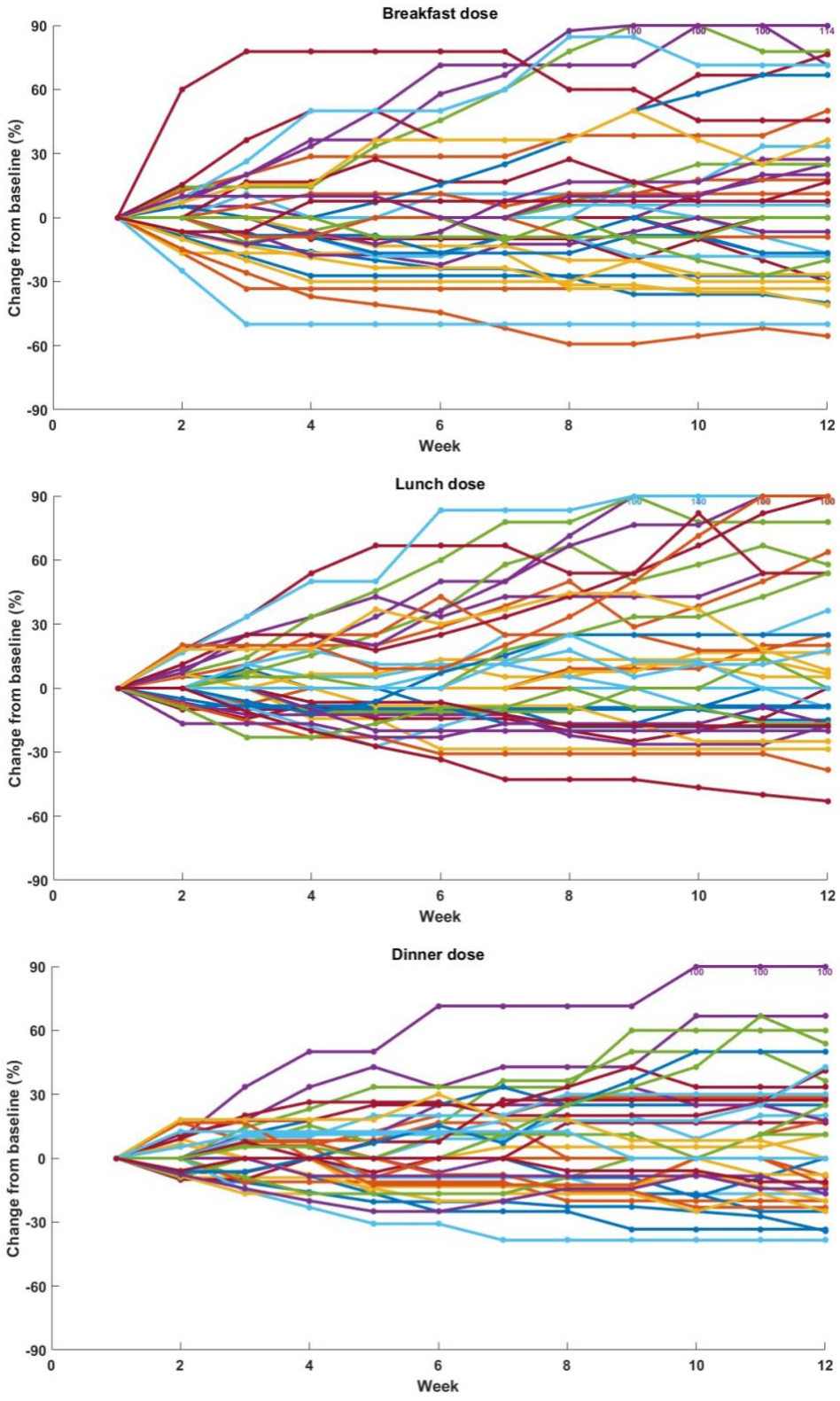
Supplementary Figure 3.4 Individual change in HbA1c (%) from baseline to 12 weeks.



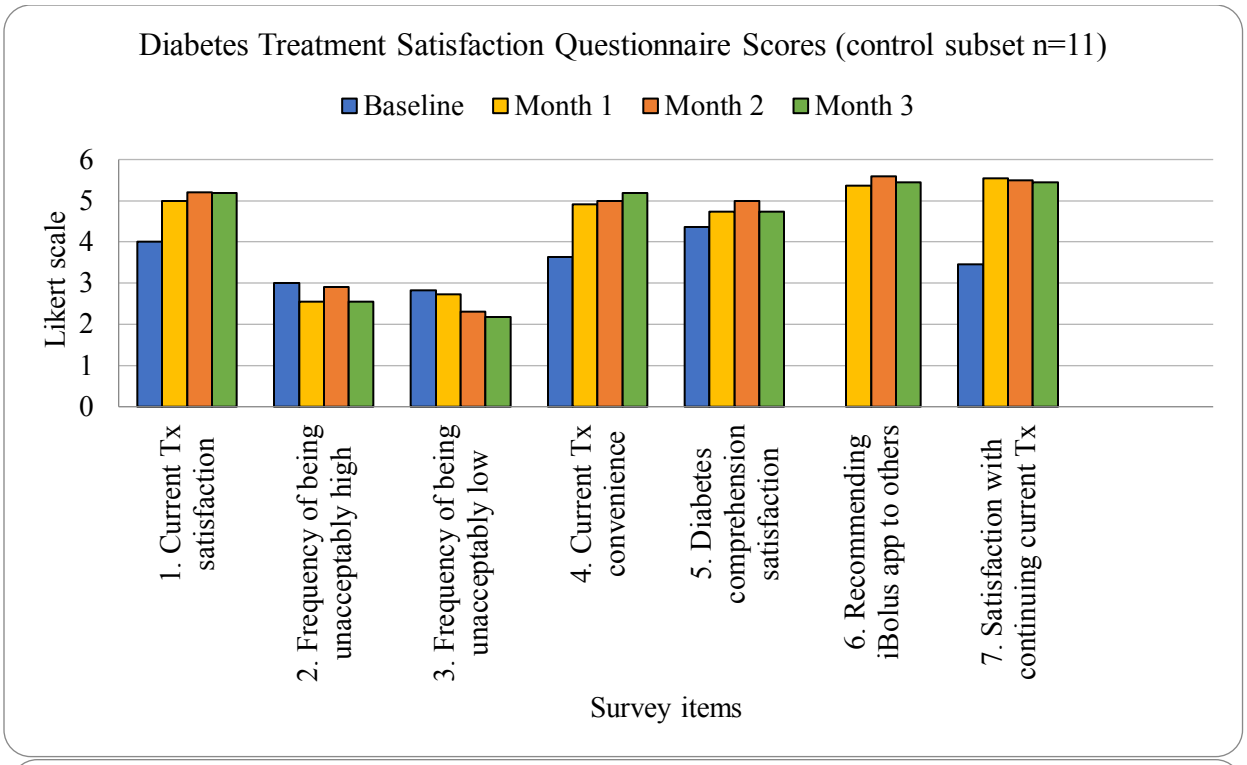
Supplementary Figure 3.5 Week-by-week average app usage per day in experimental (n=42) and control (n=42) participants.

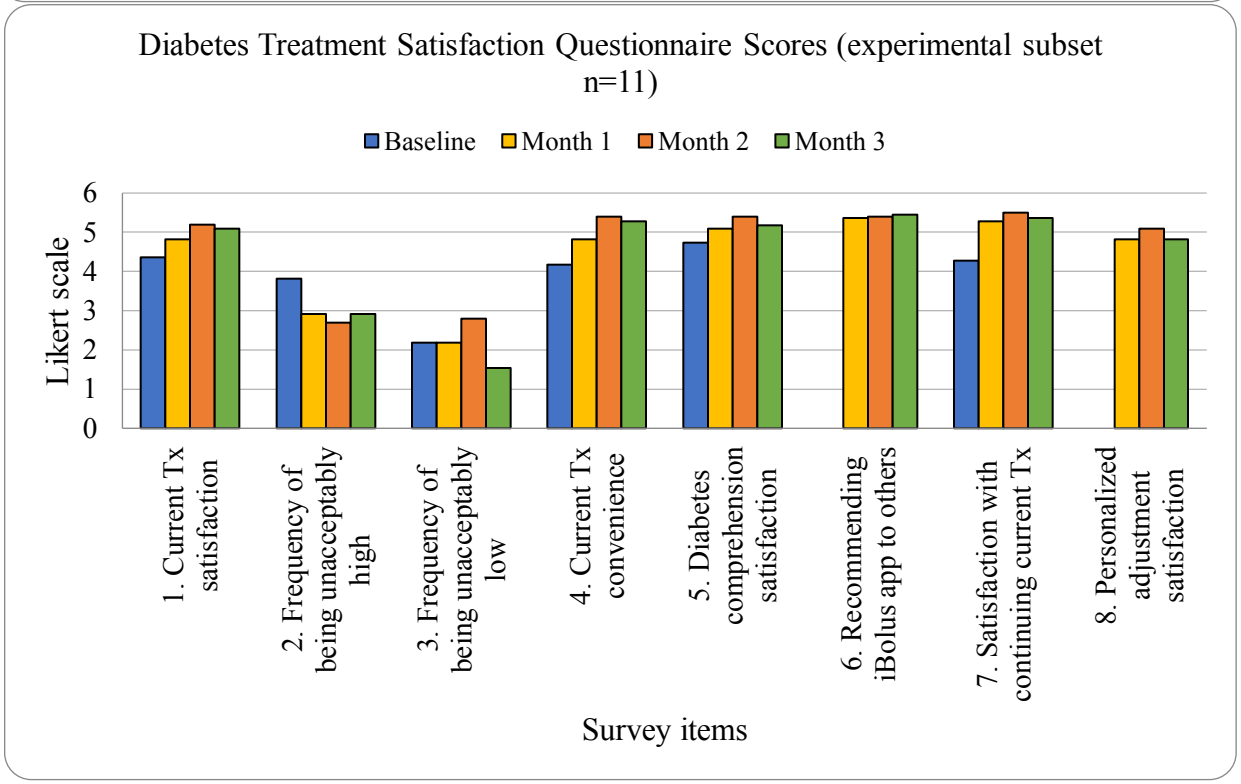


Supplementary Figure 3.6 Individual relative changes from baseline in basal doses throughout the 12-week intervention in the experimental arm (n=42).

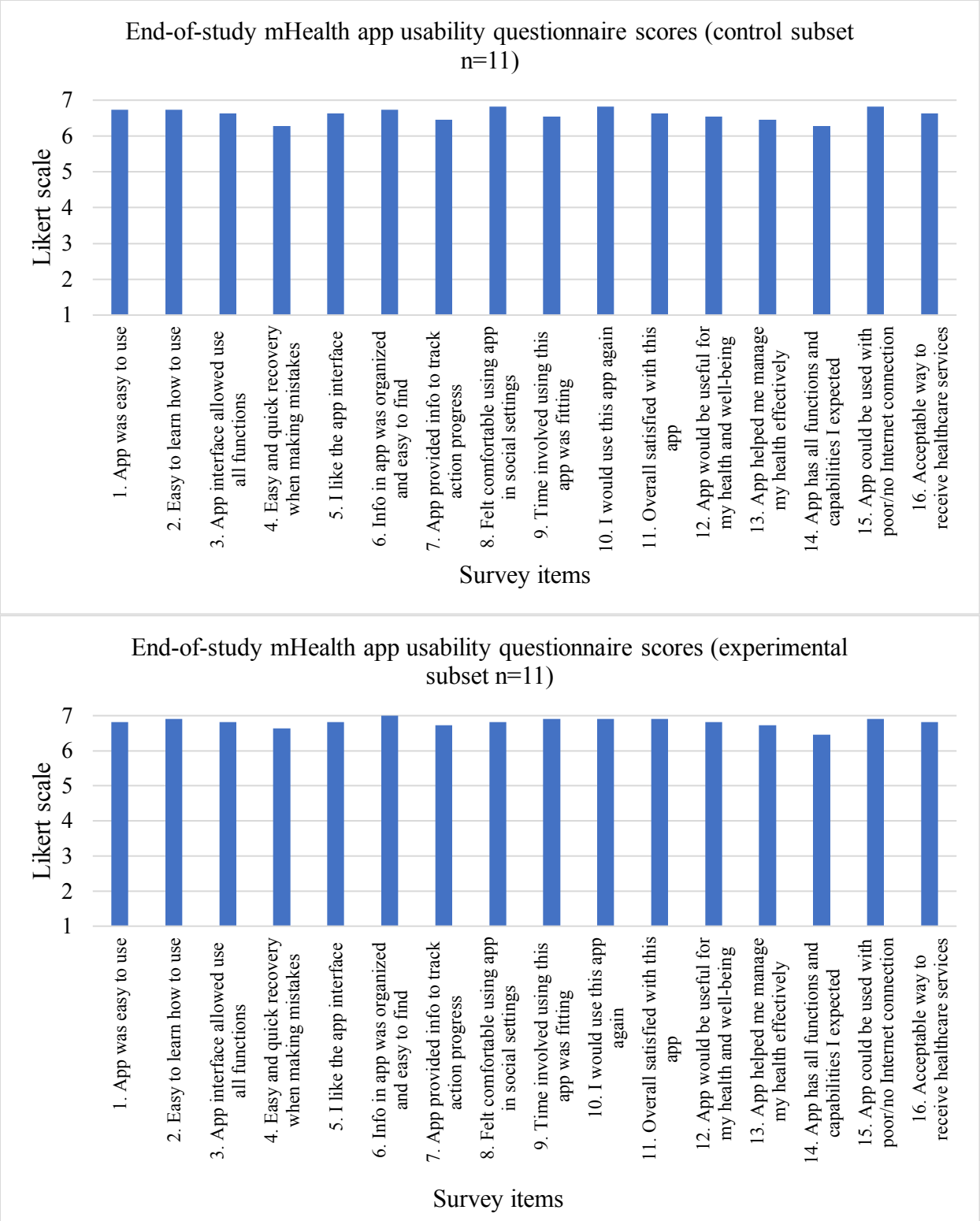


Supplementary Figure 3.7 Individual relative changes from baseline in prandial doses throughout the 12-week intervention in the experimental arm (n=42).

