CLINICAL STUDY PROTOCOL

Protocol Title: The GLUCAR Clinical Utility Trial

Protocol Number: 01-GLY-2018

Study Sponsor:

GlycoMark, Inc.
805 Third Avenue, 17th Floor
New York, NY 10022
Phone +1 (888) 744-0221

Protocol Date: Draft 2, March 8, 2018

PROTOCOL ACCEPTANCE PAGE

Protocol Title: The GLUCAR Clinical Utility Trial

Protocol Number: 01-GLY-2018

Protocol Date: Draft 2, March 8, 2018

Approvals:

John W Peabody MD, PhD, FACP
Principal Investigator
President, QURE, LLC

03/14/18
Date

Mary Tran
Director, QURE LLC

03/14/18
Date

Hirotaka Ishibashi
President, GlycoMark Inc.

03/14/18
Date

TABLE OF CONTENTS

REVISION HISTORY

Revision	Originator	Date Effective	Nature of Change
A			
B			
C			
D			

ACRONYMS

1,5-AG	1,5 - Anhydroglucitol
CGM	Continuous Glucose Monitoring
CPV®	Clinical Performance and Value Vignettes
EMR	Electronic Medical Record
HbAlc	Hemoglobin Alc
IGT	Impaired Glucose Tolerance
IM	Internal Medicine
GM	General Medicine
FP	Family Physician
PCP	Primary Care Physician
PPG	Post-Prandial Glucose

STUDY SYNOPSIS

Protocol Title

The GLUCAR Clinical Utility Trial: GLUcose Control using 1,5-AG Randomized Controlled Trial

Back-ground

Nearly half of the adult population, 114 million Americans, are diagnosed with diabetes or pre-diabetes, making this one of the most important public and personal health problems (CDC 2017). Diabetes is the 7th leading cause of death in America and a contributing factor in many more deaths and lost days of productivity. Its complications include vascular disease, cardiovascular disease, stroke and dementia. The cost of diabetes care and its complications lead to $176 billion in direct medical costs and $69 billion in reduced productivity (ADA 2013). With an over 2-fold increase in diabetes prevalence in the past two decades and an estimated 1.5 million new cases expected annually (CDC 2017), it is clinically and economically critical for this condition to be managed appropriately.

Diabetes treatment programs focus on controlling hyperglycemia (random glucose > 200 mg/dL) without causing hypoglycemia (glucose < 70 mg/dL). Glucose control is determined in a number of ways in current clinical practice. Immediate and fasting blood sugars are determined in routine chemistry tests. The standard measure of long-term diabetes control, HbA1c testing, provides a reliable reading of average blood glucose levels over a 2-3-month period. In patients with high HbA1c levels, HbA1c measurement guides management decisions and helps the clinician bring the long-term glucose levels under control in poorly controlled diabetic patients. Random blood sugars and HbA1c is limited in that they do not reflect glycemic control in intervals greater than the past few hours and 2-3 months. In particular, they do not provide an indication of frequent, temporary increases in blood glucose, termed glycemic excursions, which have been independently associated with several health complications. Since it takes months for HbA1c levels to stabilize, HbA1c levels are also not helpful for patients starting medication or changing drug therapy.

1,5-anhydroglucitol (1,5-AG) is a molecule found in the blood and is a validated indicator of glucose excursions and short-term (1–2 weeks) hyperglycemia (Khaw

GlycoMark testing, therefore, provides missing clinical details on peak glucose levels, daily spikes, and response to drugs, including short term effects, of hypoglycemic agents that are otherwise not available, giving physicians a more complete understanding of their patient's glycemic control. This information is potentially clinically useful to help physicians make better management decisions, to improve diabetes outcomes, avoid complications and reduce unnecessary spending. However, no studies have yet been published demonstrating the clinical utility of GlycoMark on physician decision making. GlycoMark clinical utility, its clinical and economic value, and public health benefits need to be scientifically assessed and demonstrated among practicing physicians to warrant broad adoption and reimbursement.

Study Objective

To determine if primary care physicians are able to identify and address glycemic variability and hyperglycemia in their patients and, when given access to GlycoMark assay results, improve their patient management decisions by taking steps to optimize glycemic control, and reduce unnecessary resource utilization.

