TITLE:

Assessing the Feasibility of Continuous Glucose Monitoring in Reimagine Primary Care Clinics

SUMMARY:

A parallel randomized, multi-site prospective trial was conducted at four Intermountain Healthcare Clinics using a new CGM device (Dexcom G6) compared to a standard of care finger stick glucometer (FSG) (Contour Next One). All participants received usual care in Primary Care clinics for six consecutive months while using these devices. Data were collected via electronic medical records, device outputs, exit surveys, and insurance company (SelectHealth) claims in accordance with Institutional Review Board approval.

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STUDY INFORMATION	
Title	Assessing the Feasibility of Continuous Glucose Monitoring in Reimagine Primary Care Clinics
Short Title	CGM - Reimagine Primary Care
Protocol ID #	1050955
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IRB Approval Date	19Nov2018
Amendment Date(s)	N/A
Location of Research	Intermountain Healthcare's Reimagine Primary Care Clinics (Cottonwood Family Practice, Cottonwood Senior, Avenues Internal Medicine and Holladay Internal Medicine)
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External Collaborators	Savvysherpa (but no access to PHI)
Sponsor	Business Development Intermountain Healthcare 36 South State Street, Suite 1600 Salt Lake City, UT 84111

Contract Research Organization (CRO) (if applicable)	N/A
Study Team	The study team is the internal collaborators noted above

PROTOCOL SUMMARY	
Purpose of Study	To assess the impact of continuous glucose monitoring versus standard of care (e.g. a finger-prick protocol using a glucometer) on clinical outcomes, healthcare utilization, and cost in patients with type I or II diabetes treated within the Reimagine Primary Care clinics.
Design	Parallel Randomized Controlled Trial
Research Designation	The team intends to consent patients, collect data, analyze and publish; this will likely be a research designation.
Study Duration	13 Months (November 1, 2018 – December 31, 2019)
Number of Subjects	We aim to recruit 125 patients, expecting 20% attrition rate by the sixthmonth follow-up, yielding about 100 patients for analysis (Section *7.2 Sample Size and Power*).
Description of Subject Population	Patients with diabetes treated within the Intermountain Healthcare Reimagine Primary Care program between 1 November 2018 through 31 December 2019.
Eligibility Criteria	Inclusion Criteria: Patients with type 1 or type 2 diabetes, having a HbA1c ≥6.5%, currently using glucometers or are prescribed a glucose meter at their index encounter, treated within Intermountain Healthcare's Reimagine Primary Care (RPC) program, and being seen by an RPC provider during the period of 1 November 2018 to 31 December 2019. Patients must have access to a smart phone to download applications, have Bluetooth capabilities for data sharing, log/view their continuous glucose monitor (CGM) data, and to take an exit survey. Exclusion Criteria: Patients who are pregnant, not classified as having diabetes based on A1c levels, presence of vascular disease, age >80 years, diagnosis of dementia, and patients not currently using a glucose meter to monitor their sugar levels (and not being provided during the consulting visit).
Screening and/or Recruitment Location	Patients will be recruited while in the waiting room at the Reimagine Primary Care Clinics by a CITI/HIPAA trained coordinator or contacted by phone as per phone script instructs. These persons will maintain recruitment logs and load data in Tableau for real-time evaluation.

Brief Description of Study Procedures	This is a parallel randomized controlled trial. Eligible patients who consent will be randomized to one of two groups: (1) the intervention group who will be given a Dexcom G6 for CGM, or (2) the control group who will follow their current standard finger-prick protocol via a provided Contour Next ONE glucometer. The CGM group must download the Dexcom G6 and Clarity mobile apps for data capture, whereas the standard of care group will use the Contour Next mobile app for their respective readings. The Dexcom G6 captures real-time, dynamic glucose data every five minutes. Devices used in this study are FDA approved and commercially available.
Primary Endpoint	Hemoglobin A1c (HbA1c) level
Secondary Endpoints	Glycemic variability per mean amplitude of glycemic excursion (MAGE), coefficient of variation of HbA1c, range of HbA1c, frequency of hypoglycemic events, healthcare utilization per count of inpatient/outpatient visits, cost of care, current HEDIS performance on diabetes and behavioral health measures, coding specificity for diabetes, emergency department visit per 1000 rate, overall and for patients with diabetes, and hospitalization per 1000 rate related to
	diabetes, and self-reported behavioral changes (e.g. feeling more empowered to self-manage care, engaged with changing healthcare behaviors, and patient perceptions of the technology).
Analysis Population(s)	Patients with diabetes treated at all Reimagine Primary Care facilities (Avenues Internal Medicine, Cottonwood Family Medicine, Cottonwood Senior Clinic, and Holladay Internal Medicine) from 1 November 2018 to 31 December 2019 will be included in this study.
Benefits	Successful demonstration of CGM will allow patients to manage their condition, which may avoid the highs and lows of glucose monitoring and make patients feel better. This may reduce healthcare utilization and cost for the patients and the healthcare system as a whole. Furthermore, general knowledge on how to engage with patients in remote monitoring pilots will be better understood through this study.
Risks	This study includes recruiting patients and data will be collected. To minimize any breach in of private information the team will store data within the enterprise data warehouse/medical record, REDCap, and on secured mobile applications from Contour Next and Dexcom. While all devices used are FDA approved, there could be challenges for new users when using the new Dexcom G6
Authors	Liz Joy, MD Mike Phillips, MD, MBA Brad Isaacson, PhD, MBA, MSF Anne Pendo, MD Christopher Jones, MD Stephanie Kaufusi, MS Jeff Sorensen, MStat

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ABBREVIATIONS AND DEFINITIONS