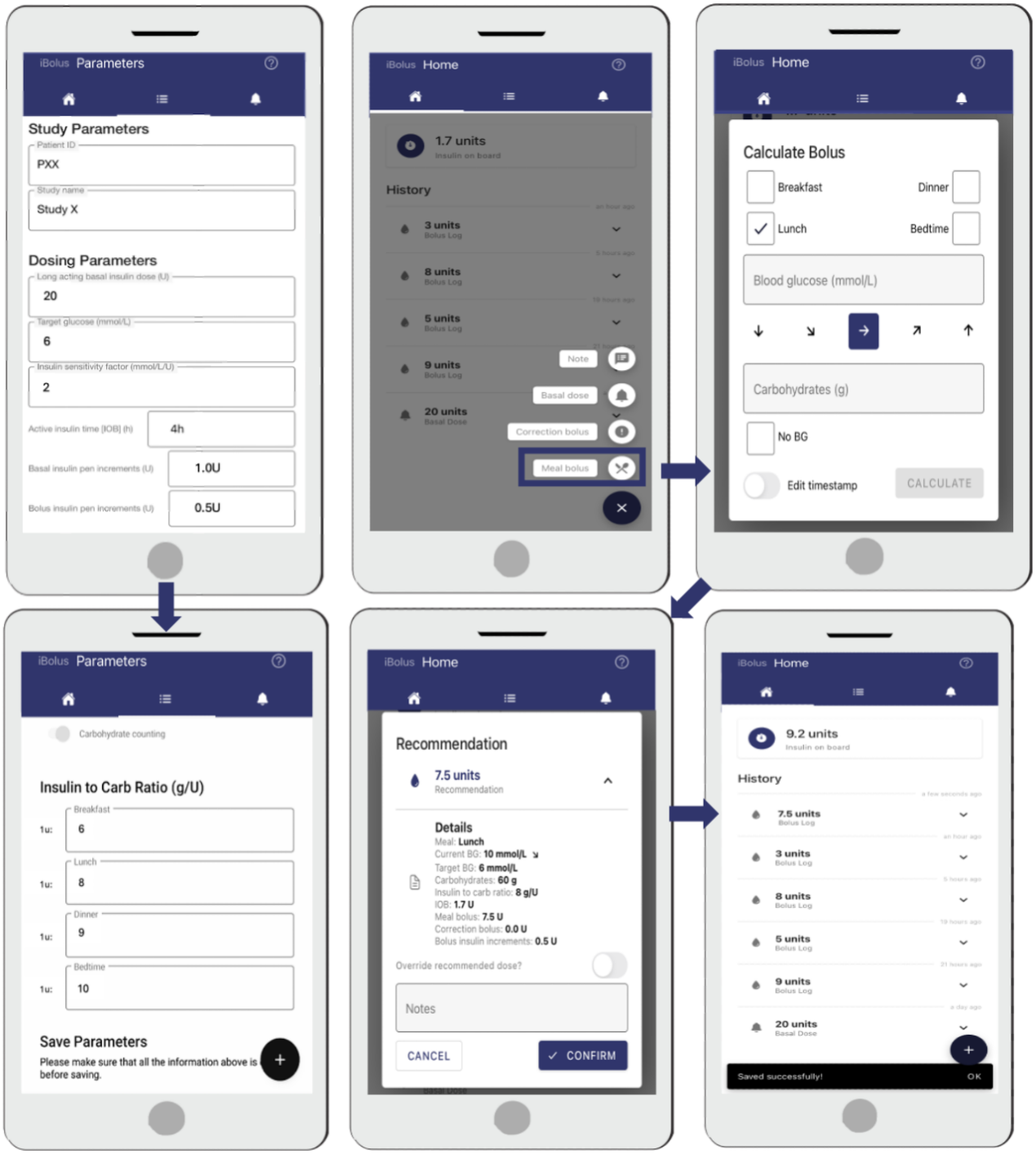




Supplementary Figure 3.8 Diabetes Treatment Satisfaction Questionnaire monthly scores in control (n=11; top bars) and experimental (n=11; bottom bars) sub-study participants.



Supplementary Figure 3.9 End-of-study mHealth app usability questionnaire responses from control (n=11; top bars) and experimental (n=11; bottom bars) sub-study participants.



Supplementary Figure 3.10 Overview of the iBolus app's graphical user interface, showing the parameters screen, the main home screen with active insulin-on-board, and the meal bolus function.

Chapter 4. Inter- and Intra-Physician Variability in Insulin Injection Adjustments Compared to Bayesian Algorithm Recommendations in Type 1 Diabetes

4.1 Preface

In the previous chapter, the clinical effectiveness of the McGill DSS was demonstrated. This trial is the first to show glycemic improvement with a DSS for MDI therapy, all while being the first to include qualitative outcomes on MDI user experiences.

In this chapter, the integrated manuscript presents a survey sub-study that assessed the practical utility of the McGill DSS algorithm by comparing the insulin adjustments made by this system to mock adjustments made by group of endocrinologists. This study involved a structured automated process to obtain physician assessments in three different parts.

Parts A and B, completed 8-12 weeks apart, involved an identical 4-week dataset of weekly meal, insulin, and sensor glucose graphical summaries from 15 experimental participants who received algorithm-made adjustments in the parent trial. Part A captured inter-physician variability between 13 physicians and Part B captured intra-physician variability within 12 physicians (i.e., adjustments made in Part B were compared to those made in Part A). Part C involved optional biweekly assessments, comparing newly generated mock recommendations made by the algorithm to those made by physicians based on two 14-day datasets from 13 control participants whose baseline parameters remained unchanged in each evaluation period. We chiefly evaluated whether the proportions of agreement and disagreement in directional insulin dosing for prandial bolus and basal parameters between the algorithm and physicians were statistically non-inferior to the proportions between the physicians.

4.2 Contribution of Authors

Alessandra Kobayati designed and developed this sub-study under Ahmad Haidar's supervision. Alessandra Kobayati conceptually designed the physician online portal and platform specification requirements to support the study purpose, collaborating with Prolucid Technologies Inc. for platform development and deployment. Alessandra Kobayati recruited physician collaborators to participate in this study. Anas El Fathi drafted the initial platform graphs, and Joanna Rutkowski updated and generated all final graphs, which were verified for quality control by Alessandra Kobayati. Alessandra Kobayati and Joanna Rutkowski performed platform testing with simulated pilot runs. Alessandra Kobayati developed the physician training materials, consisting of user guides and YouTube videos.

Dr. Jean-François Yale and Dr. Sara Meltzer provided clinical feedback on mock platform graphs and performed pilot runs to gauge the estimated weekly time requirements to complete online assessments.

Dr. Michael Tsoukas, Dr. Natasha Garfield, Dr. Laurent Legault, Dr. Melissa-Rosina Pasqua, Dr. Jean-François Yale, Dr. Sara Meltzer, Dr. Simon Wing, Dr. Stéphanie Michaud, Dr. Vanessa Tardio, Dr. Tricia Peters, Dr. Rachel Bond, Dr. Preetha Krishnamoorthy, and Dr. Ivan George Fantus all completed Part A. The first 12 physicians listed also completed Part B. Furthermore, Dr. Tsoukas, Dr. Garfield, Dr. Legault, Dr. Pasqua, Dr. Wing, Dr. Michaud, Dr. Tardio, Dr. Peters, and Dr. Bond all completed Part C.

Anh Ngo processed the raw data and generated the box plots included in the manuscript and appendix. Leif Erik Lovblom conducted the non-inferiority statistical analysis. Alessandra Kobayati and Ahmad Haidar interpreted the results.

Alessandra Kobayati wrote the original manuscript and appendix and made revisions in accordance with Ahmad Haidar's feedback. The other co-authors reviewed and approved the final manuscript prior to journal submission.

Inter- and Intra-Physician Variability in Insulin Injection Adjustments Compared to Bayesian Algorithm Recommendations in Type 1 Diabetes

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Number of references: 13
Number of tables: 4
Number of figures: 3

4.3 Abstract

Objective: There is an unmet need for automated insulin adjustments for multiple daily injections in type 1 diabetes under unsupervised use. The McGill decision support system (DSS), comprising a Bayesian algorithm, previously demonstrated glycemic benefit among injection-treated adults in a randomized controlled trial. The primary objective of this sub-study is to assess the algorithm's utility by comparing its insulin dose adjustments to those made by endocrinologists.

Methods: We surveyed 13 Canadian endocrinologists who made mock insulin adjustments in three separate parts on retrospective participants' data from the parent trial. Part A (weekly) and Part C (biweekly) compared recommendations from physicians (inter-physician variability) with those of the algorithm. Part B evaluated intra-physician variability by comparing recommendations made within the same physician over time based on identical datasets. The primary endpoint was the proportion of full agreement (increase, decrease, or no change) and full disagreement (increase versus decrease) on the direction of prandial bolus and basal adjustments between the algorithm and physicians compared to those among physicians.

Results: In Part A, the proportion (mean (SD)) of full agreement on weekly insulin adjustments between the algorithm and physicians was statistically non-inferior to the proportion between physicians for prandial boluses (55% (5) vs. 56% (7); p=0.014) and basal (48% (6) vs. 51% (11), respectively; p=0.019). Much lower full disagreements were also comparable between the pairs. Similar proportions were observed for biweekly adjustments in Part C. When comparing intra-physician decisions in Part A to Part B, the average physician fully agreed with themselves 66% (7) and 67% (7) of the time for prandial and basal adjustments, respectively.

Conclusions: The direction of insulin adjustments was comparable between physicians and the McGill DSS algorithm. The intra-physician variability emphasizes the subjective nature of insulin management. Overall, these findings highlight the practical utility of this algorithm.

4.4 Introduction

Type 1 diabetes is a chronic condition that requires intensive insulin therapy in the form of multiple daily injections (MDI) or continuous subcutaneous insulin infusion via a pump to mitigate the risk of long-term complications (1). MDI remains the predominant insulin delivery method used worldwide (2). Continuous glucose monitoring (CGM) via glucose sensors has revolutionized insulin therapy, yet most adults with type 1 diabetes still struggle to achieve optimal glycemic targets (3).

People with type 1 diabetes are typically limited to quarterly follow-ups in clinical practice (4), in part due to shortages in health care professionals (5). This poses an impediment to optimal insulin management due to continuous changes in insulin needs. Moreover, this problem is amplified by having to identify optimal insulin dose parameters from a conglomerate of data over the span of many months all in a short visit. A decision support system (DSS) that is deemed comparable to expert physicians may improve standard of care by offering insulin dose adjustments in between follow-up appointments, which in turn, may also help with in-clinic review of insulin management.

Several studies have compared recommendations of DSSs to physicians' recommendations for insulin dose adjustments in type 1 diabetes. Nimri et al. conducted survey studies to compare recommendations for insulin parameters made by a group of physicians to their DreamMed Advisor Pro in youth using insulin pump therapy with CGM (6) and with capillary glucose meters (7). Irrespective of the glucose monitoring method, the adjustments made by their DSS was found

to be not inferior to physician-made adjustments (6,7). More recently, the same group conducted a similar study with their refined DSS for MDI users, which was also found to be not inferior to recommendations made by 20 expert physicians (8). Similarly, Tyler et al. (9) assessed a different DSS for MDI by comparing each recommendation to one of three physicians and reported similar directional agreement rates as those found by Nimri et al. (8).

Recently, a 12-week randomized controlled trial was completed in 84 MDI-treated adults with type 1 diabetes and suboptimal baseline glycemic control to assess the effectiveness of the McGill DSS (NCT04123054). Half of the study participants received the McGill DSS encompassing the iBolus smartphone application that integrates a bolus calculator with weekly parameter adjustments made by the algorithm. The system utilizes individual meal, insulin, and sensor glucose data from the previous week to make recommendations for the following week. The other 42 control participants received the non-adaptive iBolus application (i.e., bolus calculator using their programmed parameters without weekly automated adjustments). This trial reported a clinically meaningful and statistically significant improvement in glycemic control with a between-group reduction in HbA1c of -0.4% ($p=0.025$) in favor of the McGill DSS. To further assess the practical utility of the McGill DSS algorithm, we conducted a sub-study in which we compared the insulin dose recommendations of the algorithm to those made by a group of practicing endocrinologists.

4.5 Materials and Methods

This study had three parts and involved the secondary use of de-identified data from participants in the parent trial. In Part A, physicians retrospectively reviewed data from participants in the experimental group of the parent trial, who had received weekly insulin adjustment recommendations from the DSS. The physicians were given the same information used by the DSS

algorithm – one week of data on participants' announced meals (including carbohydrates if applicable), insulin usage, and continuous glucose monitoring – but were blinded to the algorithm's recommendations. Physicians made insulin parameter adjustments weekly for four weeks. This phase aimed to compare the algorithm's recommendations with those of different physicians. After an 8-12 week washout period, Part B began, where the same dataset was reviewed by the same physicians, allowing for the assessment of intra-physician variability. In Part C (an optional phase), physicians reviewed 14-day retrospective data from participants in the control group, who had not received algorithm-driven adjustments. The DSS algorithm also retrospectively analyzed the same 14-day dataset and made mock recommendations. Similarly to Part A, this phase compared the algorithm's recommendations with those of the physicians, with the key difference of using biweekly data to reflect clinical practice decisions typically based on 14-day CGM reports. The protocol addendum for this sub-study was approved by the McGill University Health Center Research Ethics Board.