Study Design

The study is a pre-post, two-round, randomized controlled study of a nationally representative sample of primary care physicians, including internists and family physicians, randomly assigned to a control or intervention arm. Once eligibility is determined and providers are enrolled in the study, they will be asked to complete a questionnaire describing their practice and professional background. They will then care for a total of 6 CPV® simulated patients over the two rounds (3 per round). The simulated patients are adults aged 18-75 who present with diabetes, different levels of glycemic control and various co-morbidities. The study design consists of two study arms, a control arm and an intervention-arm that receives educational materials and the 1,5-AG results. as follows:

- Round 1 (Baseline Assessment): Providers in both the control and intervention groups will care for 3 CPV simulated patients, to evaluate their work-up, diagnostic and treatment decisions, including awareness of glycemic variability.
- Intervention/GlycoMark Education: Approximately 3 weeks after CPV Round 1 is complete, the intervention arms will receive GlycoMark assay education materials, consisting of two or more of the following:
    - On-demand, online video of the GlycoMark assay
    - Test interpretation guide
    - Example test results
    - Example case study
    - Option to connect directly with GlycoMark customer service
- Round 2 (Post-Educational Intervention Assessment): Approximately 3 weeks after the intervention, all providers in the control and intervention

arm will receive another 3 simulated patients, with similar characteristics to the CPV patients in the first round. All participants will again be asked to care for these patients to determine if practice has improved in the intervention arm relative to controls. The intervention participants will also have access to GlycoMark assay results for their patients to help guide their decisionmaking.

Study instruments

There are two data collection instruments:

A questionnaire is administered to all providers prior to CPV Round 1 data collection to assess physician and practice characteristics.

The Clinical Performance and Value (CPV®) vignettes, which are simulated patients aged 18-75, who visit primary care physicians in the outpatient setting are used to measure physician practice. CPVs are validated measures of actual provider practice that control for variations in case mix presentation and are widely used to measure changes in clinical practice (Peabody, 2004). Six CPV patient simulations will be developed representing a spectrum population of diabetic patients, with different manifestations that will potentially distinguish the clinical advantages of 1,5-AG testing. Cases will be randomly assigned. Each participant will care for an individual CPV patient only once. Each provider will care for these simulated patients as they would patients in their own practice (Peabody, 2000) by responding to open-ended questions regarding their clinical care in five domains: 1) taking a medical history, 2) conducting a physical examination, 3) ordering appropriate tests, 4) making a diagnosis, and 5) prescribing treatment and follow-up recommendations. Participant responses are scored against explicit evidence-based criteria determined by expert physician reviewers. Results are presented as a percentage of correct care items identified. Each case will take approximately 15 - 20 minutes to complete. All case responses will be completed online and the results kept confidential.

Intervention

The intervention arm participants will receive GlycoMark assay education materials, consisting of two or more of the following:

- On-demand, online video on the GlycoMark assay

CPV Patient Types

Six CPV vignettes will be designed under 3 patient profiles with a higher likelihood of glycemic variance between 1,5-AG and their HbA1C test results.

1.	**Routine care**	Post-prandial excursion	Post-prandial excursion
2.	**Change in Drug Treatment**	New oral hypoglycemic	High-dose steroid therapy
3.	**Other clinical conditions**	Anemia/ Transfusion	Poorly controlled gestational diabetic

Outcome Measures

Primary Outcome

- Difference in difference between the control and the intervention group in their identification and treatment of hyperglycemia as measured by their diagnostic and treatment CPV domain scores.

Secondary Outcomes

- Difference in difference between the control and the intervention groups in the overall quality of care as measured by their combined domain and individual item CPV scores for the 6 patients in aggregate and by case type
- Difference in expected health care utilization and/or costs in patients tested with GlycoMark versus the control group in aggregate and by case type.

Pop-ulation

150 primary care physicians across 2 study arms will be recruited and randomized to participate in the study.

Inclusion eligibility criteria for general medicine physicians:

- A minimum of 2 years post residency but no more than 30 years in practice
- Board-certified in internal medicine or family practice, primary care physicians
- In a private solo or multi-group practice

- Minimum threshold of patients (40+) currently seen weekly
- A minimum of 15% of their panel under their care for diabetes
- Have not used GlycoMark assay in the past
- Informed, signed and voluntarily consented to be in the study

Physician Recruitment

Primary care physician participants will be randomly selected from lists of approximately 30,000 primary care physicians obtained by a third-party recruitment partner. Potential participant physicians will be contacted by email, telephone, fax and/or recruitment letter sent via postal mail. A dedicated script will be used by experienced trained recruiters to assess eligibility and willingness to participate. Participation is voluntary and fair market compensation is provided to those that enroll and agree to complete the study.