- ACO: Accountable Care Organization
- CGM: Continuous Glucose Monitoring
- C_v: Coefficient of Variation
- GDM: Gestational Diabetes Mellitus
- GLMM: Generalized Linear Mixed Models
- HbA1c: Hemoglobin A1c
- HTE: Heterogeneity of Treatment Effect
- MAGE: Mean Amplitude of Glycemic Excursion
- T2DM: Type II Diabetes Mellitus
- SOC: Standard of Care

1.0 INTRODUCTION

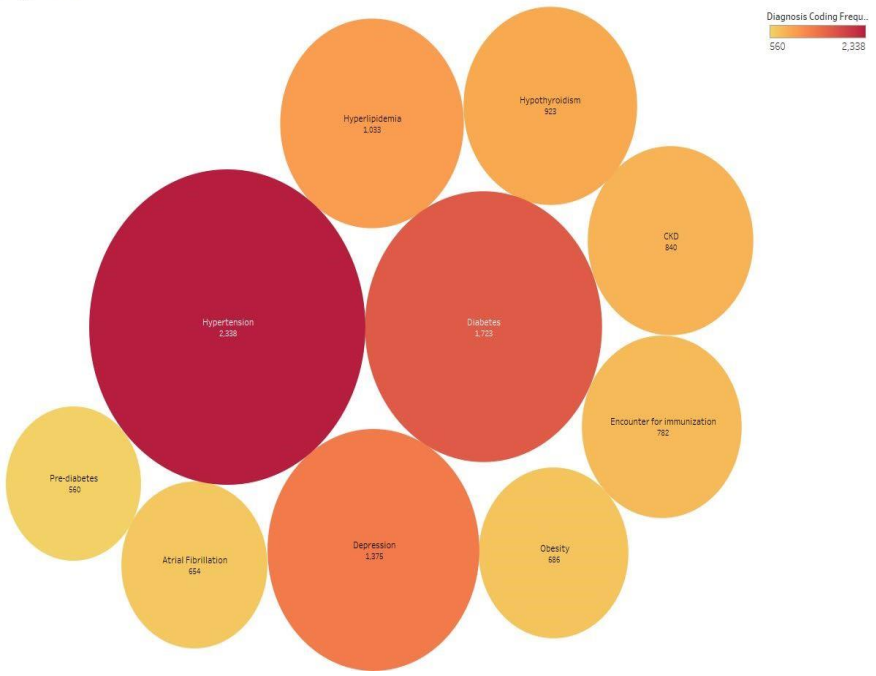
1.1 Background and Rationale

Approximately 30 million Americans, or 9% of the population has diabetes, a condition in which a person does not make enough insulin, or the body cannot use its own to effectively manage blood glucose levels [1]. Improper diabetes management is associated with severe comorbidities which include: heart disease, stroke, kidney disease, ocular problems, dental disease, nerve damage, and vascularity issues. The epidemic continues to challenge systems like Intermountain Healthcare, an accountable care organization (ACO), since diabetes cost $327 billion per year (representing $1 in every $7 dollars spent) on healthcare in the United States [2]. Furthermore, people with diagnosed diabetes incur average medical expenditures of $16,752 per year, of which about $9,601 is directly attributed to diabetes [2]. New treatment options are needed to manage population health, especially with 84 million adults having been diagnosed with prediabetes diabetes [3].

In an effort to reduce the physical, economic and social burden of diabetes, several healthcare systems have evaluated the use of telehealth to monitor glucose levels. In a metanalysis by Lee et al., the authors demonstrated that telehealth interventions produced a small, but significant improvement in hemoglobin A1c (HbA1c) levels compared with usual care (mean difference: -0.55, 95% CI: -0.73 to − 0.36) [4]. The Ontario Health Technology Advisory Committee also showed that the blood glucose home telemonitoring technologies they used yielded a statistically significant reduction in HbA1c of ~0.50% in comparison to usual care when used adjunctively to a broader telemedicine initiative for adults with type 2 diabetes [5].

Intermountain Healthcare has piloted continuous glucose monitoring (CGM) and continues to expand its digital health services. However, to date, these services have not been used in Reimagine Primary Care Clinics (Cottonwood Senior, Cottonwood Family Medicine, Avenues Internal Medicine, Holladay Internal Medicine) to treat atrisk patients. These patients have, on average, four comorbidities and represent a challenging cohort to treat. Furthermore, data from the first eight months of operations in the Reimagine Primary Care Clinics have reported 1723 diagnoses of diabetes and 560 cases of pre-diabetes (**Figure 1**). Understanding if these patients will use remote CGM technology, learning how real-time knowledge influences their behavior, and assessing the impact on cost, care and utilization, is critical prior to expanding the number of Reimagine Primary Care sites within Intermountain Healthcare.

Figure 1



1.2 Previous Work

Intermountain Healthcare has participated in two previous CGM studies with Drs. Christopher Jones and Liz Joy (IRB #: 1050741 and 1050410). Each are described in detail below:

- *IRB #1050741* – This recently completed quality improvement study successfully recruited n=20 patients with Type 2 Diabetes Mellitus (T2DM) to evaluate an integrated, CGM-based lifestyle modification program for glucose management in patients >65 years of age. The team is currently evaluating the data, but results will highlight the importance of education, self-discovery, and the way that we engage with our patients.

- *IRB #1050410* – Each year there are approximately 3000 gestational diabetes mellitus (GDM) pregnancies in the United States— contributing to an additional $10,200 per affected pregnancy in cost. Most concerning is that women who have had GDM are 7x more likely to develop type 2 diabetes than women who did not have GDM during their pregnancy, and at least 40% of women with GDM will develop this disease. Therefore, the goal of our second CGM pilot was to: (1) accurately predict which women are at risk, (2) optimize recruitment and enrollment, (3) provide behavioral support to promote adherence to interventions, and (4) collect actionable data.

