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Document:

Protocol and Statistical Analysis Plan

Official Study Title:

Dulce Digital-Me: An Adaptive mHealth Intervention for Underserved Hispanics with Diabetes

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Dulce Digital-Me Protocol

The proposed randomized controlled clinical trial will enroll 414 participants according to the inclusion and exclusion criteria listed below to compare the effectiveness of Dulce Digital (DD) and Dulce Digital-Me (DD-Me) in improving participants' clinical control (HbA1c-primary, LDL-c, and SBP), adherence, and patient-provider communication in underserved Hispanics with poorly controlled type 2 diabetes mellitus (T2DM) across 12 months. The protocol was developed in accordance with Good Clinical Practice, SPIRIT, and CONSORT 2013 guidelines.

The primary aim of this study is to compare the effectiveness of DD-Me versus DD in improving diabetes clinical control [HbA1c-primary, low-density lipoprotein cholesterol (LDL-c), and systolic blood pressure (SBP)] over 12 months. The secondary aims are to compare the effectiveness of DD-Me versus Dulce Digital in improving patient adherence and patient-provider communication over 12 months, and to examine the cost-effectiveness of DD-Me versus DD. An exploratory aim will examine whether effectiveness, cost and/or acceptability differ significantly between DD-Me adaptive feedback methods [i.e., automated messaging versus telephonic MA Health Coach-delivery].

1. INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria:

- Self-identified as Latino/Hispanic
- Age 18 or older
- Registered patient of the collaborating Federally Qualified Health Center (FQHC)
- Diagnosed with T2DM (Type 2 Diabetes Mellitus)
- HbA1c ≥ 8.0% and/or SBP ≥ 140 and/or LDL-c ≥ 100 mg/dL) within 90 days of enrollment

Exclusion Criteria:

- Severe illness precluding regular clinic visits
- Pregnant or lactating
- Type 1 or gestational diabetes
- Lack of minimal literacy
- Plans to relocate
- Severe auditory or visual problems
- Primary language other than Spanish or English
- Not willing to carry a mobile phone

Individuals who meet inclusion criteria (and do not meet exclusion criteria) will be randomized to the Dulce Digital or DD-Me intervention condition.

2. SETTING AND SCREENING

The trial will be conducted at, a Federally Qualified Health Center (FQHC) that serves a low-income, largely Hispanic population of over 66,500 patients in San Diego County. A business agreement between Scripps Health and the FQHC will be established and approved by Scripps Health legal department.

Patient census data retrieved in preparing the current proposal support the feasibility of the proposed timeline and target sample. Electronic health records (EHR) will be used to identify potentially eligible patients who will be contacted by specially trained, bilingual research assistants. The support of the FQHC administrative leadership, staff, and utilization of EHRs for recruitment, our experience in recruiting patient samples from community settings, and the large number of potentially eligible patients will maximize our ability to recruit the sample in a timely manner. Recruitment and screening at all stages and for all study components will use IRB approved scripts and data collection forms. Established standards of practice for clinical research will be followed for consenting and enrollment of participants. A screening database will be developed and maintained throughout the trial. All information necessary for clinical trials reporting will occur in accordance with (NIH) CONSORT guidelines.

3. RECRUITMENT

Referrals to the trial will be made through review of EHR, which compiles all patients meeting criteria according to demographics and clinical indicators. Guidance on participant recruitment will be provided by clinic physicians. Potentially eligible participants will be contacted on behalf of the clinic by trained, bi-lingual research staff, who will describe the study, and review eligibility and interest.

4. WRITTEN INFORMED CONSENT; ENROLLMENT AND RANDOMIZATION

Written Informed Consent and Enrollment:

Patients who are eligible and interested will be invited to an in-person, group-based, “Initial Visit,” at which the study will be fully described, written informed consent will be obtained (Informed Consent document uploaded with this initial Study Application), and baseline self-report and clinical assessments will be performed. Approximate duration for this visit is 3 hours.