The study protocol and all consent materials will be submitted to and reviewed by a certified multi-site IRB before recruitment begins. We will maintain physician privacy and confidentiality in accordance with standard ethical practice standards codified in the IRB submission. Accordingly, informed consent is obtained by having physicians read the consent form and provide their electronic signature. Once obtained, physicians will be considered enrolled into the study.

Sample Size

The study is adequately powered to detect differences in the combined diagnosis and treatment score as measured by the CPVs. A sample size of 75 physicians in each of the 2 study arms (150) provides over 80% power to detect an estimated 6-7% difference in scores with alpha=0.05 and beta=0.20.

Study Hypotheses

1. Primary care physicians are highly variable in their ability to maintain glycemic control in their patients with diabetes.
2. Primary care physicians lack the appropriate resources to adequately identify and address hyperglycemic excursions when HbA1c levels are otherwise normal.
3. Physicians who use GlycoMark are more likely to recognize glycemic deterioration and/or the impact of new glycemic therapy earlier.
4. Physicians ordering GlycoMark for diabetic patients are more likely to recommend a more effective, more efficient, evidence-based work-up and management strategy for patients presenting with glycemic variability

Data Analysis

Summary statistics will be determined for all variables. Simple cross tabulations will be prepared as part of the data resolution process. The calculation of basic descriptive statistics is used to check distributions and find outliers and out-of-range data. Numerical variables will be characterized in terms of means and standard deviations or by medians and interquartile range for skewed or highly non-normally distributed variables. For hypothesis testing, tests will be conducted with a two-sided $\alpha = 0.05$.

With experimental data we can estimate the effect of the GlycoMark assay on the primary outcomes comparing treatment and control groups. We will use a difference in difference analysis approach comparing differences between groups before and after intervention. We will control for all potential confounders, including physician-level characteristics, such as age, gender, specialty, years in practice, and practice-level characteristics, multi- versus solo- group practice, rural or urban location, and payer mix.

1. BACKGROUND INFORMATION AND RATIONALE

1.1 Background Information:

Nearly half of the adult population, 114 million Americans, are diagnosed with diabetes or pre-diabetes, making this one of the most important public and personal health problems (CDC 2017). Diabetes is a condition where the body does not properly process food for energy, creating an excess of glucose sugar in the blood. This excess sugar can produce a long list of complications, including hypertension, stroke, kidney disease, and mental health issues. Diabetes is the 7th leading cause of death in America and a contributing factor in many more deaths and lost days of productivity. Its complications include vascular disease, cardiovascular disease, stroke and dementia. The cost of diabetes care and its complications lead to $176 billion in direct medical costs and $69 billion in reduced productivity (ADA 2013). With an over 2-fold increase in diabetes prevalence in the past two decades and an estimated 1.5 million new cases expected annually (CDC 2017), it is clinically and economically critical for this condition to be managed appropriately.

Diabetes treatment programs focus on controlling hyperglycemia (random glucose > 200 mg/dL) without causing hypoglycemia (glucose < 70 mg/dL). The American Diabetes Association recommends the goal for diabetic therapy in most patients to be an average glucose level of 154 mg/dL. Glucose control is determined in a number of ways in current clinical practice. Immediate and fasting blood sugars are determined in routine chemistry tests. The standard measure of long-term diabetes control, HbA1c testing, provides a reliable reading of average blood glucose levels over a 2-3-month period. In patients with high HbA1c levels, HbA1c measurement guides management decisions and helps the clinician bring the long-term glucose levels under control in poorly controlled diabetic patients. Random blood sugars and HbA1c is limited in that they do not reflect glycemic control in intervals greater than the past few hours and 2-3 months. In particular, they do not provide an indication of frequent, temporary increases in blood glucose, termed glycemic excursions, which have been independently associated with several health complications. Since it takes months for HbA1c levels to stabilize, HbA1c levels are also not helpful for patients starting medication or changing drug therapy (McGill 2004). Also, nearly 40% of patients shown to have "good control" with HbAlc may actually have significant hyperglycemia (Erlinger 2001, Boranger 2006). HbAlc has also been shown to be problematic in select clinical conditions, such as anemias, hemoglobinopathies, dialysis, pregnancy and liver disease (Selvin 2014).

