



UVA CENTER FOR DIABETES TECHNOLOGY

Adaptive Behavioral Control (ABC) in a Closed-Loop System: A Randomized Clinical Trial

Statistical Analysis Plan

Version 2.0

September 17, 2024

Based on Protocol Version 1.1

Version History

Version	Author	Effective Date	Revision Description	Study Stage
1.0	Boris Kovatchev	7/29/2022	Original Version	Statistical Analysis Plan included in Protocol. The trial started enrollment on 1/18/2023.
2.0	Boris Kovatchev Sue Brown	9/17/2024	Revision	Statistical Analysis Plan copied from protocol including study synopsis, formatted with signature fields added.

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Study PI Approver: Boris Kovatchev

Protocol Summary

PARTICIPANT AREA	DESCRIPTION
Title	Adaptive Biobehavioral Control (ABC) in a Closed-Loop System: A Randomized Clinical Trial
Investigational Device	There is Investigational software known as a Web-based Information Tool (WIT) that consists of three components collectively known as ABC: - Behavioral Adaptation Module (BAM), - Physical Adaptation Module (PAM) and Web-based Simulation Tool (WST). - There is no investigational device.
Investigational Medication	None
Objectives	This study is intended to test a Web-based Information Tool (WIT) software providing additional information regarding glucose variability, glucose management indicator, risks for hypo- and hyperglycemia, and potential changes of insulin pump parameters, to users of the Control-IQ system.
Study Design	Randomized parallel group trial.
Number of Sites	1
Endpoint	<u>Primary Outcome:</u> CGM-measured % time in range 70-180 over last 4 weeks of CLC+ABC vs 2 weeks of CLC. <u>Secondary Outcomes:</u> The secondary outcome of interest will be primarily CGM-based metrics using the last four weeks of the CLC+ABC, 4 weeks of CLC+BAM and the two-week CLC data to compare: CLC +ABC vs CLC +BAM and CLC+BAM vs CLC
Population	Key Inclusion Criteria - Age 18-70, inclusive, with Type 1 Diabetes for at least one year - Current user of t:slim X2 insulin pump with Control-IQ Technology (Closed-loop control or CLC) Key Exclusion Criteria - Recent severe hypoglycemic event or DKA during the past one year
Sample Size	Recruit up to 90 participants with the objective of randomizing 72 subjects
Treatment Groups	Group 1: CLC use (2wk) followed by CLC + BAM (4wk) followed by CLC +ABC (16 wk) Group 2: CLC+ABC (16 wks) followed by CLC + BAM (4wk) followed by CLC use (2wk)
Participant Duration	Approximately 26 weeks
Protocol Overview/Synopsis	Each group will undergo screening and collection of baseline data from their personal CLC system (Control-IQ) followed by randomization 1:1 into two groups. Both groups will have the same three interventions but will progress in the study in a different order. The three interventions are: Use of personal CLC system for 2 weeks Use of personal CLC system and adding a behavioral adaptation module (BAM) for 4 weeks Use of personal CLC system and adding the ABC which includes three components: BAM, PAM (also known as Autotitration Module) and WST. The BAM will consist of modules in which information only is given to participants (e.g. time in range, GMI, hyper- and hypoglycemic risks, daily glycemic profiles, and variability tracker). The PAM or ATM includes auto-titration of insulin pump parameters every two weeks. This PAM can be aided by a web simulation tool (WST) which can replay several 'what if' scenarios for the participant based on various combinations of insulin pump parameter changes.

Schedule of Study Visits and Procedures

Visit Name	Visit 1	Visit 2	Visit 3	Visit 4-13	Visit 14
Description	Screening Visit	Device Training & Data Collection	Randomization	Bi-Weekly Check-In	Final Visit
Timing	-8 to -2 weeks	-28 to -14 days	Day 1	Every 14 +/-5 days	Day 154±7 days
Location	O/P	O/P	O/P	O/P	O/P
Informed Consent	X				
Eligibility Assessment	X				
Medical History	X				
HbA1c	X				X
Screening Blood Testing: CMP, TSH if applicable	X				
Pregnancy test (if applicable)	X	X	X		X
Physical Exam (if applicable)	X				
Vital Signs (including height/weight)	X				
Training on Relevant Devices or Modules		X	X		
Randomization			X		
Questionnaires		X		Only at the end of each phase: Group 1: Visit 4, 6 Group 2: Visit 11, 13	X (Both Groups)
Review diabetes management and AEs	X	X	X	X	X

1. Design and Randomization

The participants will be randomized 1:1 to two groups experimental and control. The randomization list will use a sequence of computer-generated pseudorandom Bernoulli trials.