  In this study, n=403 women were consented (n=189 at Intermountain Medical Center and n=214 at LDS Hospital). Dr. Joy and her staff discovered through qualitative feedback that women will wear a CGM device, are excited to see their data, and did not expect compensation for participation. Data is still being analyzed by Savvysherpa to assess patient outcomes.

2.0 STUDY OBJECTIVES/PURPOSE OF THE STUDY

The purpose of this study is to assess the effect of using CGM versus a standard of care (e.g. traditional fingerprick protocol) in an at-risk, diabetic patient population. The impact will be measured in terms of clinical outcomes (e.g., HbA1c level, glycemic variability), health care utilization (inpatient/outpatient visits), self-reported patient perceptions, and costs. We expect that CGM will empower patients to better manage their diabetes—ultimately, improving their health and reducing the burden of disease.

In this study, patients with type I and II diabetes will record their blood glucose levels since the output of the Dexcom G6 and the Contour Next ONE measure interstitial glucose. However, as noted in the *3.0 Study Design*, although the American Diabetes Association has provided a conversion table in which blood glucose = 28.7 X A1C – 46.7 [6], the current standard of care is to have patients directly measure their blood glucose in the clinic rather than approximating. Thus, patients enrolled in this study will track their glucose with the general hypothesis being that those who more consistently monitor their blood glucose levels (and avoid the high peak to valley changes), will have a lower HbA1c at the end of the study. This will be tested by having HbA1c levels measured at two distinct time points: (1) at the time of enrollment, and (2) at the end of the pilot (six months). HbA1c levels may also be checked at the study midpoint (three months) if determined to be current standard of care by the provider and this data will also be considered. The aims below are written for HbA1c to confirm to the current standard of care.

Aim 1: Assess impact of CGM on glycosylated hemoglobin levels

Specific Aim 1a (primary analysis): Measure the effect of CGM vs. standard finger-prick protocol on HbA1c

- ***Hypothesis for Aim 1a***: The patient-level six-month reduction in HbA1c will be greater among those randomized to CGM than that among those randomized to standard finger-prick protocol.
- ***Process for Aim 1a***: We will compare the distributions of the patient-level, six-month change in HbA1c between randomized groups using the two-sided Wilcoxon rank-sum test.

Specific Aim 1b: Measure the longitudinal change in mean amplitude of glycemic excursion (MAGE) in CGM

- ***Hypothesis for Aim 1b***: The patient-level daily MAGE will decrease over six months of CGM.

- ***Process for Aim 1b***: MAGE is a metric of glycemic variability that can be measured from CGM, but not from infrequent (daily) monitoring. Thus, among CGM patients only, we will measure the six-month longitudinal change in 24-hr average MAGE. Upon computing each CGM patient's daily MAGE, we will use patient-level hierarchical modeling (generalized linear mixed models) to estimate the overall sixmonth longitudinal trend in MAGE.

Specific Aim 1c: Measure longitudinal change in daily coefficient of variation (C_v) of blood glucose in CGM

- ***Hypothesis for Aim 1c***: The patient-level daily C_v of blood glucose will decrease over six months of CGM.
- ***Process for Aim 1c***: Like that of MAGE, C_v of blood glucose is a metric of glycemic variability that requires near continuous monitoring. Thus, among CGM patients only, we will measure the six-month longitudinal change in daily C_v of blood glucose using the standard equation: $C_v = \sigma/\mu$. Once we have computed each CGM patient's daily C_v of blood glucose, we will use patient-level hierarchical modeling (generalized linear mixed models) to estimate the overall six-month longitudinal trend in C_v of blood glucose. Additionally, we will report the patient- and group-level distributions in daily blood glucose extrema (i.e., minimum and maximum).

Specific Aim 1d: Measure longitudinal change in overall blood glucose range and "time in range" ($max - min$) in CGM

- ***Hypothesis for Aim 1d***: The patient-level daily blood glucose range will decrease and time in range (which is defined by glucose levels from 70 to 180) will increase over six months of CGM usage.
- ***Process for Aim 1d***: Again, like MAGE and C_v, the blood glucose range is a metric of glycemic variability that is most meaningful with near continuous monitoring. So, among CGM patients only, we will measure the blood glucose range for the ith day as $Range_i = maxHbA1c - minHbA1c$, and then use patient-level hierarchical modeling (e.g., generalized linear mixed models) to estimate the overall six-month longitudinal trend in HbA1c range.

Specific Aim 1e: Measure the effect of CGM vs. the standard finger-prick protocol on frequency of hypoglycemic events

- ***Hypothesis for Aim 1e***: The patient-level six-month reduction in frequency of hypoglycemic events will be greater among those randomized to CGM than that among those randomized to control.
- ***Process for Aim 1e***: Measure the patient-level change in rate of hypoglycemic events as the patientlevel slope of the six-month linear change in the so-called "intensity" (λ) of the estimated nonhomogeneous Poisson point process. Once we've computed each patient's six-month linear change in λ, we will compare the distributions between randomized groups. Note that the motivation for measuring change in frequency as the slope of λ estimated from a non-homogeneous Poisson process is that it allows us to compare changes in frequency of hypoglycemic events between groups with different modes of monitoring (continuous vs daily).