4.5.1 Physician Selection

Through convenience sampling, we invited endocrinologists from multiple academic centers in Quebec, Canada, who had at least one year of experience in managing MDI therapy for type 1 diabetes to be surveyed and participate as collaborators. Those who agreed completed a baseline questionnaire on their affiliations and information about their practice. Physician collaborators were also asked to complete mandatory training materials, which entailed training videos and user guides, to get accustomed with the study design, objectives, and procedures.

4.5.2 Participant Selection

To fit the design and purpose of this sub-study, specific criteria were applied when selecting data from the parent trial for retrospective analysis. This ensured sufficient data to compare adjustments

made by the algorithm to those made by physicians. Parts A and B used the same dataset, selected from participants in the experimental group who received weekly insulin adjustments from the McGill DSS. To qualify, participants had to have four consecutive weeks of data that met the following criteria: 1) ≥70% of CGM use per week, 2) ≥70% of iBolus application usage per week (assuming three meals per day), 3) no manual participant-initiated insulin parameter changes within the analysis period, 4) <30% of participant-initiated overrides of calculated insulin doses per week, and 5) at least one algorithm-made parameter change per week.

The dataset for Part C consisted of a sub-group of control participants, selected based on having four consecutive weeks of data that met the following criteria: 1) at least 70% CGM usage per week, 2) at least 70% usage of the iBolus application per week, and 3) no insulin parameter changes within the analysis period.

4.5.3 McGill Decision Support System and Online Physician Platform

The McGill DSS, containing an optimization algorithm employing a Bayesian model-based approach (10), estimates weekly insulin parameter recommendations for MDI users. In the parent trial (NCT04123054), the algorithm was executed weekly on a software (MATLAB R2018b) to compute new adjustments to the insulin parameters based on the previous week's data. The system analyzed individual meal and insulin data that recorded in the iBolus application by participants, along with intermittently scanned CGM data. This analysis generated adjustments in basal insulin doses and in prandial parameters, either as fixed insulin doses or as insulin-to-carbohydrate ratios, depending on the participant's meal strategy. The prandial parameters were calculated for breakfast, lunch, dinner, and bedtime. The new adjustments were automatically pushed to the participant's iBolus application and applied in the following week. Participants had the option to

override the algorithm adjustments as needed. The clinical effectiveness results of the McGill DSS on glycemic management were described elsewhere (11).

For this current sub-study, we created an online physician platform to simulate the weekly assessments in the parent trial. Physician collaborators were asked to provide mock adjustments in the platform for once-daily long-acting basal dose and rapid-acting prandial bolus parameters (breakfast, lunch, dinner, and bedtime) for the subsequent week based on isolated weekly de-identified participant data cases (for Parts A and B). They were also asked to optionally participate in Part C to provide mock adjustments for the following two weeks based on different datasets containing 14 days of de-identified participant data (Supplementary Figure 4.4).

The weekly (Part A and B) or biweekly (Part C) retrospective data was presented in the platform as (i) summaries of insulin and glucose metrics, (ii) a detailed graph displaying intermittently scanned CGM data and logged meal and insulin data, and (iii) an ambulatory glucose profile graph displaying trends across a 24-hour period (12) (Supplementary Figure 4.5, Supplementary Figure 4.6). For additional context, the platform also displayed participant's meal strategy (carbohydrate counting or fixed-dose), brand name of the long-acting and rapid-acting insulins with the corresponding insulin pen unit increments, and participant's correction factor and blood glucose target.

The blinded participant data cases were presented in the platform at set intervals (weekly for Parts A and B and biweekly for Part C) in random order to minimize confirmation bias. This approach aimed to prevent dosing trends based off memory of entries from the previous batch of submissions, in attempt to capture decision-making without preconceptions. By default, the current therapy parameters were pre-populated in editable boxes. Physicians were asked to increase or decrease basal doses and prandial parameters, according to the corresponding pen unit increments

(when applicable), or to leave a parameter unchanged, based on their assessment of the data. Physicians were allowed to contribute ad hoc comments for supplemental observations or feedback to complement their review of each parameter. The DSS algorithm outputs were not displayed to maintain blinding.

4.5.4 Study Design

This study involved three parts, capturing inter-physician variability (Part A) and intra-physician variability over time (Part B) for weekly datasets, as well as inter-physician variability for biweekly datasets (Part C) to simulate 14-day CGM reports used in practice. Each physician collaborator selected their own start dates for Part A and Part B, separated by an 8-12-week washout period, mimicking quarterly follow-ups in clinical practice. For practicability, only four weeks of data from the main trial (instead of all 12 weeks) were used in each part of the study (Supplementary Figure 4.4). Physicians were asked to select dates that would allow them to meet their weekly commitments; however, missed assessments were permitted to be completed in the subsequent week prior to initiating the new batch of assessments.

For Part A, each physician received weekly access in the platform to 15 retrospective participant data cases. When a physician submitted an assessment of mock adjustments, the data was immediately captured by our secure server, and they were prompted to review the next assessment. Adjustments were not allowed after submission. After submitting their final assessment in a given week, their access was disabled until the following week. Physicians then regained access to a new set of randomly assorted data cases. This process was repeated for four consecutive weeks. Following the completion of Part A, physicians waited at least eight but no more than 12 weeks before starting Part B where they received the same 4-week dataset and repeated the procedures from Part A without access to their former submissions.

Upon completion of Part B, physicians had the option to participate in Part C at any start date of their choice. Part C involved a review of two datasets of 14 consecutive days of 13 participants in the control group, whose insulin therapy parameters remained unchanged during each 14-day evaluation period (Supplementary Figure 4.4). Similar to Parts A and B, the data cases were presented within the physician platform in random order. Examples of the physician platform interface are provided in Supplementary Figure 4.5 and Supplementary Figure 4.6. In parallel, we retrospectively generated algorithm recommendations based on the 14-day data for comparison with the physicians by executing the algorithm on the Part C datasets. The core logic of the algorithm remained unchanged from the version used in the parent trial.

4.5.5 Study Endpoints

The primary endpoint was the mean proportion of full agreement (increase, decrease, or no change) and full disagreement (increase vs. decrease) on the direction of prandial bolus and basal parameter adjustments between the algorithm and physicians compared to those made among the physicians in Part A.

The secondary endpoints included the mean proportion of partial disagreement (increase vs. no change or decrease vs. no change) on the direction of insulin dosing, as well as the mean absolute difference in relative magnitude of change for cases of full agreement and full agreement with active change (defined as a non-zero numerical change in the same direction) between the algorithm and physicians compared to those made among physicians in Part A. The analysis for magnitude of change was separated according to fixed-dose and carbohydrate counting users to account for the differences in implications (e.g. a decrease in carbohydrate ratio is intended to increase the amount of insulin administered while a decrease in a fixed-dose reduces the amount of insulin). The comparative analyses were carried out individually for each parameter (basal and

breakfast, lunch, dinner, and bedtime boluses). For prandial boluses, the average of all meal outcomes (breakfast, lunch, dinner, and bedtime) were reported.

Exploratory comparisons included directional change and magnitude of change for mock biweekly adjustments of prandial bolus and basal parameters between the algorithm and physicians to those between physicians in Part C. Additional comparisons included the mean proportion of full agreement, full disagreement, and partial disagreement on the dosing direction of adjustments made by each physician in Part A to those made on the identical dataset by the same physician in Part B.

4.5.6 Statistical Analysis

Summary statistics are presented as mean (SD), median [Q1–Q3], or as n(%). A one-tailed, one-sample, non-inferiority t test was used to assess whether the proportion of agreement and disagreement in the directional changes between the algorithm and physicians was non-inferior to the proportion between pairs of physicians. The non-inferiority margin for the agreement and disagreement tests were set as the 25th and 75th percentile of the distribution of the level of agreement and disagreement among the physicians, respectively; an upper-tailed test was used for agreement, and a lower-tailed test was used for disagreement. The same approach was employed for the mean absolute difference in relative change outcomes for cases of full agreement. P-values less than 0.05 indicated non-inferiority. The analyses were performed using MATLAB R2024a and SAS version 9.4.

4.6 Results

4.6.1 Participant Cohort

For Parts A and B, the same de-identified data from 15 experimental participants were used. The mean age was 42 (SD 12) years, with a mean diabetes duration of 23 (13) years and a median baseline HbA1c of 8.2% [Q1–Q3 7.9–8.7]. Of these, 10 (67%) participants were female, and 8 (53%) were practicing carbohydrate counting while 7 (47%) were on a fixed-dose regimen. Furthermore, 40% of participants used Degludec and one-third used Glargine U-100 as the long-acting basal. One-third used Lispro, and over half of the sample used either Aspart or fast-acting Aspart (Supplementary Table 4.5).

For Part C, de-identified data from 13 control participants were used. For this sample, the mean age was 41 (12) years, mean diabetes duration was 28 (13) years, and the median baseline HbA1c was 8.4% [8.0-8.9]. Of these, 8 (62%) were carbohydrate counting and 5 (38%) used fixed-doses. The most commonly used basal insulin was Degludec (54%), followed by Glargine U-100 (23%). The most commonly used bolus insulin was Aspart (62%), followed by Lispro (31%) (Supplementary Table 4.5).

4.6.2 Physician Collaborators

A total of 13 practicing endocrinologists across the province of Quebec (Royal Victoria Hospital (n=9), Montreal Children's Hospital (n=2), Jewish General Hospital (n=1), Charles-Le Moyne Hospital (n=1)) agreed to participate as physician collaborators in this sub-study. Most physicians specialized in adult endocrinology, with two specializing in pediatric endocrinology. All participating physicians were experienced in monitoring individuals with type 1 diabetes, with the majority of them dedicating more than half of their practice treating MDI as declared in their self-

reported baseline questionnaire. In addition, 54% of them had over 15 years of experience in practice. More details about their experience are indicated in Table 4.1.

For Part A, the number of insulin therapy recommendations (combined prandial boluses and basals) made by the algorithm was 300 and made by 13 physicians was 3900. For Part B, 3600 additional recommendations from 12 physicians were used for the intra-physician variability evaluation. For Part C, the number of biweekly insulin recommendations was 130 by the algorithm and 1170 by nine physicians.

Table 4.1 Characteristics of the physician collaborators.

	Physicians (N=13) n (%)
Sex (female/male)	8 (62) /5 (38)
Primary specialty	
Adult endocrinology	11 (85)
Pediatric endocrinology	2 (15)
Experience in clinical practice	
>15 years	7 (54)
6-10 years	2 (15)
2-5 years	3 (23)
1-2 years	1 (8)
Current institutional position	
Professor	4 (31)
Associate Professor	4 (31)
Assistant Professor	4 (31)
Independent endocrinologist	1 (8)
Estimated number of type 1 diabetes patients seen annually	
>100	6 (46)
76-100	1 (8)
51-75	2 (15)
26-50	2 (15)
0-25	2 (15)
Estimated % of patients with type 1 diabetes on MDI in their practice	
76-100	1 (8)
50-75	10 (77)
25-49	2 (15)

MDI: multiple daily injections.

4.6.3 Algorithm versus Inter-Physician Weekly Insulin Adjustments (Part A)

To evaluate how weekly insulin dose recommendations among different physicians compared to those of the algorithm, each of the 13 physicians completed 60 weekly assessments in Part A. There were 78 between-physician pairs with 9360 comparison points from the adjustments in basal and prandial doses. There were 13 algorithm-physician pairs with 1560 comparison points.

The mean (SD) proportion of full agreement on the directional dosing (increase, decrease, or no change) for prandial boluses was 56% (7%) among physicians compared to 55% (5%) between the algorithm and physicians (p-value for non-inferiority=0.014). For basal, the proportion of full agreement was 51% (11%) between physicians compared to 48% (6%) between the algorithm and physicians (p=0.019) (Table 4.2; Figure 4.1).

The proportion of full disagreement on the direction of insulin dosing (increase versus decrease) for prandial boluses was 4.1% (2.3%) among physicians compared to 3.9% (2.3%) between the algorithm and physicians (p=0.014). For basal, the proportion of full disagreement was 9.2% (7.1%) among physicians compared to 10.6% (4.6%) between the algorithm and physicians (p=0.22). The proportion of partial disagreement (increase versus no change or decrease versus no change) for prandial boluses was 39% (5%) among physicians and 42% (4%) between the algorithm and physicians. For basal, the partial disagreement was 39% (7%) among physicians and 41% (6%) between the algorithm and physicians (Table 4.2; Figure 4.1).

Table 4.2 Proportion of full agreement, full disagreement, and partial disagreement in the direction of weekly insulin adjustments (Part A) among 13 physicians vs. the algorithm and physicians (top panel) and biweekly insulin adjustments (Part C) among 9 physicians vs. the algorithm and physicians (bottom panel).

