USE CASE FOR DEVELOPING NOVEL ENDPOINTS GENERATED USING DIGITAL HEALTH TECHNOLOGY:
DIABETES MELLITUS

OVERVIEW

This use case explores the development of a novel endpoint for diabetes studies using continuous glucose monitors (CGMs) as a measure of interstitial glucose values. CGMs are currently widely used as a disease management tool by persons with type 1 diabetes mellitus (T1DM) in their everyday care and have been shown to have a benefit on clinical outcomes. However, this use case focused exclusively on using CGMs for generating data for use in clinical trials.

HbA1c, a biomarker that reflects average plasma glucose levels over a 3-month period, is currently accepted as the gold-standard surrogate endpoint for diabetes studies. It is accepted as a validated surrogate endpoint because reductions in HbA1c reflect improvements in glycemic control that have been correlated with reduction in diabetes-related complications (including microvascular complications such as retinopathy). CGM has been used in clinical practice to aid in the management of patients with diabetes, but its value as a tool to measure an endpoint such as hypoglycemia has not been clinically proven. Additionally, at present the use of CGM as a tool to measure an endpoint in a clinical study would be more expensive than using HbA1c, the current gold standard.

Despite recent advances in diabetes therapeutics and technology, there are still areas of unmet need. Management of diabetes can be difficult and complex, particularly for persons with T1DM, and can impact patients' quality of life due to glycemic variation or events of hypoglycemia. Fear of hypoglycemia has been shown to inhibit glycemic control.[1] There is currently no validated way to identify therapies that can positively affect these areas. There is currently no data to show that glucose variability assessed by CGM affects feel or function for people with diabetes, or can predict a clinical benefit (for example, reducing risk of hypoglycemia). CGM offers us the opportunity to collect this data, but its validity must be established first.

The continuous nature of the measures taken with CGM enable the detection of glycemic variability, excursions, and trends that would not be evident using traditional finger-stick blood glucose (BG) measures or with HbA1c. CGM measures glucose concentration frequently (every 1-5 minutes) via a subcutaneous sensor in the interstitial fluid. The sensor is physically connected to a small wireless transmitter, which sends the data to a CGM-dedicated receiver, an insulin pump, or a smart phone.

SPECIFIC AIMS

This use case aims to leverage CGM-derived data to demonstrate that some aspect of the data (for example, capture of CGM glucose values below a defined threshold) is predictive of severe hypoglycemia or other meaningful effects on persons with diabetes (such as those affecting feel and function). It also seeks to show that reduction of non-severe hypoglycemia has a meaningful impact on people with diabetes. Assessments used throughout this use case include CGM-based biomarkers, performance outcome assessments, and patient-reported outcome assessments.

STAKEHOLDERS AND INTERESTS

Stakeholders represent a broad cross-section of the clinical trials landscape including regulators, industry, technology manufacturers, patients and caregivers, patient advocates, and clinical investigators. Stakeholders and their interests are listed below:

Regulatory

Regulators are interested in identifying new endpoints that show a meaningful impact on patients' daily lives and facilitate advancement of effective therapies.

Industry

Industry is interested in issues affecting trial feasibility in terms of size, time, and expense and using the endpoint to gain FDA approval of labeling claims. Industry is also interested in developing new therapies that are truly meaningful to persons affected by diabetes (specifically, therapies that address aspects of the disease that are important to people with diabetes, but that are not adequately assessed by HbA1c).

Technology Manufacturers

Manufacturers seek to expand the utility of a device that has been proven successful for disease management, and to develop understanding of how to use the CGM to measure data for endpoint(s) that address aspects of health not adequately assessed by HbA1c.

Patients

Patients with diabetes are primarily interested in an endpoint that allows the use of CGM to study non-severe hypoglycemia and glycemic variability in general, how hypoglycemia and variability influence disease burden, and how this information can be used to improve their daily lives.

Clinicians/Investigators

Clinicians and investigators are interested in improving patient treatment options and enhancing patient safety.

ASSUMPTIONS

The CGM technology generating the data for this use case is assumed to be measuring what it is expected to be measuring and to produce data that are reliable, valid, and sensitive:

- ▶ Interstitial glucose can be accurately and easily extrapolated back to plasma glucose.
- ▶ CGM-derived measures of interstitial glucose (frequency in and out of range; rate of change; magnitude) are qualified as biomarkers.