Aim 2: Assess impact of CGM on healthcare utilization and cost

Specific Aim 2a: Measure the effect of CGM vs. standard finger-prick protocol on healthcare utilization

- ***Hypothesis for Aim 2a***: The count of primary care, specialist, and emergency department visits or hospital stays over six months will be fewer among those randomized to CGM than that among those randomized to standard finger-prick protocol.
- ***Process for Aim 2a***: For each patient, count their visits to a primary care provider or specialist or emergency department/hospital admission. Next, compare the distributions of visit counts between randomized groups using a Poisson test, aggregated as well as stratified by visit type. Other metrics for evaluating utilization may include: current HEDIS performance on diabetes and behavioral health measures, coding specificity for diabetes, emergency department visit per 1000 rate, overall and for patients with diabetes, and hospitalization per 1000 rate related to diabetes.

Specific Aim 2b: Measure the effect of CGM vs standard finger-prick protocol on cost

- ***Hypothesis for Aim 2b***: The total variable cost associated with healthcare services/visits over six months will be fewer among those randomized to CGM than that among those randomized to standard fingerprick protocol.
- ***Process for Aim 2b***: For each patient, measure total variable cost of associated healthcare services and visits. Then compare the distribution of costs between randomized groups using the Wilcoxon rank-sum test, a non-parametric analogue of Student's *t*-test.

Aim 3: Qualitatively understand patient perspective of CGM

Specific Aim 3a: Record patients' self-reported willingness to participate in a CGM pilot

- ***Hypothesis for Aim 3a***: Greater than 80% of patients who will have been approached to participate in this study will consent to participation.
  Process for Aim 3a: The team will record the number of patients approached, consented and those that participate in this study. Metrics will be helpful for estimating future recruitment in other Reimagine Primary Care studies.

Specific Aim 3b: Understand patient satisfaction with CGM

- ***Hypothesis for Aim 3b***: Patient's will be satisfied with CGM device.
- ***Process for Aim 3b***: Develop and deploy exit surveys targeting patients randomized to CGM to assess satisfaction with the CGM device and related digital health monitoring services.

Specific Aim 3c: Understand how CGM changed patient behavior •
Hypothesis for Aim 3c: Patients will have felt empowered by CGM.

- ***Process for Aim 3c***: Within the survey developed/deployed per Aim 3b, include 5-point Likert-based questions soliciting patient opinions and perspectives. Summarize those perspectives so that research investigators and operational leaders can use this information to change clinical operations (as needed).

3.0 STUDY DESIGN

This is a pilot, parallel randomized controlled trial of CGM versus a standard finger-prick protocol among patients with type I and II diabetes treated at Intermountain Healthcare's Reimagine Primary Care Clinics. Patients will

be eligible if their most recent HbA1c level is ≥6.5% and they are either currently using a glucose meter or are prescribed a glucose meter at their index encounter. Upon consent, which will occur within in a private office/room within the Reimagine Care Clinic, patients will be randomized into one of two groups:

- ***Intervention group***: CGM using a Dexcom G6 to measure glycosylated hemoglobin levels every five minutes. Patients will be asked to download the Dexcom G6 and Clarity applications (to have access to their real-time data) and be given a link to complete an exit survey in REDCap near the end of their study participation. Data will be sent via Bluetooth and then exported by the Intermountain research team into a Tableau (or similar) dashboard for data analysis/comparison **(Appendix A)**

- ***Control group***: A standard finger-prick protocol that will require patients to continue with their daily fingerprick regimen established by their physician. This group will be given a Contour Next One meter to ensure that each patient is receiving the same level of accuracy by the same device. A review by Ekhlaspour et al of 17 glucose meters demonstrated wide variability, with only two devices achieving the 2013 ISO standard (with the most accurate being the Contour Next) [7]. Patients in the control group will be asked to download the Contour Next application which will send data via Bluetooth similar to above. Data will be aggregated, and protected health information removed prior to analysis (by Intermountain Healthcare and Savvysherpa). At the end of the study, patients will be asked to complete a short survey in REDCap about their willingness to participate in future studies **(Appendix A)**.

Randomization will be assigned *a priori* using a random number generator from Microsoft Excel. Sub-Investigator will then transcribe these numbers and order them individually in concealed envelops and present them to the Research Coordinators to ensure the CRC is blinded. At time of consent the Research Coordinator will hand the patient the earliest numbered envelope to randomize. . Patients in both randomized groups will be given the devices and one month supplies to ensure compliance with the protocol. The Study Coordinator and patient will exchange contact information so that the CRC may resupply the patient with necessary equipment at the end of their month supply. The CRC may meet the patient at their Reimagine Care Clinic or off site for patient convenience. All patients are expected to participate for six months, which is near the minimum duration sufficient to measure clinically meaningful changes in hemoglobin A1c related to gradual behavioral changes (e.g., diet, exercise, insulin administration). Further, each patient will complete 2 mandatory blood draws and one elective blood draw at their designated Reimagine Care Clinic to evaluate HbA1c level changes over the course of the study. Baseline HbA1c must be completed on day of enrollment (± 2 days) which Intermountain Heathcare may choose to cover if not paid for by patient's SOC. An elective blood draw will be considered for data if completed at 3 months (±1 week) and a third required blood draw upon study completion (±2 weeks) which the study may also choose to cover if not SOC. 2 weeks from 180 enrollment) which the study may pay for if not covered by patient's SOC. We postulate that those that have a more consistent interstitial glucose profile (which avoid the high peak to valley swings), will have a more pronounced difference in pre and post HbA1c levels. Specific Aim #1 above will help our team understand the relationship between interstitial glucose and HbA1c, along with other outcomes of interest which include weight loss, alterations in diet, change in physical activity, etc.