Parameter	Inter-physicians	Between algorithm and physicians	Non-inferiority P value
Directional change proportions (%) in Part A (n=15 experimental participants*)			
Full agreement on basal change	51 (11)	48 (6)	0.019
Full agreement on bolus change	56 (7)	55 (5)	0.014
Full disagreement on basal change	9.2 (7.1)	10.6 (4.6)	0.22
Full disagreement on bolus change	4.1 (2.3)	3.9 (2.3)	0.014
Partial disagreement on basal change	39 (7)	41 (6)	-
Partial disagreement on bolus change	39 (5)	42 (4)	-
Directional change proportions (%) in Part C (n=13 control participants†)			
Full agreement on basal change	43 (15)	49 (9)	0.0005
Full agreement on bolus change	54 (9)	51 (6)	0.14
Full disagreement on basal change	8.1 (8.0)	8.1 (5.9)	0.061
Full disagreement on bolus change	5.5 (3.5)	5.1 (4.0)	0.044
Partial disagreement on basal change	49 (13)	43 (8)	-
Partial disagreement on bolus change	41 (6)	43 (5)	-

Data are presented as mean (SD).

Full agreement applied when both pairs agreed on the same dosing direction.

Full disagreement applied when one pair indicated one dosing direction and the other indicated the opposite direction.

Partial disagreement applied when one pair indicated one dosing direction and the other indicated no change.

*Retrospective data was based on a 4-week dataset from experimental participants who received weekly algorithm-made adjustments in the parent trial.

†Retrospective data was based on two 14-day datasets from control participants from the parent trial whose baseline parameters remained unchanged during each biweekly evaluation period.

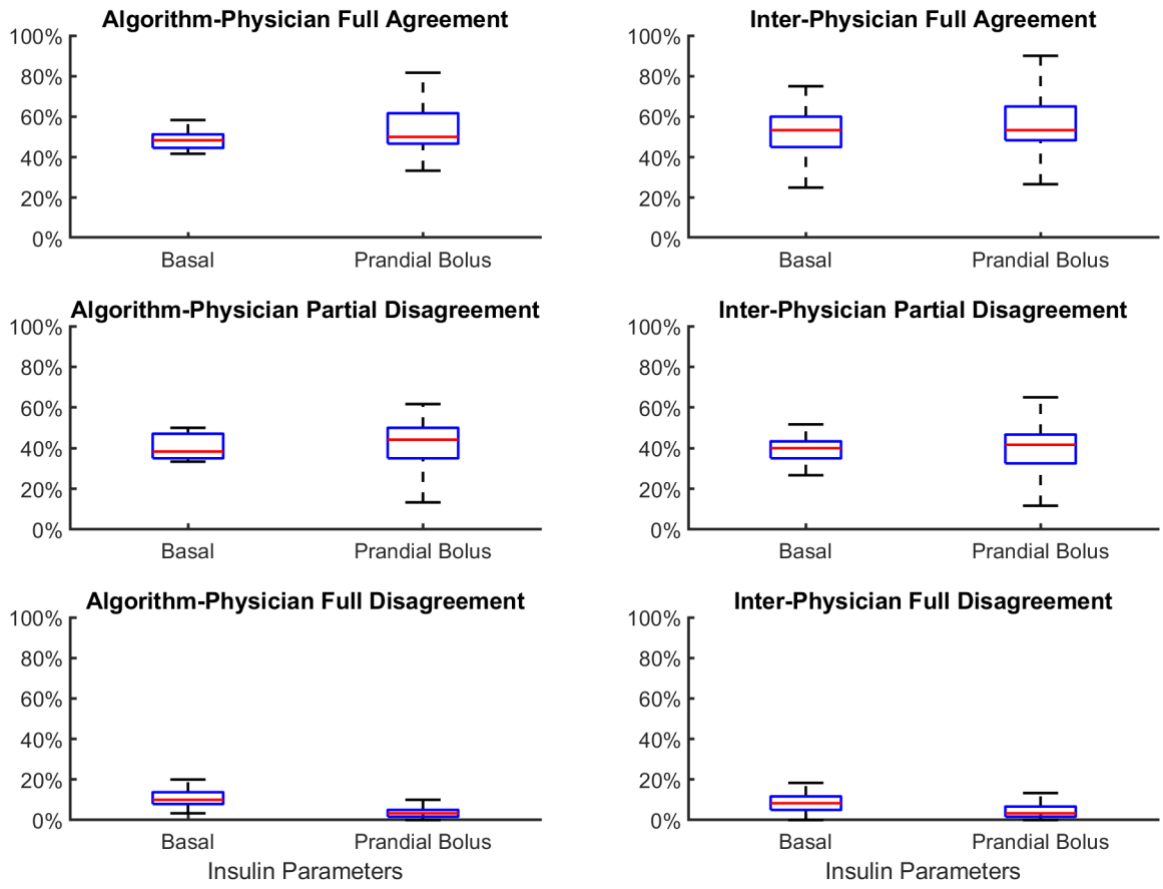

Figure 4.1 Box plots for the level of directional full agreement, partial disagreement, and full disagreement for weekly insulin adjustments in Part A between the algorithm and physicians (left column) and between physicians (right column).

The mean absolute difference in relative magnitude of change in cases of full agreement for prandial boluses from the carbohydrate counters' data (n=8) was 1.8% (2.5%) between physicians compared to 1.7% (0.8%) between the algorithm and physicians (p=0.20). For basal, the difference was 3.4% (2.0%) between physicians compared to 2.8% (2.1%) between the algorithm and physicians (p=0.035). For the fixed-dose cases (n=7), the difference was 1.5% (1.1%) between physicians compared to 1.0% (0.8%) between the algorithm and physicians (p<0.0001) for prandial boluses, and 2.7% (1.2%) versus 3.7% (1.0%) for basal (p=0.90) (Table 4.3; Supplementary Figure 4.7).

Table 4.3 The mean absolute difference in the relative magnitude of change for cases of full agreement in weekly insulin adjustments (Part A) among 13 physicians vs. the algorithm and physicians (top panel) and biweekly insulin adjustments (Part C) among 9 physicians vs. the algorithm and physicians (bottom panel).

Parameter	Inter-physicians	Between algorithm and physicians	Non-inferiority P value
Difference in magnitude of change (%) in Part A (n=15 experimental participants*)			
Carbohydrate counters (n=8)			
Basal	3.4 (2.0)	2.8 (2.1)	0.035
Carbohydrate ratio**	1.8 (2.5)	1.7 (0.8)	0.20
Fixed-dose users (n=7)			
Basal	2.7 (1.2)	3.7 (1.0)	0.90
Prandial bolus dose**	1.5 (1.1)	1.0 (0.8)	<0.0001
Difference in magnitude of change (%) in Part C (n=13 control participants†)			
Carbohydrate counters (n=8)			
Basal	2.5 (2.4)	1.3 (1.9)	0.0029
Carbohydrate ratio**	5.0 (12.0)	2.6 (1.5)	0.0066
Fixed-dose users (n=5)			
Basal	3.3 (4.7)	3.4 (3.7)	0.38
Prandial bolus dose**	3.6 (3.8)	0.7 (1.0)	<0.0001

Data are presented as mean (SD).

*Retrospective data was based on a 4-week dataset from experimental participants who received weekly algorithm-made adjustments in the parent trial.

†Retrospective data was based on two 14-day datasets from control participants from the parent trial whose baseline parameters remained unchanged during each biweekly evaluation period.

**Average for breakfast, lunch, dinner, and bedtime snack.

When comparing the mean absolute percentage of weekly change in cases of active full agreement for the carbohydrate counters' data, the physicians averaged a change of about 12% for prandial boluses and 10% for basal adjustments while the algorithm averaged a change of about 9% and 7% for bolus and basal, respectively. For fixed-dose cases, on average, physicians made a change of about 15% for prandial boluses and 9% for basal while the algorithm made an average change of 11% for boluses and 5% for basal adjustments (Supplementary Table 4.6).

4.6.4 Intra-Physician Variability in Weekly Insulin Adjustments (Part B)

To evaluate intra-physician variability in their recommendations on identical datasets over time, 12 physicians completed Part B, repeating the same assessments as Part A, after the washout period. The mean proportion of full agreement on the direction of insulin adjustments within the same physician over time based on identical datasets was 66% (7%) for prandial boluses and 67% (7%) for basal adjustments (Table 4.4; Figure 4.2).

The proportion of full disagreement on the direction of insulin adjustments within the same physician over time was 2.7% (2.5%) for prandial boluses and 2.1% (3.3%) for basal. The proportion of directional partial disagreement within each physician and themselves was 31% (5%) for prandial boluses and 31% (6%) for basal adjustments (Table 4.4; Figure 4.2).

Table 4.4 Proportion of full agreement, full disagreement, and partial disagreement on the direction of insulin adjustments within the same physician over time on identical datasets presented in Part A and Part B.

Directional change proportions [%] (Part A vs Part B)	Intra-physician
Full agreement on basal change	67 (7)
Full agreement on bolus change	66 (7)
Full disagreement on basal change	2.1 (3.3)
Full disagreement on bolus change	2.7 (2.5)
Partial disagreement on basal change	31 (6)
Partial disagreement on bolus change	31 (5)

Data are presented as mean (SD).

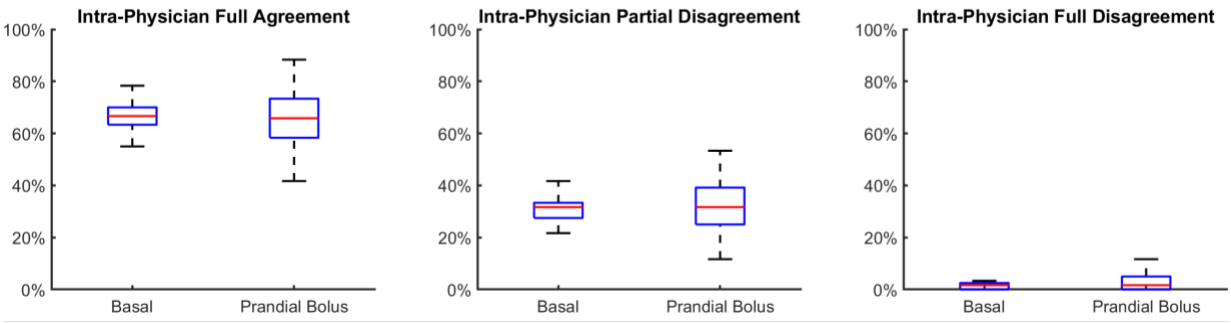

Figure 4.2 Box plots for the level of directional full agreement, partial disagreement, and full disagreement for weekly insulin adjustments between the same physician and themselves from Part A to Part B.

The mean absolute difference in the relative magnitude of change within the same physician over time for cases of full agreement in the carbohydrate counters' data (n=8) was 1.7% (1.6%) for prandial boluses and 2.2% (1.2%) for basal. For the fixed-dose data (n=7), the difference was 1.2 % (1.3%) for prandial boluses and 2.2% (1.4%) for basal (Supplementary Figure 4.8).

4.6.5 Algorithm versus Inter-physician Biweekly Insulin Adjustments (Part C)

To evaluate how biweekly insulin dose recommendations among different physicians compared to those of the algorithm, each of the nine participating physicians completed 26 biweekly assessments in Part C. There were 36 between-physician pairs with 1872 comparison points from the changes in basal and prandial parameters. There were nine algorithm-physician pairs with 468 comparison points.

The proportion of full agreement on the direction of biweekly adjustments for prandial boluses was 54% (9%) between physicians compared to 51% (6%) between the algorithm and physicians (p=0.14). For the basal parameter, the full agreement was 43% (15%) among physicians compared to 49% (9%) between the algorithm and physicians (p=0.0005) (Table 4.2; Figure 4.3).

The proportion of full disagreement on the direction of biweekly prandial bolus adjustments was 5.5% (3.5%) among physicians compared to 5.1% (4.0%) between the algorithm and physicians (p=0.044). The full disagreement for basal adjustments was 8.1% (8.0%) between physicians compared to 8.1% (5.9%) between the algorithm and physicians (p=0.061). The proportion of partial disagreement for biweekly prandial adjustments among physicians was 41% (6%) between physicians and 43% (5%) between the algorithm and physicians, and 49% (13%) versus 43% (8%) for basal (Table 4.2; Figure 4.3).

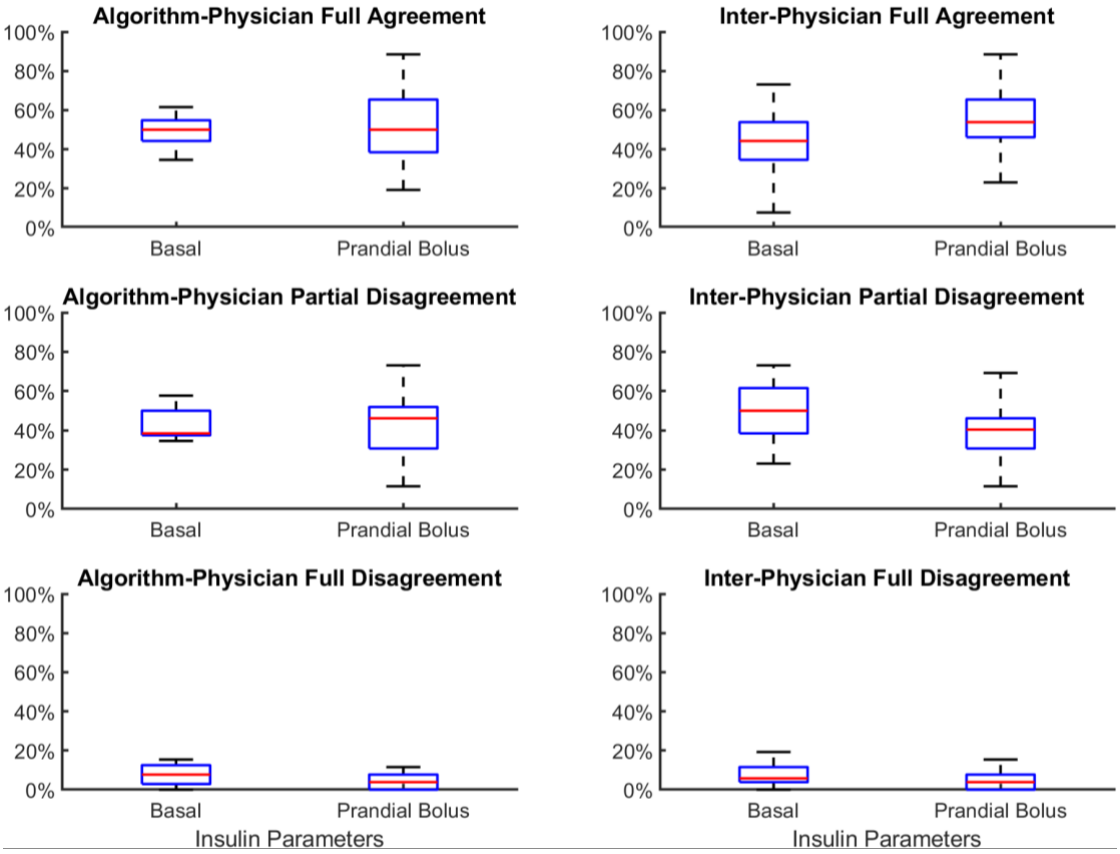

Figure 4.3 Box plots for the level of directional full agreement, partial disagreement, and full disagreement for biweekly insulin adjustments in Part C between the algorithm and physicians (left column) and between physicians (right column).