1,5-anhydroglucitol (1,5-AG) is a molecule found in the blood and is a validated indicator of glucose excursions and short-term (1–2 weeks) hyperglycemia (Khaw 2004, Dungan 2008). 1,5

GlycoMark testing, therefore, provides missing clinical details on peak glucose levels, daily spikes, and response to drugs, including short term effects, of hypoglycemic agents that are otherwise not available, giving physicians a more complete understanding of their patient's glycemic control. This information is potentially clinically useful to help physicians make better management decisions, to improve diabetes outcomes, avoid complications and reduce unnecessary spending. However, no studies have yet been published demonstrating the clinical utility of GlycoMark on physician decision making. GlycoMark clinical utility, its clinical and economic value, and public health benefits need to be scientifically assessed and demonstrated among practicing physicians to warrant broad adoption and reimbursement.

1.2 Rationale for the Study

Current strategies to manage patients' glycemic indices often overlook hyperglycemic states, which may indicate suboptimal glycemic control, which is associated with complications that lead to poorer quality of life, additional medical costs and even death. The GlycoMark assay, using 1,5- AG as a proxy for blood glucose, may provide a better, detailed picture of a patients' glycemic control. However, GlycoMark clinical utility, economic value, and public health benefits must be scientifically assessed among practicing physicians to warrant broad adoption and reimbursement.

2. STUDY DESIGN

The study is an interventional longitudinal study design of physician practice. 150 primary care physicians will be selected from a nationally representative list of approximately 30,000 board-certified physicians recruited from lists compiled by a third-party recruitment firm. These physicians will be **randomized** into one of 2 arms:

1. Control: not receiving any intervention or access to GlycoMark test results
2. Intervention: receiving educational material on the GlycoMark assay prior to Round 2 CPV administration and assay results during Round 2 CPV administration

2.1 Intervention Details

The intervention arm will receive educational materials on the GlycoMark assay, consisting of 2 or more of the following:

- On-demand, online video of the GlycoMark assay
- Test interpretation guide
- Example assay results
- Example case study

- Option to connect directly with GlycoMark customer service

Each educational material will be tracked for complete review by intervention participants. In the second round of simulated cases, the intervention arm will also be given the results of GlycoMark within the cases.

2.2 Study Instruments

A physician screening questionnaire will be administered to all physicians. This questionnaire will assess physician, patient and practice characteristics. Data gathered from this set of questions will become a part of the Round 1 Baseline (pre-intervention) assessment and used for analysis. At the Baseline assessment, CPV simulated patients will be administered. CPVs are validated measures of actual provider practice that are regularly used to determine changes in clinical practice while controlling for variations in case mix presentation (Peabody, 2004). CPV patient simulations have been used to establish clinical utility in the molecular diagnostic space (Peabody, 2012).

The CPV vignettes used in this study will simulate visits for adult diabetic patients (age 18 -75 years). Each physician cares for these simulated patients the way they would their own patients (Peabody, 2000) by answering open-ended responses regarding clinical care. These responses are scored in five domains: 1) taking a medical history, 2) performing a physical examination, 3) ordering appropriate tests, 4) making a diagnosis and 5) prescribing treatment against explicit evidence and criteria as determined by the literature and by expert physicians. Results are presented as percentage correct controlling for primacy effects using case within pair randomization. Each case will take approximately 15-20 minutes to complete. All case responses will be completed electronically online and will remain confidential. No physician or practice names are used when reporting the results of the study.

Round 2 of CPV data collection (Post-Intervention Assessment) for the control and the intervention groups will occur approximately 3 weeks after the introduction of the educational materials to the intervention group. CPV scores will be used to compare baseline practice with post-intervention practice in all arms.

This study will test the following hypotheses:

1. Primary care physicians are highly variable in their ability to maintain glycemic control in their patients with diabetes

These hypotheses will be tested through a total of 6 CPV simulated patients. CPVs will be designed under 3 patient profiles with a higher likelihood of glycemic variance between 1,5-AG and their HbA1C test results.