3.1 Study Duration

This study will be conducted from 1 November 2018 through 31 December 2019 (13 months). This will allow sufficient time for study preparation (November 2018; 1 month), enrollment (approximately 3 months, starting December 1, 2018), follow-up (approximately 6 months from the time the last patient is consented), analysis (August 2019 – September 2019; 2 months), delivery of a final report to the Intermountain Healthcare Executive Leadership Team and co-authoring a manuscript for submission in a high-impact, peer-reviewed journal (October 2019 – December 2019; 2 months).

3.2 Number of Subjects

We aim to recruit 125 patients, expecting 20% attrition by the six-month follow-up, yielding about 100 patients for analysis (see *7.2 Sample Size and Power*).

3.3 Screening and Selection of Subjects

Subjects will be screened and recruited by Research Coordinators with CITI/HIPAA training. These coordinators will be trained in advance by Drs. Christopher Jones and Liz Joy, on how to instruct patients of proper usage of their device, how to effectively interact with subjects, the questions that may be posed, how patients should interpret feedback from the devices/cellphones, etc. Dr. Jones will also consult with the providers so that they understand the questions that may be asked by the patients and how to provide best care practices.

If a patient agrees to participate, a consent form will be electronically signed using REDCap. Participants will receive a paper copy of the consent containing all relevant and study pertaining information including important contact information. The subject will then be randomized into a study group and given the appropriate device by a Research Coordinator. Each patient will download the mobile apps relevant to their group, so their data can be tracked and transmitted by the study team.

- Group #1 will download the Dexcom G6 and Clarity apps
- Group #2 will download the Contour Next ONE Diabetes application.
- Both groups will also use REDCap to complete the end of study survey **(Appendix A)**.

All devices will be registered prior to study startup and will be matched to a deidentified subject identifier (e.g. Subject_001). The coordinators will answer any study related questions that the patients may have before and during the study along with the Reimagine Primary Care clinicians who have agreed to participate as collaborators during the patient's regular appointments. Before patient's leave the clinic, (or ±2 days) a blood draw will be conducted at the Reimagine site by a certified phlebotomist or approved healthcare provider to collect initial HbA1c level.

3.3.1 Inclusion Criteria

- Type 1 or type 2 diabetes mellitus with a HbA1c ≥6.5%
- Patients that are currently managing their glucose levels for diabetes with a glucose meter (or will be prescribed one by their healthcare provider)
- Patients that are treated within the four Reimagine Primary Care clinics (Cottonwood Family Medicine, Cottonwood Senior, Avenues Internal Medicine, and Holladay Internal Medicine).
- Patients 18-80 years of age

3.3.2 Exclusion Criteria

- Patients that are not managing their glucose levels for diabetes (and not advised to use a glucose monitor by their physician)
- Patients that are not treated within the four Reimagine Primary Care clinics
- Patients less than 18 years of age, and 81 years of age and older
- Patients with a diagnosis of dementia
- If the patient is currently using a Continuous Glucose Monitor
- Patients with previous hospitalization for hypoglycemia within the last 18 months
- No access to a mobile phone to download the Dexcom or Contour Next applications
- Patients who are pregnant or planning to become pregnant over the course of their six-month participation

4.0 STUDY PROCEDURES

4.1 Informed Consent

Patients that meet eligibility criteria and agree to participate will be considered for the study. These patients will be identified in advance through Tableau/PowerChart or on the day of the appointment in the clinic. Patients may be approached with a brochure and ICF in the lobby prior to their appointment but will not be consented until their clinic visit is completed as to not disrupt clinic flow. If approved by the patient's provider, they may also be contacted by phone from a Research Coordinator (using IRB approved phone script) to schedule a time to meet at their RPC Clinic for recruiting. A consent that is approved by the Intermountain

Healthcare Institutional Review Board (IRB) will be obtained prior to study inclusion, signed electronically in REDCap by the subject or his/her legally authorized representative, in accordance with applicable regulations.

The informed consent process will occur at a Reimagine Primary Care facility. Research Coordinators, the Principal Investigator, Co-Investigators, or an appropriately delegated member of the study team may administer the informed consent process.

Patients will be given as much time as they need to consider participation, ask questions, and obtain satisfactory answers to their questions. If a patient cannot consent due to time restraints or other conflicting obligations it will be allowable for the patient to return to the Reimagine Care Clinic to meet with the Research Coordinator to finish consenting at a later time. Patients who agree to participate, will receive a unique study identifier. Lastly, since patients are signing electronically, they will be provided a handout that matches their exact consent form to take home which will have information on who to call with questions, comments or concerns.

4.2 Methods

Patients will be screened for eligibility per Inclusion and Exclusion criteria (See Sections 3.3.1 and 3.3.2 respectively) and consented as described in Section 4.1.

The following information will be obtained from each subject's medical records, and/or during procedures, treatments, study-specific visits, and/or follow-up visits that are generally part of their usual or specialized care:

- Patient's ID number (EMPI)
- General demographic information (age, gender, height, weight, race, ethnicity)
- Patient's contact information (email, home address, and phone)
- Health history (personal health history, previous laboratory and glucose test results, medications, healthcare utilization and cost data)
- Current medications/medication history
- Glucose levels and historical A1c reports

Group #2 data will be transmitted from the Contour Next One device to the Contour mobile app via Bluetooth. Should this process fail, a contingency plan has been devised for patients to manually record their readings in an online REDCap form or provide their readings to their Research Coordinator who will properly store the data. Patients in the intervention group will have their data automatically uploaded via the Dexcom G6 app where it will then be obtained by Intermountain Healthcare researchers. No protected health information will be shared with those outside of this research study unless approved by the IRB. Coordinators will check in with the patients on a monthly basis (or more frequently for non-compliance) to ensure proper data entry and to answer any questions (if necessary).