Randomization:

The study will apply a block randomization scheme, which will be computer-generated by the trial statistical consultant and administered by designated research staff. The study statistician will place assignments into sealed envelopes labeled with participant ID numbers. At the conclusion of the Initial Visit, the Project Manager will unveil group assignment. Laboratory staff who perform the clinical assays (primary study outcomes), data analysts, and research staff (with the exception of the Project Manager who will conduct randomization) will be blinded to group assignment.

At the conclusion of the Initial Visit, participants will be randomized to DD or DD-Me, delivered through automated text message, or telephonic communication, meet study staff (nurse, medical assistant [MA]), and receive training on intervention devices. All participants will continue to receive standard care at the clinic. Month-6 and month-12 assessments will be conducted at the same site. DD and DD-Me will be delivered between baseline and month-6 assessments, and are both intended to enhance the self-management support component of the Chronic Care Model (CCM).

5. INTERVENTION

5.a. Dulce Digital:

Practical barriers (e.g., work, caregiving, transportation) limit the reach of traditional or face-to-face DSME programs for underserved, at-risk patients. mHealth technologies have the potential to circumvent some of these obstacles. Recently we developed Dulce Digital (DD), which included culturally-tailored and health literacy-sensitive educational and supportive text messages [i.e., short message service (SMS)], combined with patient monitoring and transmission of blood glucose values. Dulce Digital participants received text messages derived from the Project Dulce DSME curriculum, medication reminders, and blood glucose monitoring prompts. As a "static" intervention, all Dulce Digital participants received the same content and dosage of messages (2-3 messages daily initially, with frequency tapered over 6 months). A care-team nurse monitored transmitted glucose values, assessed possible reasons for high-risk values, and encouraged follow up with the primary care provider as needed. In a recent RCT of N=126 Hispanic patients with poorly controlled T2DM (HbA1c ≥ 8%), Dulce Digital led to improved glycemic control across 6 months, relative to usual care [HbA1c mean Δ = -1.0% vs. -0.2%, $p<.05$]. Our process evaluation indicated that DD was both feasible and acceptable; however, patients expressed a preference for intervention content tailored to their individual self-management needs and behavioral progress (i.e., an "adaptive" intervention).

Participants in this group receive the original DD, culturally and health literacy-appropriate text messages between baseline and six months ("Core Content"). Over this same period, participants are encouraged to regularly check glucose using a cellular-enabled monitor ("Remote Glucose Monitoring"), manage their oral medication(s) monitor their medication taking using the cellular-enabled pillbox ("Remote Medication Adherence Monitoring") and respond to ecological momentary assessment ("EMA") questions about health behaviors and well-being via text message.

5b. Dulce Digital Me (DD-Me):

To accommodate patient and provider feedback and consistent with research asserting the value of adaptive interventions, Dulce Digital Me (DD-Me) will include the DD components described above plus adaptive behavioral feedback/goal-setting. The adaptive behavioral feedback and goal-setting component will be facilitated by the CYCORE system (developed and maintained by UCSD – a subcontracted institution on this grant), and will be informed by participants' real-time, wirelessly-transmitted ecological momentary assessment (EMA) and medication adherence data. The feedback/goal-setting specific to DD-Me will be delivered electronically using a computer-generated algorithm in 50% of the DD-Me sample, and by a specially trained, bilingual medical assistant (MA) in the other 50% to evaluate difference in delivery mode.

6. STUDY DEVICES

Blood glucose monitor. Telcare Verizon blood glucose meter (BioTelemetry, Inc, Malvern, PA). *Wireless medication adherence device*. WisePill Dispenser Int 3G (WisePill Technologies, Western Cape, South

Africa). *Cellphone*. Participants not owning a cell phone received an option of two different types of cell phones, a BLU Jenny (Doral, Florida) or an LG Expression with qwerty keyboard (Englewood Cliffs, New Jersey). Wireless service will be provided by U.S. Mobile with unlimited text and voice plans for the duration of the intervention. Data plans will not provided to any study participants.

7. STUDY SCHEDULE

Intervention assignments are described above. The follow-up periods at months 6 and 12 were chosen to assess immediate and longer-term impact of the intervention, respectively.