The mean absolute difference in the relative magnitude of change in cases of full agreement among the carbohydrate counters' data (n=8) was 5.0% (12.0%) between physicians compared to 2.6% (1.5%) between the algorithm and physicians (p=0.0066) for prandial boluses. The difference for basal was 2.5% (2.4%) between physicians compared to 1.3% (1.9%) between the algorithm and physicians (p=0.0029). Among the fixed-dose users' data (n=5), the difference in prandial boluses was 3.6% (3.8%) between physicians compared to 0.7% (1.0%) between the algorithm and physicians (p<0.0001). For basal, the difference was 3.3% (4.7%) between physicians compared to 3.4% (3.7%) between the algorithm and physicians (p=0.38) (Table 4.3; Supplementary Figure 4.9).

When comparing the mean absolute percentage of biweekly changes in cases of active full agreement for carbohydrate counters' data, the physicians averaged a change of about 14% for prandial boluses and 10% for basal adjustments while the algorithm averaged a change of about 9% and 6% for bolus and basal, respectively. Similar averages were found for the fixed-dose cases with an average physician change of 11% for both bolus and basal parameters compared to the algorithm's average change of about 8% (bolus) and 6% (basal) (Supplementary Table 4.6).

4.7 Discussion

Overall, the direction and magnitude of change of insulin adjustments for adults on MDI therapy made by the McGill DSS algorithm were similar to the adjustments recommended by a group of expert physicians. This was the case for weekly and biweekly basal and prandial parameter adjustments, and most non-inferiority comparisons reached statistical significance. These results illustrate the practical utility of the algorithm.

This is the first study to report intra-physician variability in the insulin decision-making process in standardized blinded settings. Interestingly, on average, the same physician only fully

agreed with themselves roughly two-thirds of the time, despite their level of expertise. Furthermore, about one-third of the time, a physician partially disagreed with themselves, where they either made a change in Part A and no change on the same data in Part B, or vice versa. They were found to even fully disagree with themselves, opposing the direction of insulin dosing for identical data cases at different timepoints, albeit seldom. Nevertheless, these findings illustrate the complexities involved with insulin dose optimization, including personal factors that may impact expert decision making, such as stress, fatigue, motivation, environment, mood, and experience (13).

Our results had several similarities to the findings of Nimri et al. (8) and Tyler et al. (9). First, we also found lower than expected agreement rates between different physicians, reinforcing the subjective nature of insulin management and the inherent variability among expert decision making. Second, we found comparable agreement rates for both prandial bolus and basal parameters among physicians to those between the algorithm and physicians, rendering the McGill DSS algorithm also not inferior to physicians. However, a notable difference to the studies of Nimri et al. (8) and Tyler et al. (9) is that we classified full agreement, full disagreement, and partial disagreement separately while they defined agreement rates as the combined full and partial agreement and their disagreement rates as the combined full and partial disagreement. Accordingly, by definition, this led to lower numerical agreement and disagreement rates in our study than their studies, preventing any direct numeral comparison. Nevertheless, similar to Nimri et al. (8), we also noted overall greater absolute percentage of changes made by physicians, with more conservative algorithm changes explained by its safety limits. Another consistent observation was the recommendation of more intensive changes to prandial insulin than basal by physicians and the algorithm.

A major strength of this study is the unique comparison of both weekly and biweekly recommendations. Additionally, the novel assessment of intra-physician variability provided interesting insights that have not been previously explored. Another strength is that all participating physicians were specialized endocrinologists of varying levels of expertise, ranging from junior to senior, albeit all adequately experienced in managing MDI therapy for type 1 diabetes. This is representative of the heterogeneous level of expertise found in clinical practice. Furthermore, the physicians came from multiple centers, further increasing diversity. Another asset is the use of a tailored platform created specifically for remote data collection in accordance with the design and purpose of the study. Finally, all participant data from the parent trial involved CGM.

There are a number of limitations in our study. First, the outcomes reflect the decision making from expert physicians in four centers in a single province of Canada, limiting the generalizability of decision making done in other parts of the world. Additionally, the subgroup of trial participant data used in this study may further limit generalizability; although, the selection process was intended to ensure sufficient data for the purpose of comparing the adjustment decisions. Moreover, while the restricted demographics presented per data case were intended to limit bias, routine clinical decisions are typically based on a more complete understanding of a patient's background history, lifestyle, and dietary patterns. Similarly, the lack of real patient interaction further precluded a comprehensive overview that usually influences decisions. Another limitation was the absence of comparisons for both the correction factor and behavioral recommendations (e.g., diet, exercise) because the algorithm did not optimize the correction factor, nor did it recommend behavioral changes in the parent trial.

In conclusion, in this survey sub-study, we found comparable recommendations in the direction and magnitude of change of insulin dosing made by the McGill optimization algorithm

to those made by a group of treating endocrinologists. Furthermore, the variability found among and within physicians confirms the subjective nature of human decision making around insulin management. Therefore, this algorithm could be useful for MDI users to utilize in between clinical visits.

4.8 References

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4.9 Appendix

Supplementary Table 4.5 Baseline demographics of the participant cohort.

	Parts A & B (n=15)	Part C (n=13)
Age (years)	42 (12)	41 (12)
Female sex, n (%)	10 (67)	5 (38)
Weight (kg)	75 (14)	75 (16)
BMI (kg/m^2)	27 (3.9)	25 (3.8)
Duration of diabetes (years)	23 (13)	28 (13)
HbA1c (%)	8.2 [7.9–8.7]	8.4 [8.0–8.9]
Prior rt/isCGM use*, n (%)	12 (80)	10 (77)
Total daily insulin (U/kg)	47 [31–66]	35 [30–50]
Meal strategy regimen, n (%)	3 (7.1)	4 (10)
Carb-counting	8 (53)	8 (62)
Fixed-dose	7 (47)	5 (38)
Basal pen increment, n (%)		
1.0U	15 (100)	11 (85)
0.5U	0 (0.0)	2 (15)
Bolus pen increment, n (%)		
1.0U	13 (87)	10 (77)
0.5U	2 (13)	3 (23)
Basal insulin types, n (%)		
Degludec	6 (40)	7 (54)
Glargine U-300	2 (13)	0 (0.0)
Glargine U-100	5 (33)	3 (23)
Biosimilar glargine U-100	0 (0.0)	1 (7.7)
Determir	2 (13)	2 (15)
Bolus insulin types, n (%)		
Aspart	4 (27)	8 (62)
Lispro	5 (33)	4 (31)
Biosimilar lispro	2 (13)	0 (0.0)
Fast-acting Aspart	4 (27)	1 (7.7)

Data presented as mean (SD) or median [Q1-Q3], unless stated otherwise.

*rtCGM: real-time continuous glucose monitoring; isCGM: intermittently scanned continuous glucose monitoring; new user was defined as <3 months of uninterrupted use prior to study enrolment, and regular user was defined as ≥3months.

Supplementary Table 4.6 The mean absolute percentage of change recommended by physicians and the algorithm for cases of active full agreement in Part A and Part C.

Parameter	Algorithm	Physicians	Difference
Absolute percentage of change (%) in Part A (n=15 experimental participants*)			
Carbohydrate counters (n=8)			
Basal	6.8 (0.8)	10.2 (2.7)	3.4 (3.1)
Carbohydrate ratio**	8.9 (0.5)	12.4 (2.2)	3.5 (2.1)
Fixed-dose users (n=7)			
Basal	5.1 (0.5)	9.3 (1.7)	4.2 (1.8)
Prandial bolus dose**	10.7 (0.8)	15.4 (6.4)	4.7 (6.6)
Absolute percentage of change (%) in Part C (n=13 control participants†)			
Carbohydrate counters (n=8)			
Basal	5.5 (1.3)	10.3 (4.0)	4.8 (3.6)
Carbohydrate ratio**	9.4 (1.0)	14.1 (2.1)	4.8 (2.2)
Fixed-dose users (n=5)			
Basal	6.2 (1.8)	11.2 (6.5)	5.0 (5.1)
Prandial bolus dose**	8.1 (1.5)	11.1 (2.6)	3.0 (2.6)

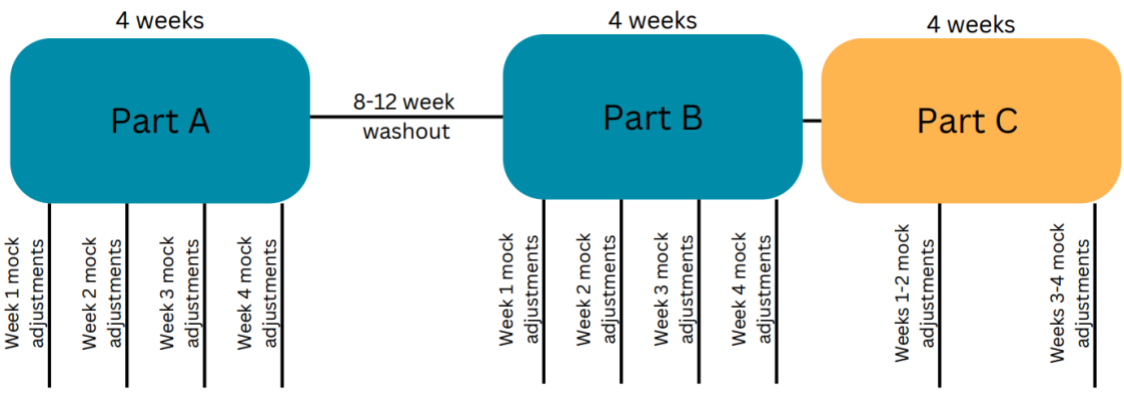
Data are presented as mean (SD).

Active full agreement is defined as a non-zero numerical change in the same direction by the pairs.

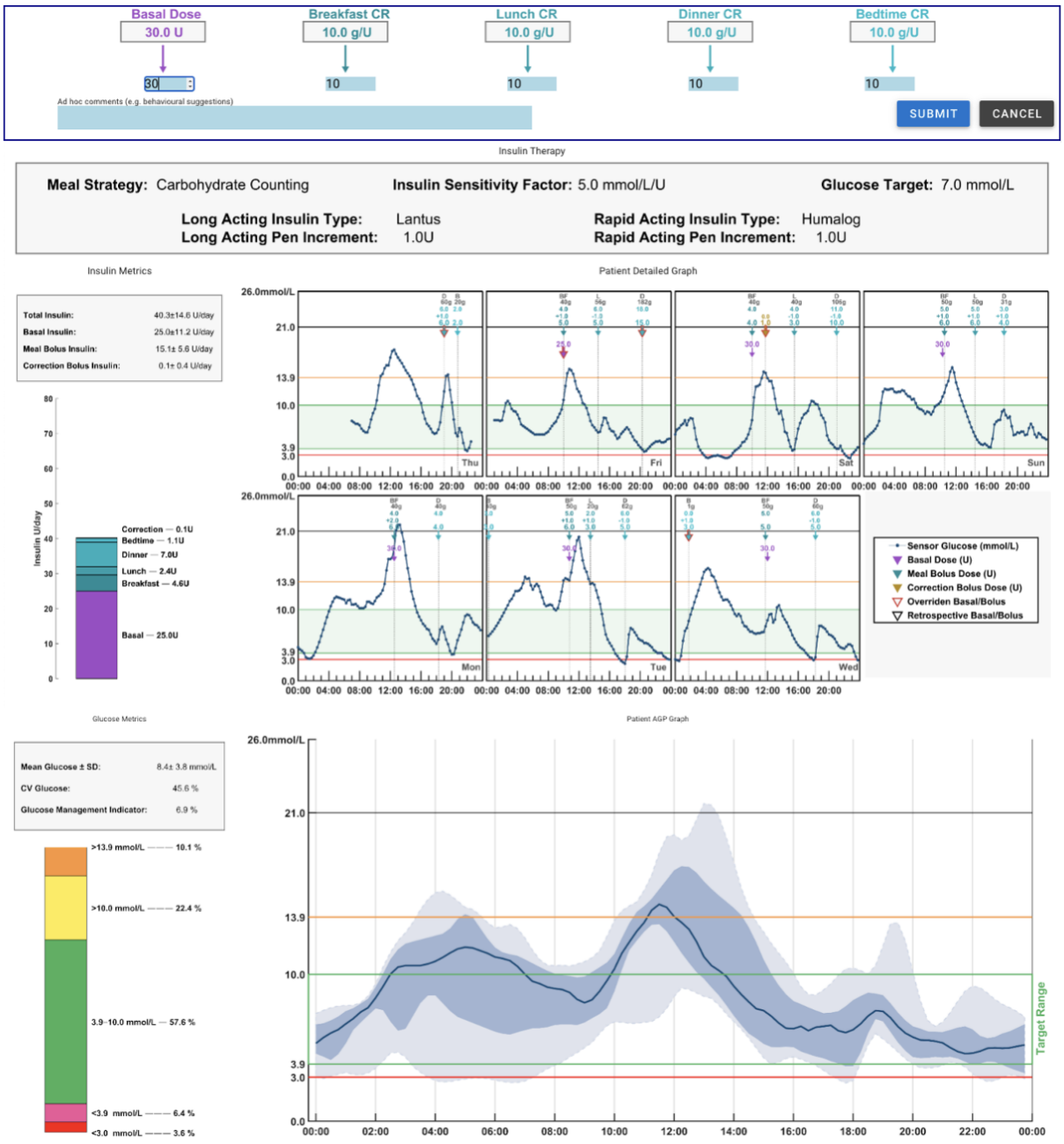
*Retrospective data was based on a 4-week dataset from experimental participants who received weekly algorithm-made adjustments in the parent trial.