On Dec 20th, 2016, the U.S. Food and Drug Administration expanded the approved use of Dexcom's G5 Mobile Continuous Glucose Monitoring System (CGM) to allow for replacement of finger-stick blood glucose (BG) testing for diabetes treatment decisions in persons 2 years of age and older. Two finger-stick BG tests must be performed each day to calibrate the CGM; however, patients are now able to base their insulin dosing calculations directly on the values displayed on the CGM receiver or smartphone app. Dexcom's G5 CGM was previously approved only to complement, not replace, traditional finger-stick BG values. The FDA's expanded indication supports the assumption that interstitial glucose can be accurately and easily extrapolated back to plasma glucose.

▶ Scope of Work on this use case is focused on the treatment benefit these outcomes can demonstrate at present.[*]
▶ The use case outcomes are to demonstrate treatment benefit, not disease prevention; i.e. the patients in studies for which these endpoints will be used have been diagnosed with the stated disease.
▶ Developing data standards are out of scope for this work, as are assessments of the impact of the use case outcomes on survival.

SUCCESS OUTCOMES

There are currently no data to show that glucose variability assessed by CGM has an impact on quality of life or can predict a clinical benefit (such as reducing risk of hypoglycemia).[1] CGM technology offers us a way to collect these data. Stakeholder needs will be met if this use case is successful in 1) developing evidence that validates the use of CGM-based data to derive endpoints in clinical trials by 2) showing that glucose variability assessed by CGM correlate to an effect on patients that is meaningful to them in their daily lives. CGM endpoints can accompany the traditional measure of HbA1c and do not need to replace it.

The box below represents important updates (current as of February 2017) arising from developments in the field subsequent to the multi-stakeholder meeting:

There are multiple studies underway on various closed-loop diabetes management systems (also called artificial pancreas or bionic pancreas) that are using CGM data as a primary outcome. These studies are testing closed-loop diabetes device hardware systems, closed loop algorithms, and/or drugs or drug combinations used in closed-loop systems.

Studies of Closed-Loop Diabetes Management Systems
The following list includes trials using CGM data as a primary outcome.
▶ USS Virginia Closed-Loop Versus SAP Therapy for Hypoglycemia Reduction in T1D
▶ International Diabetes Closed-Loop Trial
▶ Four Way Crossover Closed Loop With Exercise Detection
▶ The Monitoring Study
▶ Project Nightlight: Efficacy and System Acceptance of Dinner/Night vs. 24hr Closed Loop Control
▶ The Set-Point Study: Evaluating Effects of Changing Glucose Target on Bionic Pancreas Performance
▶ A Prospective Early Feasibility Study to Assess the Performance of the Insulet Artificial Pancreas (AP) System Using the OmniPod® Insulin Management System and the Dexcom G4® Share™ AP System
▶ A Crossover Study Comparing Two Automated Insulin Delivery System Algorithms in Adolescents and Young Adults With Type 1 Diabetes
▶ Post Bariatric Closed Loop Glucagon Trial

Several studies are solely using CGM data as a primary endpoint, while others are combining CGM data with HbA1c, self-monitored blood glucose (SMBG), or other plasma glucose measurements. Primary outcome measures often include percentage of time in hypoglycemic range or percent reduction of time in hypoglycemic range. The hypoglycemic range is defined slightly differently across studies but is most often either <60 mg/dL or <70 mg/dL.

Some studies also include primary or secondary outcome measures of time in specific ranges of hypoglycemia or severe hypoglycemia (for example, <50mg/dL), time in euglycemic range (70mg/dL – 180 mg/dL), or time in hyperglycemic range (>180 mg/dL), and other secondary outcome measures not derived by CGM, such as HbA1c and traditional SMBG obtained via glucometer. In addition, one study (not yet recruiting) includes outcome measures from questionnaires on quality of life and patient attitudes about diabetes technology.

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[*]CGM technology may become less expensive, less burdensome, easier to use, etc. over time

CONCEPT OF INTEREST

The concept of interest (COI) is hypoglycemia. Consensus definitions of hypoglycemic events are currently under consideration (see Main Success Pathway section). Patients reported that hypoglycemia has a meaningful impact on daily life by leading to feelings of being unwell (defined differently by different patients) and causing a lack of control over daily activities and schedules (also defined differently by different patients). Assessments used throughout this use case include CGM-based biomarkers, clinical performance outcome assessments, and patient-reported outcome assessments.