- *~1 week prior to Baseline Visit*: EHR Screening, Telephone Screening
- *Baseline Visit*: Informed Consent, Randomization, Brief diabetes education session to be delivered, Labs, blood pressure (BP) and anthropometric data to be obtained, Self-report surveys to be collected
- *Months 1-6*: Delivery of text messages all groups, automated (group 2) or telephonic feedback (group 3)
- *Month 6*: Labs, BP and anthropometric data to be obtained, Self-report surveys to be collected
- *Month12*: Labs, BP and anthropometric data to be obtained, Self-report surveys to be collected

7. ASSESSMENTS AND DATA COLLECTION

Clinical Measures:

• Clinical specimens (blood draws), HbA1C and lipid assays
• Physical measures (blood pressure, weight, height)

As part of Aim 1, we will evaluate key clinical indicators of diabetes control by measuring HbA1c, lipids, and BP. At baseline, month-6, and month-12 assessments, blood will be drawn at the clinic by existing Neighborhood Healthcare laboratory staff following a 12-hour fast and processed by Quest Diagnostics Inc., which adheres to all guidelines set forth by the College of American Pathologists. The primary outcome of HbA1c will be assayed by Immunoturbidimetry (Integra 800, Roche). Research assistants will measure BP and anthropometrics using standardized protocols and instrumentation.

Self-Reported Measures and EHR Data Extraction:

• Participant responses to survey instruments
• Records of demographics, comorbidities, and medications extracted from EHRs;

For Aim 2, participants will complete self-report measures of patient-provider communication, and adherence to medication and other diabetes self-management behaviors (dietary intake, physical activity, blood glucose monitoring) at all 3 time-points. Via self-report we will also assess demographic

and health related factors (including medication use) for screening and sample description purposes, and the fit of the overall theoretical model. Patient EHRs will also be reviewed for patient information (i.e., demographics, comorbidities, and medications).

Patient Focus Groups:

As part of the Process Evaluation, 20 participants from the DD-Me condition [split evenly between automated messaging (n=10) and MA-delivered (n=10)] will be invited to key informant interviews to share their experiences with the intervention. Focus group participants must be willing to provide informed consent; available for scheduled focus group/s; and speak Spanish or English. We will not conduct focus groups with Dulce Digital participants as a process evaluation has already been conducted as part of our original RCT.

Electronic health records abstraction:

Demographic and other data are extracted from the EHR for each participant upon enrollment, and clinical and health service utilization data is abstracted for 12 months from each patient's unique enrollment date from all laboratory and ambulatory clinic sites. Standard of care laboratory or anthropometric values resulted in the EHR within the qualifying assessment window will be used for outcome analysis purposes for any participants with missed follow up visits to enhance data completeness. The Scripps Health IRB approval provides permission to audit the EHR for patient identification and outcome analysis purposes.

8. DATA TRACKING

All data are tracked in a Research Electronic Data Capture (REDCap) database and reviewed on a regular basis by supervising research staff. Intervention fidelity forms are used to track the frequency, duration, and content of all telephone outreach to participants, including blood glucose triage and "no (EMA, blood glucose, or Wisepill) data" calls for all participants; and weekly MA Health Coach feedback calls for the DD-Me telephonic Health Coach group. The CYCORE system actively tracks the content and date/time of delivery or receipt of outgoing core content, EMA items, and feedback messages, as well as participants' responses to EMA items. CYCORE reports are reviewed on a regular basis to ensure that intervention content is delivered as designed; any deviations from protocol or temporary system outages are tracked in REDCap.

9. CONFIDENTIALITY AND DATA ACCESSIBILITY

Confidentiality will be protected by identifying all data forms with a participant ID number, which will be linked to participant identifiable information only on a master list, stored in password protected form on a password protected computer at both primary performance sites, separate from any other study data, and available only to the study PIs, project managers, and other trained research personnel working under the PIs' supervision if necessary for participant contact, tracking, or follow-up purposes. In general, the trial will take every possible precaution to protect data and ensure that confidentiality is protected both within and across performance sites, via use of ID numbers, safe transport, and other IRB approved procedures. All procedures will be discussed with clinic staff prior to implementation and will be reviewed and approved by the Scripps, SDSU, and UC San Diego IRBs.