1.	**Routine care**	Post-prandial excursion	Post-prandial excursion
2.	**Change in Drug Treatment**	New oral hypoglycemic	High-dose steroid therapy
3.	**Other clinical conditions**	Anemia/ Transfusion	Poorly controlled gestational diabetic

One CPV from case type 1-3 will be randomly assigned to each physician to complete 6 CPVs total (3 CPVs in the Baseline and 3 CPVs in the Post-intervention rounds) in this phase. No CPV will be administered more than once to a single participant. Each CPV will be scored by physicians for changes in clinical practice including treatment changes, frequency of follow up, and diagnostic tests ordered and referrals.

3. STUDY OBJECTIVES

To determine if primary care physicians are able to identify and address glycemic variability and hyperglycemia in their patients and, when given access to GlycoMark assay results, improve their patient management decisions by taking steps to optimize glycemic control, and reduce unnecessary resource utilization.

Primary Outcome

- Difference in difference between the control and the intervention group in their identification and treatment of hyperglycemia as measured by their diagnostic and treatment CPV domain scores.

Secondary Outcomes

- Difference in difference between the control and the intervention groups in the overall quality of care as measured by their combined domain and individual item CPV scores for the 6 patient types in aggregate and by case type

- Difference in expected health care utilization and/or costs in patients tested with GlycoMark versus the control group in aggregate and by case type.

4. ELIGIBILITY CRITERIA

4.1 Description of subjects

Practicing physicians will be the study subjects with the following eligibility criteria.

4.1.1 Inclusion Criteria

Subjects must meet the following criteria to be enrolled in the study:

1. Provide consent to participate in the study
2. Board-certified physician currently practicing in the following areas:
   a. Internal medicine
   b. Family medicine
3. Have practiced as a board-certified physician in internal or family medicine for greater than 2 but less than 30 years.
4. Have not used the GlycoMark assay
5. English-speaking
6. Community / non-academic based practice setting
7. ≥ 40 patients under care weekly
8. ≥ 15% of their patient panel under their care for diabetes
9. Access to the internet

4.1.2 Exclusion Criteria

Subjects will not be included in the study if they meet any of the following exclusion criteria:

1. Not board certified in their respective area of care
2. Academic based practice

8. Unable to access the internet

4.2 Subject Screening and Enrollment

Providers will be contacted by email, telephone and/or recruitment letter sent via postal service or fax. Physicians will be randomly selected from lists of approximately 30,000 board-certified physicians obtained by a third-party recruitment partner. The study will be reviewed by a certified multi-site IRB before recruitment begins. Physician privacy and confidentiality will be maintained in accordance with standard ethical practice standards codified in the IRB submission.

Accordingly, informed consent will be obtained by having physicians read the consent and provide their signature and date and time of consent. Once this is obtained, physicians will be considered enrolled into the study.

4.3 Subject Withdrawal

If a participant fails to complete 3 CPV vignettes per round, they will be withdrawn from the study and replaced with another physician. Any CPVs from withdrawn subjects will be excluded from the analysis.

4.3.1 Withdrawal Criteria

Reasons for study withdrawal may include but are not limited to:

- Noncompliance with study procedures.
- Physician's right to withdraw consent at any time during the study with or without stated reason.

4.3.2 Documentation of Withdrawal of Subjects

The reason for withdrawal of any physician from the study will be appropriately documented.

5. TREATMENT OF SUBJECTS

The subjects are physicians, presenting limited risk to participation. Risk would be loss of confidentiality and revelation of their score. Participants (physicians) will be informed of these risks and asked to provide IRB approved consent before participation. Participation is strictly voluntary. Subjects will be appropriately compensated for their participation in the study.

6. STUDY PROCEDURES

At enrollment, each eligible physician who agrees to participate will be assigned a unique subject identification number to be applied on all forms. Only the study team will have access to the

subject's identity. The subject's name or other identifying information will not be used in analysis or reporting.

The main study procedures or assessments will include but are not limited to: collection of demographic and practice information during the screening process and completion of CPVs.

6.1 Pre-Screening and Eligibility

The evaluations for inclusion and exclusion criteria will include board certification, practice type, patient volume and years in practice.

6.2 Completion of CPVs

Enrolled physicians will be provided a unique website address to access the CPVs. Each CPV is expected to take approximately 15-20 minutes. Participants will be given 7 days to complete the CPVs. If the CPVs are not completed within this timeframe, the physician will be contacted and requested to complete the CPVs. Physicians will be reminded to complete the CPVs by phone and/or emails. If after 10 business days, they still have not completed the CPV, they will be withdrawn from the study.