†Retrospective data was based on two 14-day datasets from control participants from the parent trial whose baseline parameters remained unchanged during each biweekly evaluation period.

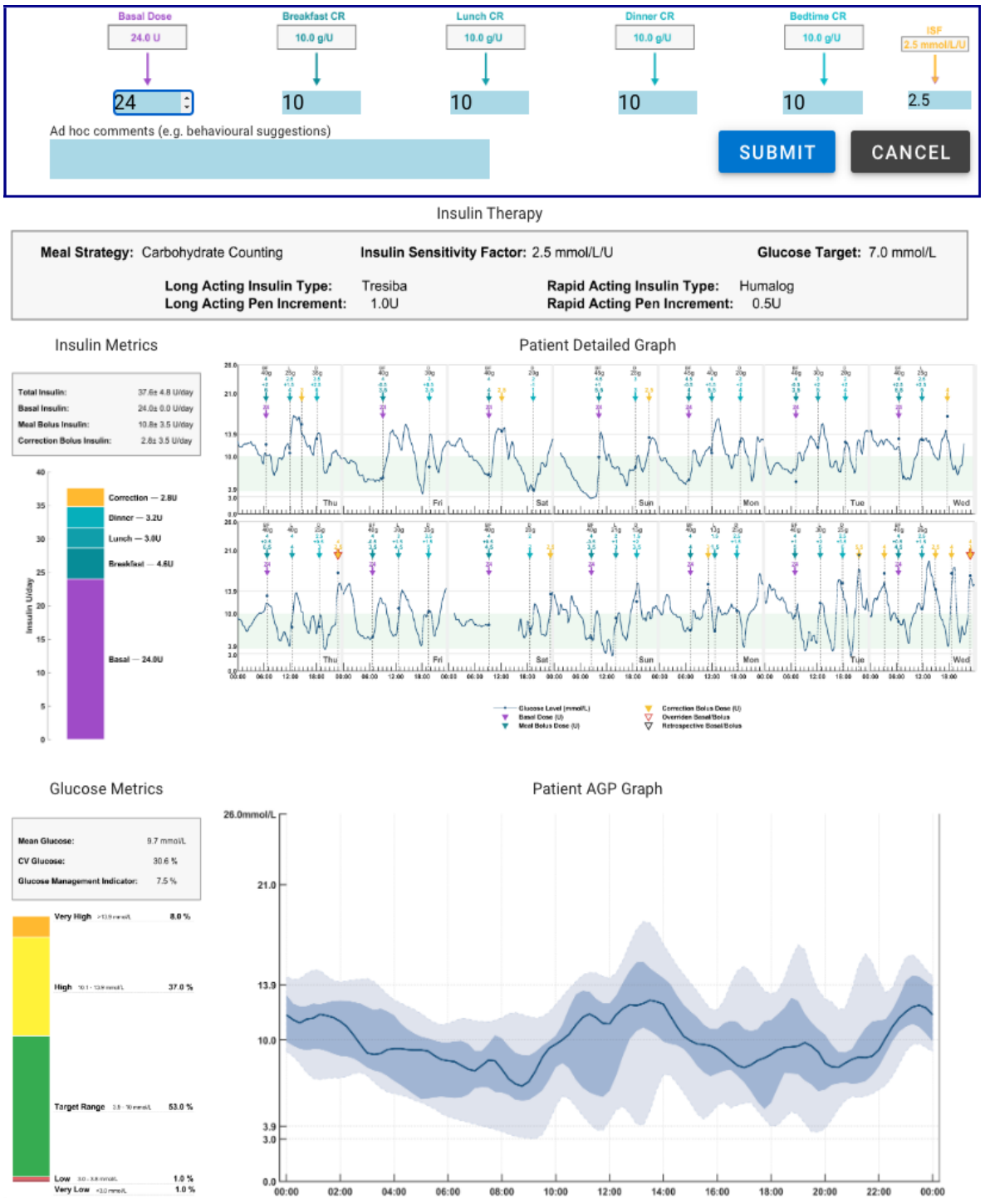
**Average for breakfast, lunch, dinner, and bedtime snack.



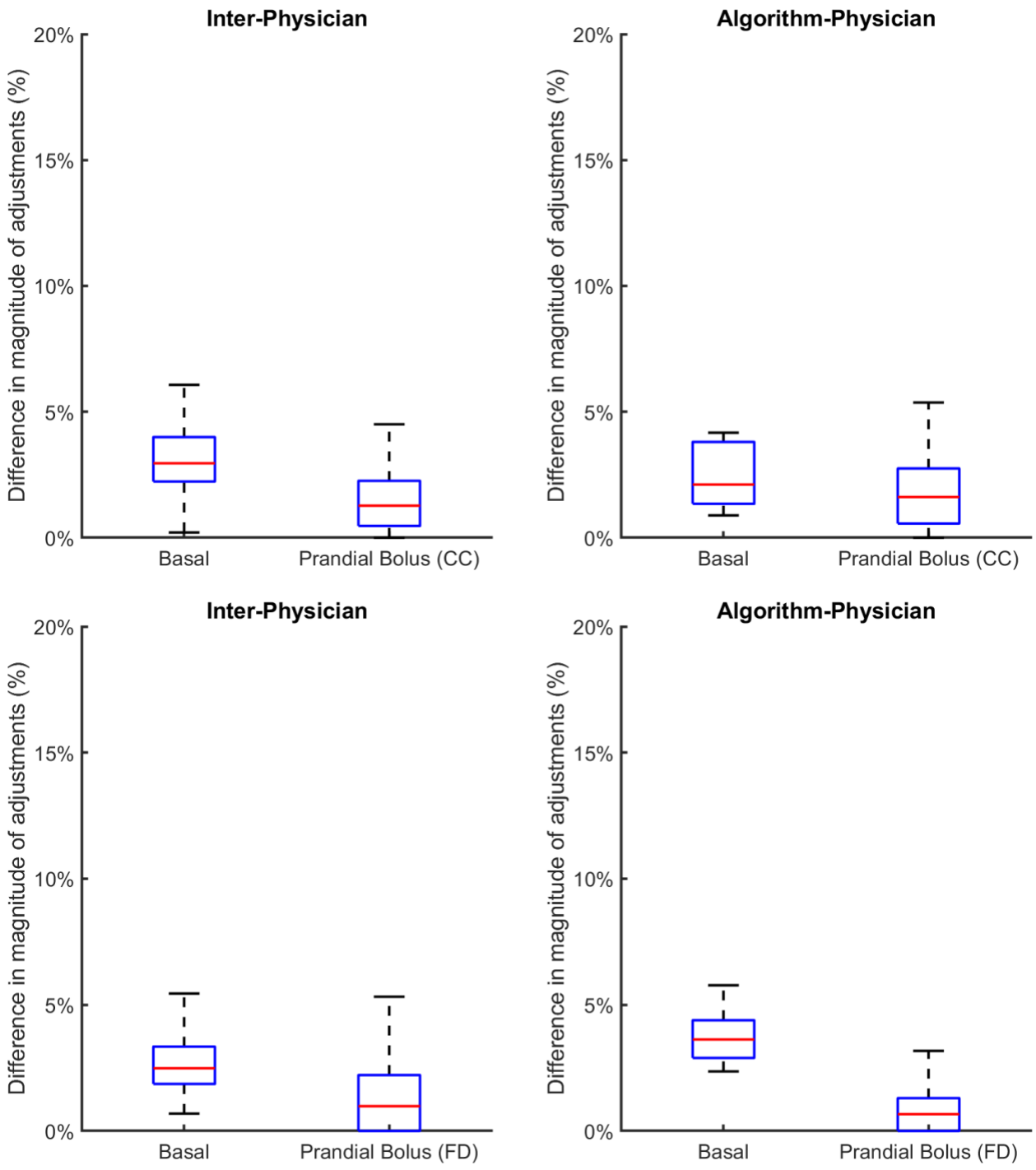
Supplementary Figure 4.4 Overview of the study design.



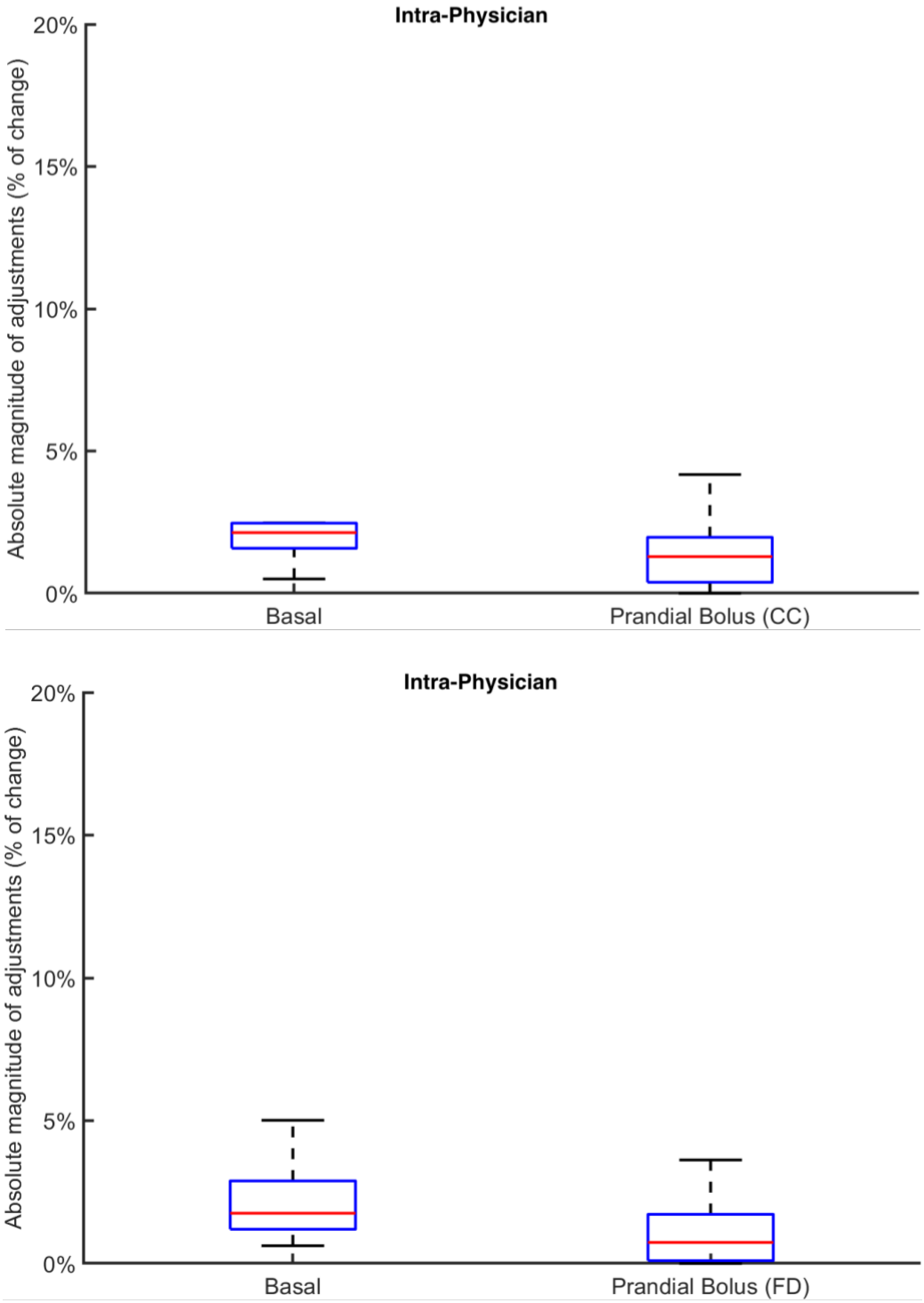
Supplementary Figure 4.5 Physician platform user interface for blinded weekly data cases in Part A and Part B.