CONTEXT OF USE CONSIDERATIONS

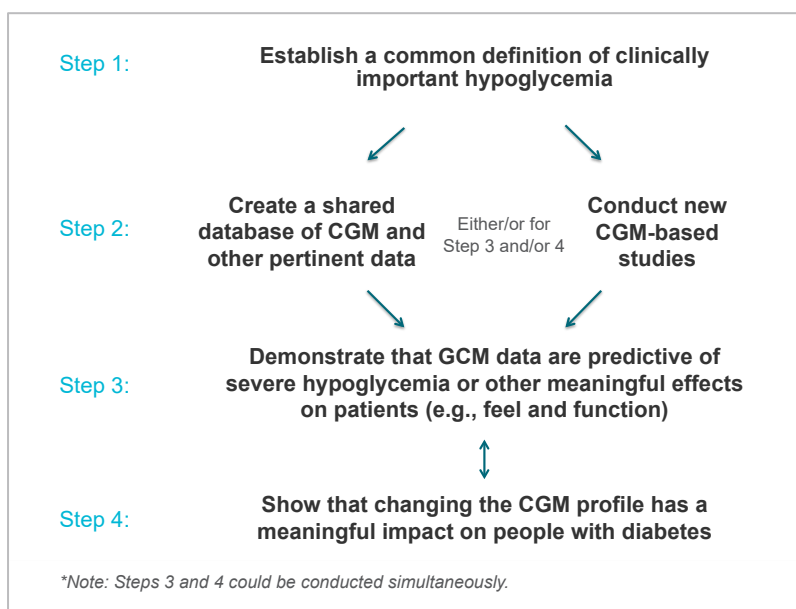This use case applies to persons with adult T1DM.

DESCRIPTION OF PROPOSED NOVEL ENDPOINT

The endpoint is n percent reduction of hypoglycemia. The value and specific unit of measure associated with the endpoint would vary based on the precise assessment(s) ultimately chosen during the course of the pathway steps above; in other words, it could be n percent reduction in duration of hypoglycemia, n percent reduction in number of clinically significant hypoglycemic events, etc.

Potential additional biomarker assessments include proportion of total time in hypoglycemic range, duration, magnitude, and/or frequency of hypoglycemic events. Coupling hypoglycemia outcome(s) with clinical outcome assessments, such as performance-based in-clinic tests, and home-based patient-reported outcome assessments.

MAIN SUCCESS PATHWAY FOR DEVELOPMENT OF ENDPOINT

The following outline lists four high-level steps along the pathway for development of the endpoint and the requirements for each step. In this use case, the order in which the steps are presented is not necessarily chronological (see process flow diagram) and some steps may only be necessary if other steps are deemed not possible. In addition, Steps 3 and 4 share some challenges and if the study was designed carefully with those in mind, solutions could potentially allow for steps 3 and 4 to be conducted simultaneously. Further investigation of each step will help identify final steps in the pathway and step order.

Step 1: **Establish a common definition of clinically important hypoglycemia**

Step 2: **Create a shared database of CGM and other pertinent data** — Either/or for Step 3 and/or 4 — **Conduct new CGM-based studies**

Step 3: **Demonstrate that GCM data are predictive of severe hypoglycemia or other meaningful effects on patients (e.g., feel and function)**

Step 4: **Show that changing the CGM profile has a meaningful impact on people with diabetes**

Note: Steps 3 and 4 could be conducted simultaneously.

Step 1. Establish a Common Definition of Clinically Important Hypoglycemia

a. Publish a Consensus Report by the major clinical societies: Work is already underway via the JDRF Diabetes Foundation, the American Diabetes Association, and others. Current trends are leaning toward defining *hypoglycemia* as less than or equal to 70 mg/dL but

greater than 55 mg/dL; *serious hypoglycemia* as less than or equal to 55 mg/dL; and *severe hypoglycemia* as requiring assistance.

b. Gain stakeholder agreement to begin using the definition to collect and/or interpret data: The group agreed that there is already an understanding among stakeholders that using a common definition across studies has value and that it may not be necessary to create an additional step of showing value.