4.3 Risks

This study is low risk. The study uses FDA approved devices that are commercially-available to track glucose monitoring. The Intervention Group should experience less pain than the standard of care since they will not have daily finger pricks, and The Control Group is the current standard of care. As with all studies that involve data, there is always a risk that this could be shared, however, study-related information will be stored within Intermountain's system and applications that have been reviewed and approved by cybersecurity. Further, by using study ID number (e.g. Subject_001) rather than referring to PHI, we will minimize the risk of incidental disclosure.

The Dexcom G6 is a pressure sensitive acrylic adhesive coated on top of a polyester spunlace fabric. The plastic housing is attached to the patch by direct pressure and heat. There is no latex or bovine components in the adhesive however, if the patient has a severe acrylic or polyester allergy it is possible they may experience skin irritation or topical allergic reactions at the site of which sensor was applied.

4.4 Benefits

Patients enrolled in this study may benefit by utilizing a new FDA-approved device which will provide real-time data on their blood glucose levels (Intervention Group). CGM may empower patients to better manage their diabetes, potentially resulting in better stabilized blood glucose levels, reduced patient costs and burden of care, as well as potentially reducing the hazard of development of diabetic complications. Additionally, data collected in this study might be used to improve clinical/operational decisions, potentially yielding a more efficient and cost-effective care process model for high-risk patients.

5.0 END OF STUDY CONSIDERATIONS

5.1 Study Completion

A participating subject will be considered to have completed the study if and only if:

- He/she completed the treatment/intervention course described in this protocol
- He/she has complied with all the procedures and completed the two required blood draws within the allowable window
- He/she finished the exit survey

5.2 Voluntary Withdrawal of Consent

Subjects shall have the ability to withdraw consent for study participation and/or the use of their clinical information at any time and for any reason, without penalty or loss of benefit to which the subject is otherwise entitled, by contacting the Principal Investigator or a designated member of his research team, preferably in writing and addressed to the Principal Investigator at the address indicated on the cover page of this protocol.

In the case a subject enrolled in this study decides to withdraw from the research, or an Investigator decides to terminate a subject's participation, study investigators must follow accepted standard practices regarding the management of collected data about these subjects, as follows:

- Investigators must document in the research record each instance of a subject withdrawal, including the reasons for the withdrawal, if known.
- If the subject withdraws and does not consent to continued follow-up and collection of clinical information, the investigator(s) will discontinue access to the subject's medical record or other confidential records, for purposes related to the study.

- Following the subject's withdrawal from the study, the Study Team will no longer contact the subject nor have access to his/her medical records for research purposes (unless specific informed consent has been obtained as described above).

5.3 Early Termination

The study sponsor or Principal Investigator of the study may decide to suspend or terminate a study for various reasons, including but not limited to the occurrence of an unanticipated problem, evidence of noncompliance, or serious adverse events and/or continuing noncompliance. If this occurs, the subject's designated Research Coordinator will send a certified letter to the patient explaining unsuccessful attempts were made to contact the patient to gain compliance and will therefore be terminated from the study. The Principal Investigator or an appointed study staff member will then notify the IRB in writing within three days of the suspension/termination. This communication will include a description of what steps have or will be taken to protect the welfare of currently enrolled participants, and what corrective actions, if applicable, will be taken to address the root cause for the suspension/termination.

5.4 Lost to Follow-Up Subjects

Because this is a 13-month study, with periods of time between research-related interactions, retention of participating subjects until study completion could be a challenging element. To facilitate subject retention, specific information will be obtained during the first research encounter and updated at all subsequent encounters. Although critically important to the successful completion of the study, if a participant expresses concern and/or refuses to provide this information, they will be excluded from the research.

The following specific information will be collected and used for this purpose:

• Contact information of the participant (i.e. phone number, email)

This contact information will be stored in a secure database and will not be shared outside of the study-specific research staff. If a research participant becomes lost to follow-up, the research team will contact the subject or designated individuals named by the participant. A maximum of 3 telephone calls and/or email will be attempted for non-compliance purposes. If there is no response, an IRB-approved certified letter signed by the Principal Investigator requesting for a response may be sent. If contact is reestablished, interest in continued participation will be verbally confirmed and documented, and the participant will return to active study participation as appropriate, based on their status/time point in the research. With failure to re-establish contact after three direct attempts and a certified letter in the mail, and failure to find new contact information, the subject will be considered lost to follow up.

5.5 Records Retention

The Principal Investigator and his/her designated research staff are responsible for maintaining accurate, complete, and current records relating to the conduct of the investigation, in accordance with ICH Good Clinical Practice guidelines (E6) and the Code of Federal Regulations (CFR) (refer to ICH GCP 8.1 to 8.4 for a list of essential documents for retention).

6.0 MONITORING AND SAFETY REPORTING

6.1 Monitoring

Internal monitoring of the study will be done weekly by the research coordinators assigned to the study. He/she will verify the accuracy of recruitment, ensure complete data entry, etc. These results will be shared monthly with the Savvysherpa Chair, Dr. Mark Briesacher, in the form of an emailed report or available hyperlink which updates in real-time. If patients are not entering their data, the research coordinator may call/email the subject to remind them about this ask.

6.2 Safety Reporting

Since all devices used in this study are FDA approved and commercially available, it is anticipated that no safety reporting will be required. However, in the event of a safety issue, safety-related data for this study will be collected on standardized reporting forms (paper and/or electronic). Safety-related events will be defined in accordance with ICH GCP E6 R2, the Code of Federal Regulations, Intermountain research policy, Intermountain SOPs, and all current applicable regulations. These will be reported to the study Principal Investigator and Institutional Review Board within 24 hours. An issue would be tracked via REDCap from the Research coordinator and an alert triggered for key research personnel.