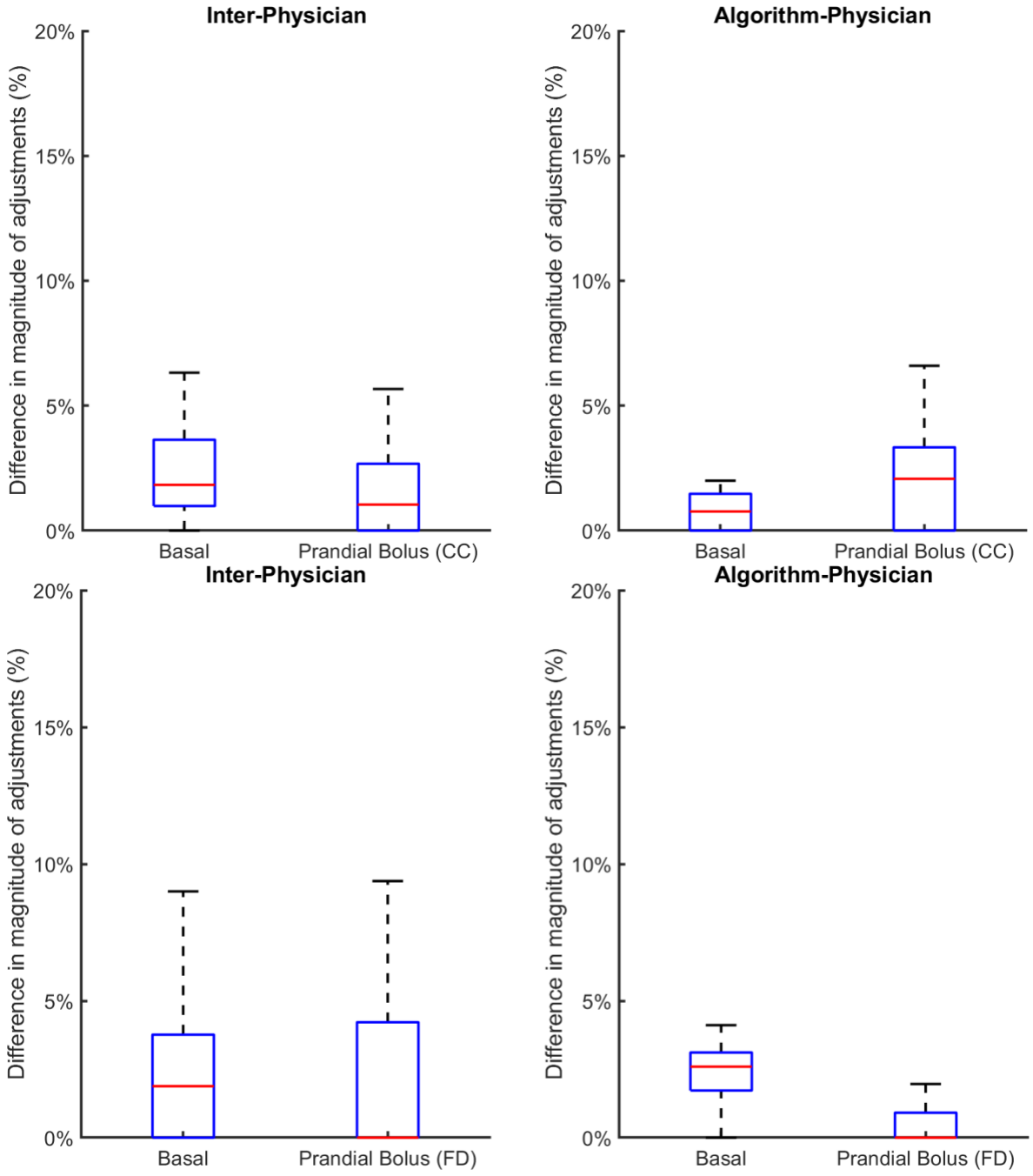
Supplementary Figure 4.6 Physician platform user interface for blinded biweekly data cases in Part C.



Supplementary Figure 4.7 Mean absolute difference in relative magnitude of change (%) for cases of full agreement among carbohydrate counting (CC) users (top panel) and fixed-dose (FD) users (bottom panel) between physicians compared to the algorithm and physicians in Part A (weekly assessments).



Supplementary Figure 4.8 Mean absolute difference in relative magnitude of change (%) for cases of full agreement among carbohydrate counting (CC) users (top panel) and fixed-dose (FD) users (bottom panel) within the same physician between Part A and Part B (identical weekly assessments).



Supplementary Figure 4.9 Mean absolute difference in relative magnitude of change (%) for cases of full agreement among carbohydrate counting (CC) users (top panel) and fixed-dose (FD) users (bottom panel) between physicians compared to the algorithm and physicians in Part C (biweekly assessments).

Chapter 5. Discussion

In this discussion chapter, I begin by succinctly situating the research within the context of the field. Next, I provide a brief summary of my core thesis work, restating the clinical evaluations sought and the high-level findings, to orient its place in the literature. Subsequently, I present an overview of the evolving connected device landscape for MDI users. Finally, this chapter concludes with foreseeable next steps for MDI treatment innovations related to this area of research.

5.1 Research in Context

MDI therapy remains the most commonly used insulin delivery method by people with T1D around the world, yet it has long trailed behind in technological advancement compared to the progress made with closed-loop technology for people using insulin pumps (57).

Prior to this thesis work, research development for advanced MDI therapy was limited to only a few DSSs that underwent investigation in large-scale randomized controlled trials, all of which were found to be safe but ineffective at improving glycemia. This highlighted the unfulfilled gaps and the ongoing unmet need for an adaptive DSS to provide optimized MDI advice for individuals with T1D that is safe, effective, and on par with typical recommendations made by expert physicians.

5.1.1 Optimization Algorithm

The McGill DSS, which was regulated as a class II investigational medical device by Health Canada, was assessed in a clinical trial, as presented in Chapter 3. Not only was this the first trial to establish glycemic benefit with an adaptive algorithm-based DSS for MDI therapy, it was also the first to incorporate exit interviews in a subset of trial participants. The qualitative outcomes

revealed insights into MDI user perspectives on the use of the study software, enriching the value of the quantitative outcomes.

In Chapter 4, the algorithm was assessed for practical use in a sub-study to evaluate how automated decision making compared to human decision making. In all, we observed comparable proportions in the mean direction of change and absolute difference in relative change between the algorithm and physicians for weekly and biweekly assessments. Furthermore, the algorithm and physicians tended to make more intensive changes to prandial insulin compared to basal, with physicians recommending overall greater absolute changes on average. Collectively, these findings propose that the advice provided by the McGill DSS algorithm may be viewed akin to that of another expert in the field.

5.1.1.1 System Limitations

One of the algorithm's shortcomings that was not addressed in Chapter 3 is the lack of behavioural advice. Consequently, the sub-study described in Chapter 4 was designed to capture ad hoc behavioural comments from physicians in addition to their mock insulin adjustments. An informal assessment of the mock behavioural suggestions revealed some recurring patterns. These include comments surrounding delayed boluses, unannounced meals, late basal logging, insulin stacking, over-corrections of hyperglycemia and hypoglycemia, and split basal dosing.

These findings, although interesting, are exploratory and did not undergo formal analysis due to the voluntary aspect of this platform feature and thus was not included in the manuscript. Instead, they serve to provide a signal to potentially gauge future development of behavioural recommendations as a means to theoretically enhance user engagement and reinforce treatment adherence of proper dose injection behavior.

5.1.1.2 Considerations for the Automated Titration Frequency

The McGill DSS demonstrated glycemic improvement without any system-related safety concerns following 12 weeks of weekly automated adjustments. A follow-up study with a longer duration and a bigger sample size is warranted to confirm long-term benefit and safety.

A more frequent optimization schedule (e.g., semi-weekly) would conceivably be less effective due to the inherent daily variability in glycemic fluctuations from MDI therapy. This challenge is further complicated by infrequent injections, particularly once-daily basal dosing. Consequently, the limited data over a shorter period could hinder the algorithm's ability to generate accurate and safe recommendations. Conversely, a less frequent optimization schedule (e.g., biweekly) may introduce other challenges, including missed opportunities for timely correction of inadequate parameters and greater variability. Accordingly, weekly algorithm-guided adjustments are likely the optimal frequency for delivering timely and effective decision support.

5.1.2 Qualitative Analysis

There has been increasing interest in incorporating qualitative aspects in clinical trials to enrich the relevance of treatment outcomes, capturing the voices and detailed patient insights to complement quantitative findings (87). Recent clinical practice guidelines further support the need for qualitative assessments in trials to ensure that any observed quantitative benefits are meaningful to individuals (88).

I conducted one-on-one semi-structured exit interviews in a subgroup of participants in the parent trial. A qualitative description methodology was selected with the aim of describing the participants' experiences and views on the current and future adoption of advanced MDI therapy. This approach was chosen because it was appropriately suited to gain insight on patient perspectives for a specific topic, generating low-inference data. Qualitative description is also well

suited in mixed methods research, offering rich qualitative data that remains close to participant narratives (89).

Several strategies were employed to increase the scientific rigor of the qualitative description design. To increase authenticity, a topic guide was selected as the instrument of choice to allow for flexibility during the interviews, letting participants freely express themselves without restriction. Another strategy involved safeguarding the credibility of the data by carefully practicing reflexivity as well as member checking (respondent validation) periodically to ensure accurate interpretations. Some member checking techniques that were used include probing for clarification, prompting elaborated responses for deeper understanding, and brief summaries recounting their experiences for verification (90).

5.1.3 Advanced Insulin Injection Technology

5.1.3.1 Connected and Smart Injection Devices

Recent focus has shifted toward precision dosing of rapid-acting insulin, involving the correct delivery of the intended dose at the right time, which has set the stage for connected devices. These devices can shed light on dosing behaviour, glucose levels, and insulin therapy holistically, which in turn, can allow healthcare providers to better identify areas of concern and more appropriately cater to one's needs (91,92).

Connected pens are refillable insulin pens that automatically record injection dose data that can be paired to a supporting diabetes management application, providing a comprehensive picture of an individual's dosing practice. Connected pens have progressed over time, initially overcoming the static nature of traditional pens by providing retrospective dose tracking, which then advanced to real-time dose tracking and subsequently to wireless communication with smartphone

applications, integrating data from multiple sources. In all, connected devices have enabled MDI therapy to enter the digital age (92,93).

Examples of connected pens include the NovoPen® 6 and NovoPen Echo® Plus (Novo Nordisk, Denmark), which come in 1-unit and 0.5-unit increments, respectively. Both pens display the last injected dose and time at the end of the cap and contain memory storage of the last 800 doses. They are also capable of integrating CGM and real-time dose tracking when paired to compatible diabetes management applications (93).

A recent real-world observational study involving nearly 4000 MDI-treated adults using the NovoPen 6 and Echo Plus connected pens reported important glycemic impacts of missed and mistimed dosing. Interestingly, omitting just two basal doses or four bolus doses within a 14-day period was linked with a meaningful 5% decline in the percentage of time in range, highlighting the importance of proper treatment adherence. These findings suggest that connected devices have the potential to reveal important implications of behavioural management on glycemia (94).

Connected devices have recently been transformed into smart devices by integrating a bolus calculator that accounts for active insulin-on-board for real-time meal and correction dose calculations. They also distinguish between priming and therapeutic doses and integrate insulin temperature and age-sensing features (92).

The InPen™ (Companion Medical Inc., United States) was the first FDA-cleared smart insulin pen equipped with Bluetooth technology to wirelessly pair with their supporting application for automatic display of injection data, real-time dose calculations, and various tracking and alert features (95). The InPen was subsequently acquired by Medtronic in 2020, who later launched the InPen system integrating rtCGM (96). A drawback of the InPen is the restricted compatibility to

aspart and lispro rapid-acting insulins, along with no accompanying basal pen, limiting widespread utility.

More recently, Bigfoot Unity™ (Bigfoot Biomedical, United States) received FDA clearance for the first basal and bolus smart pen cap system. Both caps are compatible with major disposable insulin pens and integrate second generation Freestyle Libre CGM, expanding the reach to most existing pen users. Uniquely, the cap screens display the recommended insulin doses, which are based on prescribed parameters, along with the time since the last dose, albeit without displaying the remaining number of active insulin units. Injected doses are automatically captured and relayed to the corresponding application (96). This system was recently acquired by Abbott Diabetes Care (93).

A retrospective analysis assessed real-world data from more than 5000 individuals (nearly 75% had T1D) using the smart InPen for one year. The findings revealed that nearly two-thirds of the cohort dosed at least three times daily. From that sub-cohort, those with a missed dosing rate under 20% tended to have better percentages in CGM time in and above range than those with a higher missed dosing rate. These findings also shed light on the potential to leverage data from smart devices to address barriers and target behavior modifications (97).

Smart devices are part of a developing landscape of connected pens and caps that are enabling a paradigm shift and disrupting therapeutic inertia for the MDI population. Collaborative data-driven management is now considered the future of MDI therapy to best understand and improve care (92). The next stage of smart devices would integrate DSSs based on amalgamated CGM and insulin data from smartphone and wearable devices, enabling advanced digital solutions with frequent automated dose titrations for direct patient use (92,93,97). This concept is the ultimate end goal for MDI users (98).

Currently, the ED-DSS is the only commercially available algorithm-guided system for personalized MDI adjustment advice to support youth and adults with T1D (and T2D). However, it has a restricted indication for use by healthcare providers to guide their patients' insulin management, precluding direct outpatient use (85).

5.2 Future Directions

5.2.1 Physical Activity

Based on a recent consensus statement, a total of 150 minutes of weekly physical activity is recommended for adults with T1D. Regular exercise has been shown to attenuate the risk of cardiovascular disease and mortality. However, there are various challenges associated with the type, intensity, and duration of exercise in T1D, namely the risk of exercise-induced hypoglycemia or hyperglycemia. This consensus statement published numerous strategies to mitigate these risks, which revolve around the consumption of carbohydrates or reduced insulin bolus doses at mealtimes prior to exercise (99). Despite this, many people with T1D do not exercise frequently, largely due to fear of hypoglycemia and loss of glycemic control, among others (100,101).