Step 2. Create a Shared Database of CGM and Other Pertinent Data

The goal of this step is to expedite the process of gathering sufficient data to understand how hypoglycemia affects patients and could be used as an outcome assessment:

a. Design, develop, and maintain the database: the database should first be populated with data on patients with T1DM from existing databases currently owned by various stakeholders, such as pharmaceutical companies and nationally maintained registries.

b. Define what variables will be included in the database and how they will be standardized. Data could include BG measurements, incidence of hypoglycemia/severe hypoglycemia, hypoglycemia symptoms, severe hypoglycemia symptoms, etc. Standardization should leverage standardization that already exists in registration trials, where appropriate.

c. Incentivize organizations to participate by sharing data with participants. This could be accomplished by educating stakeholders on the value of developing novel endpoints for T1DM.

d. Define who is eligible to have access to the database and institute governance structures that balance optimizing access to the data with privacy protections for participants.

The box below represents important updates (current as of February 2017) arising from developments in the field subsequent to the multi-stakeholder meeting:

> The Innovative Medicines Initiative (IMI) has recently focused on hypoglycemia and the need for the creation of shared databases to help set standards and expedite timelines for clinical research and hypoglycemia understanding.[2] On January 4th, 2017, IMI opened a call for proposals with a topic titled "Understanding hypoglycemia: the underlying mechanisms and addressing clinical determinants as well as consequences for people with diabetes by combining databases from clinical trials." Part of the specific scope of the call is for industry, non-profit, and academia to collaborate on the establishment of pooled data bases for 1) hypoglycemia captured in clinical trials across glucose lowering drug development programs from partner companies and 2) a pooled CGM database collected using various glucose-monitoring technologies.
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> Ultimately, the call aims to use this pooled data and its analysis to open a dialogue with regulatory agencies on acceptable definitions of hypoglycemia, how to define clinically meaningful endpoints and/or methods to document rates of hypoglycemia (including CGM), and the potential to reduce these rates with pharmacological intervention.

Step 3: Demonstrate that CGM Data Predict Severe Hypoglycemia or Other Meaningful Effects on Patients (for example, Feel and Function)

This step is designed to either leverage existing datasets or conduct new CGM-based studies to examine the relationship between CGM-derived data and outcomes:

a. Leverage existing datasets through a shared database to identify whether CGM data are predictive of severe hypoglycemia. Note: databases may not capture hypoglycemia in totality, as they are based only on discrete patient-reported blood glucose measures and patients may not have captured/reported all hypoglycemic excursions.

b. Conduct new CGM-based studies to specifically examine the relationship. Engage with public/private partnerships and leverage existing datasets to explore how best to design and conduct comprehensive studies.

   ▶ Determine the CGM-based biomarkers that are the best measure of clinical outcomes, such as time in hypoglycemic range; number, duration, magnitude, and/or frequency of hypoglycemic excursions; rate of change.

   ▶ Develop methods to correlate the biomarker to a clinically meaningful outcome. For example: by conducting clamp studies[†] including CGM and then correlating the data.

   ▶ Develop new assessment instruments or existing ones to measure other meaningful effects to patients. Examples include measuring patient-reported wellness via a home-based feelings assessment, which would occur randomly throughout the day and also at sensor-prompted times, and measuring disease burden via the number of diabetes actions taken each day and their associated psychosocial impact. Diabetes actions might include how many times a day patients responded to non-severe hypoglycemia by checking BG, treating a low BG value, etc.

Step 4. Show that Changing CGM Profile Has a Meaningful Impact on Persons with T1DM

This step will either leverage existing datasets or conduct new CGM-based studies to demonstrate the relationship. The challenges and sub-steps in Step 4 largely mimic those in Step 3.

   a. Leverage the proof-of-concept studies from Step 3 to conduct larger studies to help determine the percent reduction in non-severe hypoglycemia that would be meaningful to persons with T1DM.

EXCEPTIONS

Pediatric T1DM patients were excluded in order to focus on a simpler use case. The use case team focused on the adult population, but noted that a similar approach could be applied to pediatrics, recognizing that there are pediatric-specific considerations that would add complexity. For example, CGM accuracy is significantly worse for pediatric patients in the low BG ranges than it is for adults. Accuracy for adults in the range of 40-80 mg/dL is ~89% - 91%, while accuracy in the same range is only 54% - 77% for children.