Study participants who have not previously used a CGM to monitor blood glucose levels are likely to have questions and/or concerns about their blood glucose levels. These are most likely to occur if blood glucose levels decline during sleep or following exercise. Participants will be instructed to call their primary care doctor for advice.

In the event any device recalls or new information pertaining to the safety/accuracy of the devices is obtained, the study team shall take appropriate action to ensure subject safety which will be delegated by the Principal Investigator.

7.0 STATISTICAL ANALYSIS

This study is a parallel randomized control trial that will evaluate the impact of CGM versus a standard fingerprick protocol, between and within randomized groups. The primary analysis (Specific Aim 1a) will measure the intervention effect on six-month change in HbA1c. The quantitative secondary analyses will measure the withinpatient longitudinal change in glycemic variability among CGM patients (Aims 1b-d) as well as the intervention effect on hypoglycemic events, healthcare utilization and cost (Aims 1e, 2a-b) between randomized groups. Additionally, for each of these aims, we will conduct exploratory sensitivity analyses: measuring provider variability and its effect, as well as looking at patient-level heterogeneity of treatment effect (HTE) to describe

subgroups of patients in whom the benefit of CGM might be amplified or attenuated. Technical details are provided in Section *7.1 Statistical Considerations.*

7.1 Statistical Considerations

The primary analysis (Aim 1a) will measure the intervention effect on the patient-level six-month absolute reduction in mean HbA1c. Since not all patients will have their final HbA1c test at six months exactly, we will estimate each patient's six-month reduction in HbA1c by interpolating/extrapolating from their assessments, given that their HbA1c levels were assessed on at least two occasions: baseline, and >3 months post baseline. Then, among patients with a sufficient number of occasions of HbA1c assessments, we will estimate their sixmonth HbA1c using generalized linear mixed models with patient-level random slopes and intercepts, with appropriate link function and distributional family [8]. The quantitative secondary analyses (Aims 1b-e, 2a-b) will use outcomes related to the longitudinal change in various metrics of glycemic variability (MAGE, C_v, range) as well as the frequency of hypoglycemic events, healthcare utilization, and cost. The secondary analyses will also use longitudinal data analysis to assess whether there is a significant reduction in glycemic variability over six months (Aims 1b-d) among those randomized to CGM, whether there is a significant reduction in hypoglycemic events over six months (Aim 1e) among those randomized to CGM, and to assess whether overall healthcare utilization and costs differ between randomized groups [9]. Accordingly, specific aims 1b-e will rely heavily on longitudinal data analysis within a multilevel/hierarchical framework [10], specifically using generalized linear mixed models. In the sensitivity analyses, provider variability will be accounted for using three-level (provider, patient, occasion), quasi-Bayesian generalized linear mixed models [11]. Finally, the sensitivity analyses exploring HTE will use generalized additive models (GAM) to identify subgroups of patients for whom CGM is likely to have a differential effect [12-13].

7.2 Sample Size and Power

Based on 2018 data pulled from Intermountain's diabetes registry, we estimate that the four RPC clinics (Cottonwood FM, Cottonwood Sr, Holladay IM, and Avenues IM) will see about 30, 22, 17, and 6 study-eligible, unique patient encounters per month, respectively, yielding up to about 75 recruitable patients per month (up to 225 over three months of enrollment). We estimate that enrolling 125 patients – expecting 20% attrition by the sixth-month follow-up, yielding 100 patients for analysis – would be sufficient to achieve >80% power for the primary analysis (absolute reduction in HbA1c) if the standardized difference *d* of the effect size is >0.8 (**Figure 2**). Here, the standardized difference *d* is measured in terms of the difference between the randomized grouplevel means of six-month changes in HbA1c. So, for example, a standardized difference *d* in the effect size of 0.8 might be observed if the true effect size is, say, -1 (that is, if the difference between the means is -1) and the standard deviation of change is 1.25. Details of the power analysis will be made available upon request.

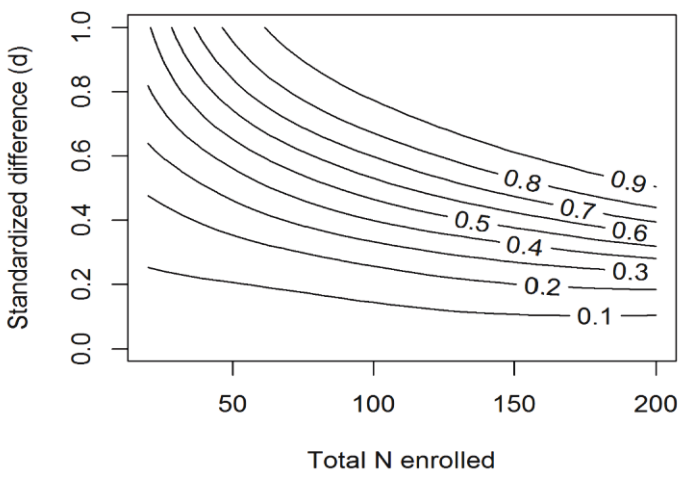
8.0 DISSEMINATION OF RESULTS

There are no current plans for dissemination of study results to participants of this study. Should this change, IRB approval will be obtained prior to use of any method for study progress information dissemination to participants.

8.1 Release of Information to Participants

Whenever possible within the limits of the study, effort will be made to keep study participants informed of significant study results. This will mainly be a 1:1 discussion between the subject and their Primary Care Physician, as appropriate. Dissemination of results to the study participants will be performed only insofar as specific tests are performed by a clinical resource, such as a clinical laboratory or clinical testing department. All other results will be considered for research only and will not be shared with the individual subject directly.