7. STUDY DATA COLLECTION

Data entry and resolution will be performed in real-time concurrent with CPV data collection. All data will be linked to physicians via a unique identification number; only the study team will have access to their identities. Electronic data files will be password protected. Periodic audits will ensure data protection procedures are being followed. No physician will be mentioned by name in any data output.

8. STATISTICAL ANALYSIS

8.1 Determination of Sample Size

The study is adequately powered to detect differences in the combined diagnosis and treatment score as measured by the CPVs. A sample size of 75 physicians in each arm (150 total) provides over 80% power to detect an estimated 6-7% difference in scores with alpha=0.05 and discriminate differences in case and physician characteristics (age, gender, specialty, etc.). Due to possible attrition, an additional 10 physicians will be enrolled in each arm to ensure that at least 150

non-normally distributed variables. For hypothesis testing, tests will be conducted at a two-sided $\alpha = 0.05$. We have one primary outcome, quality as measured by combined diagnostic and treatment CPV domain scores and/or the CPV versus baseline comparing intervention and control groups among the three patient types.

Baseline Data Analysis

At baseline parametric and non-parametric estimates of differences will be calculated between the groups (the control versus intervention groups to examine differences in CPV score and variance and utilization rates). Differences will be adjusted using multivariate and logistic regression models constructed to include age, gender, type of location (urban/suburban vs. rural), patients seen per week, practice size, single or multispecialty practice, practice ownership, and other practice characteristics and by patient characteristics such as type of payers. Non-parametric estimates of differences in care utilization will be calculated and adjusted for physician, practice and patient characteristics described above.

Summary tables for each group will be generated for the following:

- Percent in solo and multi-group practice
- Practice location
- Practice size (small, medium or large)
- Average days of week in practice
    - 1 to 2 days
    - 3 to 4 days
    - 5+ days
- Percent of patients covered by
    - Medicare
    - Commercial/Private
    - Medicaid
    - Self-pay / Uninsured
    - Other
- Mean (+/- 2 SD)
    - Years since residency
    - Number of patients seen per week
    - Age

<u>Dependent/Outcome Variables:</u>

- Behavioral
    - Composite CPV diagnosis and treatment score

<u>Main explanatory variables:</u>

- GlycoMark assay orders
- CPV scores

<u>Controlling for:</u>

- Age
  - Gender
  - Number of years since residency
  - Practice location
  - Practice size
  - Type of location (urban/suburban vs. rural)
  - Number of patients seen per week
  - Number of physicians in practice
  - Solo or multi-group practice
    - Avg. type of coverage of patients (e.g., Medicare, Medicaid, etc.)

Longitudinal Data Analysis

With longitudinal data we can estimate the effect of GlycoMark testing on our primary and secondary outcomes. After Round 2 data are collected, we will conduct the longitudinal analysis incorporating type of intervention, time (before versus after), and the primary predictor, the time by intervention interaction (to look for differential changes over time). This allows a difference in difference analysis comparing differences between groups before and after intervention to assess the effect of GlycoMark testing.

Primary Outcome Variable:

- CPV diagnostic and treatment domain scores

Secondary Outcome Variables:

- Overall quality of care score (individual and aggregate domain scores) in total and by case type
- Utilization counts of laboratory tests, imaging studies and other workup procedures ordered in aggregate and by case type
- Utilization counts of drugs prescribed, omitted or revised in aggregate and by case type
- Counts of specialist or other providers consulted in aggregate and by case type

We will control for all potential confounders, including:

- Age
- Gender
- Number of years since residency
- Practice location

CPV is the score for each physician, INTERV indicates type of intervention group and TIME indicates time period (pre and post-intervention).

Y_{it} = CPV score at time *t*, physician *i*

$Y_{it} \sim Normal(\mu_{ijt}, \sigma^2)$

$\mu_{ijt} = \beta_0 + \beta_1 TIME + \beta_2 INTERV + \beta_3 TIME \times INTERV$ + physician-practice variables

For binary outcome variables, we will use a logistic regression model. Our regression is as follows, where INTERV indicates type of intervention group and TIME indicates time period (pre and post-intervention). To account for patient clustering effects underneath physicians, we have included a $\hat{\hat{\Theta}}_{ijt}$ coefficient for the patient variables. For outcomes with a Poisson distribution, the distributional assumption would be changed from Bernoulli to Poisson and the link would be changed from logit to log. Otherwise, the basic modeling and analysis strategy will remain the same.