ISSUES

The use case team did not fully agree on the value of including any patient-reported outcome (PRO) assessments throughout the use case but ultimately decided to leave them in to help show a meaningful impact to patients. There was discussion that PRO assessments could be used on their own and would then not require CGM-based assessments, which are more costly. In addition, quality of life for persons with type 1 and type 2 diabetes mellitus has been assessed in the past but has not proven sufficiently sensitive. PRO measurement targeted at the symptoms and functional impacts experienced by persons during periods of hypoglycemia are likely to be more useful in this context.

The use case team noted that there are still technical challenges for using digital applications in clinical trials, such as how to handle phone calls interrupting application processes and operating system updates on the phones themselves. The need to develop methods to use CGM to measure established ranges was also discussed, as current CGM technology is not as

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[†]A stepwise hypoglycemic clamp that will allow thresholds for clinical signs and symptoms of hypoglycemia, and a concurrent CGM study to show that CGM can clearly identify the drops in BG.

accurate at lower BG levels. However, the use case team did not pursue discussion of a solution to these challenges as it was out of scope for this work.

TO DO

Background research should be done regarding leveraging existing datasets and public-private partnerships to determine how best to design and conduct studies, as outlined in the Main Success Pathway section.

CONCLUSION

During the course of designing this use case, significant assumptions had to be made. These, in combination with the need to precisely define outcome assessments and potentially conduct numerous proof-of-concept studies, indicates that there is still much work to be done prior to considering CGM data as a trial endpoint.

There are, however, many initial research steps that are needed and could currently be initiated, as outlined in the Main Success Pathway section, including determining the feasibility of creating a shared diabetes database, determining which CGM-based biomarkers are the best measure of a clinically-meaningful benefit for patients, and developing new (or selecting existing) assessment instruments to measure meaningful impacts on patients.

In addition to background steps that would be needed, there is also the concern that collecting CGM data in a large-scale clinical trial would be expensive and that it may not improve sufficiently upon evidence gathered from traditional PRO assessments to justify its use.

REFERENCES

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2. Nishimura E. Understanding hypoglycaemia: The underlying mechanisms and addressing clinical determinants as well as consequences for people with diabetes by combining databases from clinical trials. IMI webinar. December 13, 2016. Available at: http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2Call10/Hypoglycaemia_presentation.pdf. Accessed March 22, 2017.

3. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: A report of a workgroup of the American Diabetes Association and The Endocrine Society. *Diabetes Care.* 2013;36(5):1384-95. doi:10.2337/dc12-2480. PMID: 23589542 PMCID: PMC3631867

ADDITIONAL NOTES

Current Definition of Severe Hypoglycemia

The use case team worked with the current clinical definition of severe hypoglycemia, as defined in a report by a workshop of the American Diabetes Association and the Endocrine Society:

Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.[3]

Second COI (Discussed but not Selected)

The second COI discussed was glycemic variability as it relates to patient-reported wellness/disease burden. This COI was not chosen for several reasons, including:

- ▶ Measuring glycemic variability (or time in range) would require including both low and high excursions.
- ▶ Patient experience with excursions is not consistent between patients or even between excursions with the same patient.
- ▶ Would not have the option to use existing databases to explore relationships between the variables.

Ultimately, the variables for both glycemic variability and patient-reported disease burden were too large and the group decided to focus on only hypoglycemia. One possible future exploration of glycemic variability discussed was to examine improvements in treatment adherence/compliance, when the treatment increases time in euglycemic range. For example, approximately 90% of trial patients from the recently approved MiniMed 670G (the first automated insulin delivery device) requested to continue using the therapy at the end of the study. This tells a compelling story on the importance of time in range and glycemic variability to patients.

- ▶ *This Use Case was developed at a CTTI-hosted multi-stakeholder expert meeting in September 2016 as a part of the DHT Novel Endpoints Project. (Updates incorporated on February 24, 2017.) Three additional Use Cases were created for trials involving:*
  - ○ *Parkinson's disease*
  - ○ *Heart Failure*
  - ○ *Duchenne's muscular dystrophy*