2. Sample Size

We intend to recruit up to 90 subjects, with the objective to randomize N=72 subjects. Sample Size Determination is based on the effect observed for the primary outcome (CGM-measured TIR 70-180 mg/dL) in our prior studies, specifically TIR differences associated with technology upgrade and HbA_{1c} stratification. We conservatively estimate that the effect size of ABC vs. CLC, in a crossover design with two groups and two repeated measures, will be $f \geq 0.2$. Power calculations assuming 2-sided type 1 error of 0.05, 90% power, correlation of 0.5 between the repeated measures, and attrition of 20% yield a sample size of **N=90** subjects to be randomized, with **N=72** subjects completing the study. This sample size was computed using the G*Power 3 software. The effect size assumptions are intentionally conservative to account for uncertainties that are inherent when new technology is introduced, and to further reinforce the hierarchical comparisons described below.

3. Outcome Measures

3.1 Primary Efficacy Endpoint

CGM-measured % time in range 70-180 over last 4 weeks of CLC+ABC vs 2 weeks of CLC.

Statistical Hypotheses: The primary outcome for this study is CGM-measured % in range 70-180 mg/dL over the last 4-week periods on CLC+ABC vs 2 weeks of the current CLC system.

The intervention will be considered effective if the CLC+ABC is superior to the CLC alone in a crossover design using a statistical significance of $\alpha=0.05$.

The null/alternative hypotheses are:

Null Hypothesis: There is no difference in mean CGM-measured TIR 70-180 mg/dL between CLC+ABC and CLC;

Alternative Hypothesis: The mean CGM-measured TIR 70-180 mg/dL is different for CLC+ABC and CLC.

3.2 Secondary Outcomes

To preserve the overall type 1 error for selected key secondary endpoints, a hierarchical testing procedure will be used. If the primary analysis for time in range described above results in a statistically significant result ($p < 0.05$), then testing (similar to the model for the primary outcome) will proceed to the next outcome metric in the following order:

33 CGM-measured % in range 70-180 mg/dL (primary outcome);
34 CGM-measured % below 70 mg/dL during the day;
35 CGM-measured % above 180 mg/dL during the day;
36 CGM-measured coefficient of variation during the day;
37 CGM-measured mean glucose.

38 This process continues iteratively moving to the next variable down on the list until a non-
39 significant result ($p \geq 0.05$) is observed, or all variables have been tested. If a non-significant
40 result is encountered, then formal statistical hypothesis testing is terminated and any variables
41 below on the list are not formally tested and analysis of these variables become exploratory.

42 Other Secondary Endpoints: The following endpoints are considered exploratory including
43 questionnaire data.

44 TIR 70-140 mg/dL and TIR <60 mg/dL;
45 LBG1 and HBG1¹⁰;
46 TIR >250 mg/dL and TIR >300 mg/dL;
47 HbA1c at end of study;

48 Diabetes Distress Scale
49 Pittsburgh Sleep Quality Index
50 Fear of Hypoglycemia Survey
51 Hyperglycemia Avoidance Scale
52 Technology Acceptance Survey
53 Clarke's Hypoglycemia Awareness scale

54 Questionnaires: All questionnaires will be administered online and subjects can skip specific
55 questionnaires or items within a questionnaire. All questionnaires will be scored according to the
56 instructions given in the manual. In case no manual exists for a given questionnaire or the manual
57 does not provide guidance on how to handle missing, then the following criteria will be applied.
58 At least 75% of the questions must be completed to be included in the analysis. This 75% rule will
59 be applied separately for the total score and each subscale so it is possible the sample size will
60 be different for some subscales. The score used for analysis will be based on the average among
61 the questions that were answered and then scaled accordingly.

62 **4. Safety Analyses**

63 All randomized participants will be included in these analyses and the circumstances of all
64 reportable cases of the following will be summarized and tabulated by treatment group:

65 Severe hypoglycemia;
66 Diabetic ketoacidosis (DKA);
67 Ketone events defined as a calendar day with ketone level >1.0 mmol/L;

Serious adverse events (SAE) with a possible or greater relationship to a study device (including anticipated and unanticipated adverse device effects);
Other serious adverse events not related to a study device, and
Adverse device effects (ADE) that do not meet criteria for SAE.

5. Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of all randomized participants will be summarized in a table using summary statistics appropriate to the distribution of each variable. Descriptive statistics will be displayed overall and by treatment group, and will include:

Demographics (e.g. age, duration of diabetes, and other);
Baseline HbA1c, and
CGM-based metrics from the 2-week baseline use of Control-IQ:
Percentage of readings in the target ranges of 70-180 and 70-140 mg/dl;
Mean glucose;
Glucose variability measured by standard deviation and coefficient of variation;
Percentage of readings <70, 60, and 54 mg/dl;
Low blood glucose index (LBGI) ;
Percentage of readings >180, 250, and 300 mg/dl;
High blood glucose index (HBGI).

6. Device Issues

The following tabulations and analyses will be performed by treatment group to assess device issues:

Device malfunctions requiring study team contact and other reported device issues
Sensor performance metrics (difference, absolute relative difference, and International Organization for Standardization criteria) – if applicable, by sensor version.
% time CGM data available - overall and by month
% time in different operational modes per week - overall and by month

7. Analytical Approach

Primary and Secondary Analyses: The study design includes repeated measures on all outcomes; thus, we will use a linear mixed-effect model that corresponds well to this structure^{5,6} (e.g. Linear Mixed Models in SPSS.⁷), with “Subject” as a random factor and “Group” as a fixed factor. The models will adjust for age, prior CGM use and pump use as fixed effects. We should note that similar results may be generated by repeated measures ANOVA.

The general principles that will be followed during analysis are:

The analysis will follow an Intention-to-treat (ITT) approach.

All randomized participants will be included in the primary and secondary analyses of CGM metrics.

All covariates obtained on a continuous scale will be entered into the models as continuous variables, unless it is determined that a variable does not have a linear relationship with the outcome. In such a case, categorization and/or transformation will be explored. All p-values will be two-sided.

Standard residual diagnostics will be performed for all analyses. If values are highly skewed, then an alternate transformation or nonparametric methods will be used. Previous experience suggests that no transformation or nonparametric analyses will be necessary for TIR 70-180 mg/dL, TIR above 180 mg/dL, mean glucose, or HbA_{1c}.

Per Protocol analyses will be conducted excluding period of time when the system was not in use, e.g. periods of system downtime due to the necessity to fix software problems. This type of forced discontinuation of system use have occurred in previous studies and were handled the same way.

Sensitivity Analysis: The primary and secondary hierarchical analyses will include adjustment for pre-specified covariates. Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. However, the presence of confounding will be evaluated by additionally including factors potentially associated with the outcome for which there is an imbalance between groups (assessed based on clinical judgement reviewing the distributions in the two treatment arms, not on a p-value).

Missing Data: All subjects will be included in primary analyses and any missing post-randomization data will be handled using direct likelihood. It is also worth emphasizing that any statistical method for handling missing data makes a number of untestable assumptions. The goal will be to minimize the amount of missing data in this study so that results and conclusions will not be sensitive to which statistical method is used. To that end, sensitivity analyses will be performed to explore whether results are similar for primary and secondary hierarchical analysis when using different methods. The following methods will be applied: (i) Direct likelihood; (ii) Rubin's multiple imputation, and (iii) Available cases only.

Summary statistics (mean $\pm$ SD or median (quartiles)) will be reported for all CGM-based metrics.

8. Case Report Forms and Device Data

The study data are collected through a combination of case report forms (electronic and paper) and electronic device data files obtained from the software and individual hardware components. These electronic device files and electronic CRFs are considered the primary source documentation.

When data are directly collected in electronic case report forms, this will be considered the source data. Records will be maintained in accordance with ICH E6 and institutional regulatory requirements for the protection of confidentiality of participants.

139 **9. Study Records Retention**

140 Study documents should be retained for a minimum of 2 years after the last approval of a
141 marketing application in an ICH region and until there are no pending or contemplated marketing
142 applications in an ICH region or until at least 2 years have elapsed since the formal
143 discontinuation of clinical development of the investigational product. These documents should
144 be retained for a longer period, however, if required by local regulations. No records will be
145 destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the
146 sponsor to inform the investigator when these documents no longer need to be retained.

147 **10. Protocol Deviations**

148 A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practices
149 (GCP), or procedure requirements. The noncompliance may be either on the part of the
150 participant, the investigator, or the study site staff. As a result of deviations, corrective actions
151 may be developed by the site and implemented as appropriate. Major deviations will be reported
152 to the IRB-HSR within 7 calendar days of when the study team becomes aware of the event.