Exercise is particularly important amid a growing obesity epidemic, with recently similar prevalence rates found among individuals with T1D as those observed in the general population (102,103). Furthermore, obesity is a risk factor for cardiovascular disease (104), which is a leading cause of death among people with T1D, irrespective of optimal glycemic management (105).

The McGill Diabetes Technology Lab recently conducted a 16-week, single arm, feasibility study in 14 MDI-treated adults with T1D to assess the safety and performance of a machine-learning-based DSS that recommends personalized bolus adjustments for both high fat meals and postprandial sport-specific aerobic exercise based on data from the previous week. Overall, this study revealed large and variable reductions in boluses (up to 53%) when postprandial exercise

was announced at mealtimes, which was associated with trending improvements in postprandial outcomes at the end. Nevertheless, these findings are exploratory and warrant a larger and randomized trial (106).

Given the complexities around exercise and the intra-individual variability among people with T1D, along with the importance of regular exercise for health and longevity (99), there are various avenues in which the field can take. One important feature to focus on is the interoperability between various diabetes management devices, such as CGM and fitness and nutrition tracking applications or wearables (99,107). A simplified solution for exercise support might involve digitizing guideline recommendations into new or existing applications. Alternatively, a DSS can be utilized to tailor carbohydrate consumption and insulin adjustments to target anaerobic exercise for example.

5.2.2 Dietary Fat and Protein

Carbohydrates are known for having the biggest impact on the early postprandial glycemic response. However, dietary fat and protein macronutrients are also known to have influential effects on postprandial glycemia (108).

Studies conducted in individuals with T1D have demonstrated that meals containing high fat blunt the immediate postprandial glycemic rise, delaying the peak until two or three hours post-ingestion, likely caused by gastric emptying (109). While this phenomenon is true in individuals with and without T1D, the implications for people with T1D involve early hypoglycemia and late and extended hyperglycemia (108). A recent study conducted in adults with T1D using insulin pump further elucidated that meals containing varying amounts of fat (20-60 grams), when added to fixed carbohydrate-containing meals, all resulted in late glycemic responses in a dose-dependent manner, with different insulin requirements, irrespective of the type of fat (110).

The impact of protein has also been studied in adults and youth with T1D. Similar to fat, protein has a late impact on postprandial glycemia (109). When roughly equal amounts of protein and carbohydrates are consumed together (111), or when high protein (≥75 grams) is consumed in isolation (112), both cases result in delayed glucose excursions in the late postprandial period (3-5 hours), requiring more insulin at a later time (109). Furthermore, research has demonstrated that the combined inclusion of fat and protein to a meal have additive effects (111).

International consensus guidelines have recently recommended additional considerations of fat and protein rather than the sole dependence on carbohydrates for determining mealtime insulin. However, there is currently no guidance tailored to optimizing insulin for fat and protein, which is further complicated by intra-individual variability (113). Furthermore, it is estimated that more than half of the adult population in America struggle with numeracy skills (60), posing additional barriers for implementation and adherence with other macronutrient counting.

Klue (Klue Inc., Canada) is an emerging wearable solution comprising hand motion gesture sensing technology to detect eating behaviors and estimate the carbohydrate content, relaying it to the associated application (92). In future iterations, this could be further enhanced to estimate fat and protein too. Other macronutrient counting aids in the form of artificial intelligent-based food recognition algorithms embedded in applications have been studied and revealed some glycemic benefit in youth on MDI (114–116). Collectively, as technology evolves, the burden of macronutrient counting may be diminished. Although the evidence for split bolus dosing is less clear among MDI users, the literature has proposed a split dosing strategy ranging from 25-75% of insulin dosed upfront for meals containing roughly 20 or more grams of carbohydrates combined with fat with or without protein (117).

In the McGill Diabetes Technology Lab's feasibility study mentioned above, the algorithm recommended a split bolus regimen, with less insulin upfront and more insulin two hours postprandially, in 53% of cases during the last four weeks when high fat meals (≥20 grams) were announced. This was associated with a trend toward lower glycemic excursions five hours postprandially. Nevertheless, a randomized controlled trial is necessary to elucidate the benefit of split dosing for high fat intake among MDI users (106).

5.2.3 Youth with Type 1 Diabetes

The pediatric T1D population is notoriously more difficult to manage, owing to the fluctuating insulin needs throughout childhood and adolescence. A major challenge involves different stages of parental dependency, often leading to added burden on both the caregivers and the child. Furthermore, each age group presents additional unique complexities to T1D management (118).

Younger children require round-the-clock care with precision dosing due to lower insulin requirements and greater insulin sensitivity while lacking the ability to properly articulate their symptoms, posing an added challenge on the parents (91). School-aged children have greater unpredictability between irregular eating and activity schedules, often involving various caretakers while away from home. Adolescents face pubertal changes with fluctuating hormones that impact insulin sensitivity, alongside self-identify and autonomy development, which add behavioural challenges with timely insulin delivery and adherence, making it more difficult to control or prioritize their diabetes (118,119).

Various AID systems have proven to be safe and effective in young children aged 2-6 years (120–123), and older children and adolescents (124–129). However, while AID remains a superior approach due to its ability to closely mimic physiological insulin secretion, there are well known barriers to adopting this technology in both children and adults. While cost is an important factor,

it has been reported that physical barriers are among the top reasons for discontinuing or refusing the uptake of a pump, including aesthetic and diabetes-related visibility concerns and social stigma, especially among adolescents, as well as discomfort and interference with activities, among others (130).

Future directions should focus on bringing equivalently advanced options to market for sensor-augmented MDI users who decline or discontinue pump therapy (57). Given the greater glycemic variability observed in youth, evolving parent-child relationships, and psychosocial development, a personalized digital approach to MDI therapy could facilitate daily insulin injections, improve glycemic control, and potentially lower management burden for everyone involved (92,131). The pediatric population is a particularly important avenue to address, as a single diabetic ketoacidosis event has been linked to cognitive decline (132). Special attention should also be placed on the vulnerable population of younger children (2-6 years old) using MDI, given their increased variability in insulin requirements (133).

Effective MDI-specific DSSs could also offer value in the transition period from pediatric to adult care, targeting behavioral change in addition to algorithm-guided insulin titrations (131). This may be useful since the omission of prandial bolus doses is a major contributor to inadequate glycemic control among adolescents (134). This could be accomplished by incorporating behavioural intervention models to drive motivation using goal-driven and reward-based elements with progress feedback to positively reinforce or correct dosing behaviour and increase user engagement (135,136).

A behavioural approach was recently explored in a randomized controlled trial that assessed the CloudConnect DSS, developed at the University of Virginia, in 13 MDI- and 30 non-AID pump-treated adolescents. Participants either received advice from the CloudConnect DSS or

continued with sensor-augmented usual care for 12 weeks. Based on rtCGM, activity tracking, and insulin data, the DSS generated weekly reports with positive feedback to reinforce achievements. The reports also included advice suggesting changes in insulin or carbohydrate consumption, albeit without specific changes to the amount. In this study, the general advice provided by the CloudConnect DSS did not improve communication between adolescents and their parents, nor did it improve glycemic outcomes. Nevertheless, there continues to be an unmet need to explore DSS-led insulin dose adjustments among pediatric MDI users (131).

5.2.4 Pregnant Women with Type 1 Diabetes

During pregnancy, women with T1D are faced with more challenges than usual. They are recommended to attain more stringent glycemic targets to avoid maternal and neonatal complications. Their pregnancy is further complicated by large fluctuating changes in insulin requirements between trimesters. Consequently, pregnant women with T1D are monitored closely with more frequent follow-ups with diabetes specialists (137). Although critical, regular monitoring adds further burden on the healthcare system, which may not even be possible in lower resource settings.

Future research could involve testing a DSS that optimizes basal and bolus injection parameters in pregnant women with T1D on MDI. A potential implication of this could enhance standard of care by utilizing automated advice in between clinic appointments, catering to evolving needs while alleviating the load on the healthcare system. Another option could entail the use of a DSS during follow-up visits to assist healthcare providers in recommending more appropriate dose adjustments, all while liberating time to address other important aspects of care.

5.2.5 Automated Decision Support with Adjunctive Pharmacotherapy for Type 1 Diabetes

The prevalence of metabolic syndrome is rising among individuals with T1D, driven in part by the obesity epidemic, which increases the risk of cardiovascular disease (103,104,138). This population may need additional support beyond insulin monotherapy, especially given its added risk of weight gain (139).

Although a DSS can address evolving insulin needs by continually optimizing injection parameters, this emerging sub-cohort may benefit from adjunctive pharmacotherapy, particularly glucagon-like peptide-1 receptor agonists (GLP-1RAs). Although GLP-1RAs are currently approved for T2D, there is growing interest in repurposing them for T1D, particularly in those exhibiting features common to T2D. While their use in T1D remains off-label, GLP-1RAs have shown modest glycemic improvements alongside significant weight loss, all while offering cardiovascular and renal protection and other emerging multi-organ benefits (140).

Theoretically, the McGill DSS could be particularly useful in facilitating insulin titrations during GLP-1RA dose escalation periods. By streamlining insulin adjustments with this approach, it may alleviate burden on patients by minimizing the need for frequent follow-up visits during this time, while also liberating healthcare resources.

5.2.6 Type 2 Diabetes

Previous studies involving DSSs in individuals with T2D have demonstrated improvements in glycemic control (74,141). Notably, the d-Nav DSS and DreamMed Endo.Digital DSS have both received regulatory market approval for automated insulin adjustments in T2D (85,141). This underscores simpler glycemic management in T2D compared to T1D, suggesting that the McGill DSS could conceivably be adapted for use in individuals with T2D on basal-bolus MDI therapy.

Chapter 6. Conclusion

The primary objective of my thesis was to investigate the clinical effectiveness of the McGill DSS, comprising an optimization algorithm integrated with a smartphone application housing a bolus calculator with real-time active insulin tracking. This was achieved by conducting an outpatient, randomized, controlled, parallel trial in 84 adults with T1D and suboptimal baseline glycemic control. Participants either received the McGill DSS (adaptive application augmented by weekly algorithm-made adjustments) or the standalone non-adaptive iBolus application for 12 weeks, as described in Chapter 3.

This large clinical trial is the first to demonstrate a clinically meaningful glycemic improvement in the form of HbA1c with an MDI-specific DSS (8.6% to 8.1%) compared to control (8.6% to 8.5%), with a statistically significant between-group reduction of -0.4% in favor of the McGill DSS ($p=0.025$). Moreover, the proportion of participants who achieved an HbA1c improvement from baseline of ≥0.5%, ≥1.0%, and ≥1.5% was almost double in the experimental group (52%, 19%, and 12%) compared to control (31%, 10%, and 5%, respectively). Also, the degradations in HbA1c were substantially lower in the DSS group by approximately 2- to 9-fold. This further suggests that the algorithm provides additional benefit given that both groups had the iBolus application.

This DSS trial is also the first to report qualitative outcomes from exit interviews conducted with MDI-treated adults, shedding light into the lived experiences and perspectives of participants using the application with and without the adaptive component. Overall, three main themes were identified, along with eight sub-themes that represent the participants' voices. The overarching algorithm-related theme identified was enhanced glycemia due to personalized dose recommendations (sub-theme example: streamlined access to timely decision support). The other

algorithm-related theme was the desire for advanced MDI technologies in practice (sub-theme: anticipated future adoption). Regarding the standalone application, the main theme identified was the advantage of digital solutions over traditional standard of care (sub-theme example: alleviation of mental burden associated with dose calculations). Taken together, the implications of these innovative mixed methods findings, combining the glycemic improvement with favourable patient perspectives, highlight the potential to transform MDI with adaptive technology using the McGill DSS, paving the way toward clinical translation.

The second core objective of my thesis was to evaluate the practical utility of this algorithm. This was done by primarily comparing the directional agreement and disagreement rates of insulin recommendations made by the McGill DSS algorithm in the parent trial to recommendations made by a group of endocrinologists based on identical datasets. As explained in Chapter 4, this study found comparable proportions in the directional decisions for weekly (and biweekly) basal and bolus insulin adjustments between the algorithm and physicians to those among physicians. Importantly, most non-inferiority comparisons reached statistical significance, rendering the algorithm's general decision-making process aligned with that of expert physicians.

For the first time, we report interesting findings that reveal lower yet similar variability within the same physician over time as compared to inter-physician variability, reinforcing the subjective and complex nature involved with human decision making. Furthermore, on average, physicians recommended 3-5% greater absolute changes in insulin compared to those made by the algorithm. These findings highlight the practical potential to utilize the McGill DSS for regular insulin dose titrations in between clinic visits. Moreover, the inter- and intra-physician variability, together with the algorithm's more conservative approach may potentially alleviate concerns

around inadequate medical oversight, further supporting its future adoption. This could be particularly useful in settings of lower resources or restricted access.

To this end, I established the clinical effectiveness of a novel DSS in MDI-treated adults with T1D and suboptimal glycemic control. I also demonstrated that the algorithm's performance was generally not inferior to that of different practicing endocrinologists, underscoring its potential in clinical practice. Collectively, the findings presented in this thesis are clinically relevant and hold promise in addressing the unfulfilled need of adaptive MDI therapy. This is now conceivable in light of the recent introduction of connected MDI devices enabling digital platforms for automated personalized therapeutic solutions.

Chapter 7. References

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