Y_{it} = appropriate therapy *t*, physician *i*

p_{it} = probability of an outcome for time *t*, physician *i*

$\text{logit}(E[Y_{it}]) = \beta_0 + \beta_1 TIME + \beta_2 INTERV + \beta_3 TIME \times INTERV$

+ physician-practice variables + $\hat{\hat{\Theta}}_{ijt}$ x patient variables

For count outcome variables we will use log linear regression (i.e., using a log link in the analysis). Cluster re-sampled bootstrapping will be used to check model distributional assumptions.

9. ADMINISTRATIVE CONSIDERATIONS

9.1 Study Compliance

The study will be conducted in compliance with this protocol, principles of ICH-6, GCP and the Declaration of Helsinki and all applicable national regulations governing clinical trials.

9.2 Protected Subject Health Information

A copy of the IRB approved informed consent may be audited. The investigator or designee **must** explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects and all other elements of consent as defined in 21CFR §50.

In accordance to individual local and national subject privacy regulations, the investigator or designee **must** explain to each subject prior to screening that for the evaluation of study results, the subject's protected information obtained during the study may be shared with GlycoMark Corporation and its designees, regulatory agencies and IECs/IRBs. GlycoMark Corporation will not use the subject's protected information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility

to obtain a written permission to use protected information from each subject. Any data collected from a subject prior to withdrawal will not be used in the analysis of study results.

9.3 Retention of Records

The files of study subjects shall be retained in accordance with national legislation and the maximum period of time permitted by GlycoMark Corporation. GlycoMark Corporation will maintain records and documents on-site.

9.4 Confidentiality and Publication Policy

For publications, authorship will be determined according to the generally accepted principles of authorships and by mutual agreement.

REFERENCES

Bonora, et al. Prevalence and correlates of post-prandial hyperglycaemia in a large sample of patients with type 2 diabetes mellitus. Diabetologia (2006) 49: 846–854.

CDC's Division of Diabetes Translation. Long-term Trends in Diabetes. United States diabetes prevalence in the past decade. April 2017. http://www.cdc.gov/diabetes/data. Accessed Mar 2018

Dungan K. 1,5-anhydroglucitol (GlycoMark) as a marker of short-term glycemic control and glycemic excursions. Expert Rev Mol Diagn. 2008 Jan;8(1):9-19.

Erlinger TP et al. Postchallenge Hyperglycemia in a National Sample of U.S. Adults With Type 2 Diabetes. Diabetes Care 24:1734–1738, 2001

Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. Ann. Intern. Med.141(6), 413–420 (2004)

DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortalitiy: comparison of fasting and 2-hour diagnostic criteria. Arch. Intern. Med.161, 397–405 (2001).

McGill J, Cole T, Nowatzke et al. Circulating 1,5-Anhydroglucitol Levels in Adult Patients With Diabetes Reflect Longitudinal Changes of Glycemia. A U.S. trial of the GlycoMark assay Diabetes Care 2004 Aug; 27(8): 1859-1865.

Radin M. Pitfalls in Hemoglobin A1c Measurement: When Results may be Misleading. J Gen Intern Med. 2014 Feb; 29(2): 388–394

Peabody J, Luck J, Glassman P, et al. Comparison of Vignettes, Standardized Patients, and Chart Abstraction: A Prospective Validation Study of 3 Methods for Measuring Quality. JAMA. 2000;283(13):1715-1722. doi:10.1001/jama.283.13.1715.

Pogach L, Engelgau M, Aron David MD. Measuring progress toward achieving hemoglobin A1c goals in diabetes care: pass/fail or partial credit. JAMA297(5), 520–523 (2007). [Google Scholar]

Selvin E, Rawlings A, Grams M, Klein R, et al. Association of 1,5-Anhydroglucitol with Diabetes and Microvascular Conditions. Clinical Chemistry. 2014

Shojania KG, Ranji SR, McDonald KM et al. Effects of quality improvement strategies for type 2 diabetes on glycemic control: a meta-regression analysis. JAMA296, 427–440 (2006).