Figure 2



Contour plot of power surface for the primary analysis (six-month change in HbA1c) as a function of total enrolled and remaining at six months (N) and standardized difference of the effect size (d).

8.2 Public Release of Information

IRB approval will be obtained prior to use of any method for information dissemination to the public (if there is a policy in place by that point in time). Otherwise methods of disseminating study results and/or study progress to the public may include press releases, publications, conference abstracts, etc.

Requests for interviews, comments, or press conferences with the study investigators will be honored to more fully describe the results or explain the implications of the results, following consultation with the Intermountain public relations team. Any direct request to the investigators will be sent to the Communications team first, before the investigator responds to the media request.

8.3 Data-Sharing with Collaborators

Deidentified data obtained from this study will be shared with Savvysherpa in accordance with signed legal documents to help develop predictive models for diabetes care. Data will be transferred using either SFTP or an encrypted hard drive and in accordance with cybersecurity approval.

Further, collected data will be transcribed into visualizations on a Tableau dashboard. The specific outputs will include recruitment totals for each particular site, patient demographics, glucose tracking, etc. No protected health information will be on the Tableau dashboard—it will serve as a real-time tracking tool for Intermountain senior leadership. Furthermore, Dr. Christopher Jones, who specializes in diabetic management will be provided the dashboard link and he will interpret the CGM profiles on an interim basis. Dr. Christopher Jones will monitor subject safety within the data (Tableau) and report back any concerning findings to the study team and/or their respective Reimagine Clinic Provider. He will also regularly speak with the study team on his glucose monitoring results and data updates on a weekly basis.. This will ensure the safety of participants and be useful for developing future national standards on CGM diabetic care.

8.4 Publications

The results of this study may be published as a paper, abstract or poster, or may be presented orally at a conference or symposium. Any publication resulting from this study will comply with the guidelines recommended by the International Council of Medical Journal Editors (i.e., Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, 2013).

Opportunity will be given for Savvysherpa to also review the content and the conclusions drawn before the abstracts, papers or visual presentations are finalized, in accordance with the clinical research contract.

9.0 FINANCIAL CONSIDERATIONS

9.1 Funding Source

This project will be internally funded through the Business Development group at Intermountain Healthcare.

9.2 Compensation

Subjects will not receive any monetary or other forms of compensation for participating in this research study. Likewise, the investigators and their research staff will not receive any monetary or other forms of direct compensation for conducting this research study. Subjects who receive the Contour Next ONE will be asked to mail the device back to The Business Development Department at Intermountain Healthcare in a prepaid mailing envelope supplied to the patient upon study completion to ensure no compensating factors took part in the research study.

9.3 Disclosure of Conflicts of Information

The Principal Investigator, Co-Principal Investigator, Sub-Investigators and protocol authors declare that they have no conflicts of interest relevant to this study.

10.0 REFERENCES

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11.0 PROTOCOL SIGNATURE PAGE

PROTOCOL IDENTIFICATION

Assessing the Feasibility of Continuous Glucose Monitoring in Reimagine Primary Clinics

PRINCIPAL INVESTIGATOR AGREEMENT

I agree to conduct this research study in accordance with the design and specific provisions of this protocol. Deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment and approval by the Institutional Review Board (IRB). I also agree to report all information or data in accordance with the protocol. I agree to report any serious adverse experiences as defined in the Safety Reporting section of this protocol to the Intermountain IRB, and in accordance with the IRB's reporting requirements.

Principal Investigator (Printed Name)	Principal Investigator (Signature)	Date

12.0 APPENDIX A

This section provides the questions which will be entered into REDCap and patients asked to complete at the end of the CGM study. There will be branching logic used based on the specific group assigned.

1. **Which group were you assigned to?**
    a. Group 1 (Dexcom G6)
    b. Group 2 (ContourNext One)

2. **What was the main reason that you signed up for this trial? _____.**

3. **What was your biggest concern when you considered participating in this trial? _____.**

4. **Were you initially disappointed with your group assignment?**
    a. Yes
    b. No

    4b. Why were you disappointed with your group assignment? _____.

5. **(For Group 1 participants): Did the Dexcom G6 impact your glucose management? For example, did it change your diet?**
    a. Yes
    b. No

6. **(For Group 1 participants): Did the Dexcom G6 impact your glucose management? For example, did it change your exercise regimen?**
    a. Yes
    b. No

7. **How did Dexcom G6 impact your glucose management? _____.**

8. **(For Group 1 and 2 participants): On a scale of 1-5, where 1 is not helpful and 5 is extremely helpful, how would you rate the device?**

9. **(For Group 1 and 2 participants): On a scale of 1-5, where 1 is extremely poor and 5 is extremely healthy, how would you rate your health BEFORE starting this study?**

10. **(For Group 1 and 2 participants): On a scale of 1-5, where 1 is extremely poor and 5 was extremely healthy, how would you rate your health AFTER starting this study was completed?**

11. **(For Group 2 participants): Did the ContourNext One impact your glucose management? For example, did it change your diet?**

12. **(For Group 2 participants): Did the ContourNext One impact your glucose management? For example, did it change your exercise regimen?**

13. **How did the ContourNext One impact your glucose management? _____.**

14. **Did your glucose levels decrease between the initial enrollment and the end of the study? (Suggest inserting this filter question.)**
    a. They increased
    b. The decreased

c. No change

15. **Would you be willing to participate in future Intermountain pilots in your primary care clinic?**a. Yes
    b. No

16. **General Comments. In the space provided, please feel free to add any other comments regarding your participation in this study. _____.**