Access to individually identifiable private information about the participants will be available only to MPIs Philis-Tsimikas and Gallo and trained research staff (e.g., project managers) working under their supervision who require this information for a specific purpose. All participant information and data will be de-identified (identified by participant number only). In all cases where data transfer between sites is required, data will be directly transferred from site to site (without stops, excepting emergency) and will be transported in de-identified form, separated from consent forms or other identifying information, and carried in a locked storage box.

8. RETENTION STRATEGIES.

The research team has gained substantial experience with approaches to minimizing attrition through previous efforts. These lessons learned will be applied to maintain the cohort in the proposed study. All participants will receive cohort maintenance postcards at interim study points and reminder postcards prior to each assessment appointment, and will be contacted and rescheduled if an appointment is missed.

Participant Compensation:

Monetary compensation ($50, $25, $40 gift cards for baseline/initial visit, month-6 and month-12, respectively) for time and effort rendered will be offered to all participants following each assessment visit.

Staff Skill:

All research staff will be carefully trained in research protocols and interviewing methods including the process of developing rapport and maintaining a friendly but professional interaction style to ensure that participants have a positive experience with the study.

9. STUDY OVERSIGHT

Collaborating Sites and Plan:

Performance sites include Scripps Whittier Diabetes Institute (SWDI) of Scripps Health (MPI Philis-Tsimikas), SDSU (MPI Gallo), and UC San Diego (Co-Investigator Farcas). In addition, patient recruitment, assessment, and intervention activities will take place at a collaborating FQHC. The study investigators will work with clinic leadership, providers, and staff to optimize plans for patient identification, data collection, and study implementation, including collaboration in developing safety and protocols and staff training. Twice monthly research meetings (or more often as needed) involving the study PIs and all central study staff across both sites will maintain consistent processes and communication. All research staff will be centrally trained and supervised by the study PIs.

Oversight of Clinical Outcomes and Intervention:

SWDI will have primary oversight for Aim 1 (clinical outcomes), cohort identification process via EHR, and interventionist (nurse, MA) training and support, and will also act as the primary liaison to the clinic sites and stakeholders groups. A Project Manager will be housed at Scripps to oversee patient identification, EHR and (overall) implementation of the intervention and staff trainings.

Oversight of Self-Reported Outcomes:

SDSU (with appropriate registration volunteer staff as required) will have primary oversight for the patient reported outcomes Aim (2). MPI Gallo (SDSU) will also oversee the overall program evaluation, in close collaboration with Co-I Fortmann (Scripps), including conducting patient focus groups and obtaining nurse, MA, and other provider input regarding the intervention, and database development, data entry, data verification, and overseeing data analysis in collaboration with the study statistician. A Project Manager will be employed at SDSU to oversee and contribute to the patient reported assessment outcome and overall program evaluation.

Oversight of CYCORE System:

Co-Investigator Farcas (UC San Diego) will oversee the development and maintenance of the CYCORE (CYberinfrastructure to support COmparative effectiveness REsearch); a secure, scalable and extensible platform with the ability to support adaptive or dynamic mHealth interventions) system and study technologies, and a Project Manager will coordinate development and implementation of the CYCORE system. The CYCORE system will be responsible for the programming of text messages (DD-Me and Dulce Digital) and adaptive feedback/goal-setting (DD-Me only). For a detailed description of the CYCORE system please see below:

"CYCORE (CYberinfrastructure to support COmparative effectiveness REsearch) is a secure, scalable and extensible platform with the ability to support adaptive or dynamic mHealth interventions. With CYCORE, participants take daily measurements related to health parameters of interest [in early use cases, BP, pulse, and weight]. Through mobile phone based self-report, called EMA, researchers capture information on other indicators of interest from participants (e.g., adherence, other health behaviors, emotional well-being). The mobile phone or other Internet-connected device sends the data to CYCORE's back-end services. Clinicians can monitor these data daily to determine the need for patient outreach. CYCORE has been extremely well received by patients and their support persons. Finally, CYCORE is device and sensor agnostic and can be readily adapted to the DD-Me project. In particular it can handle both inbound data capture from the glucose and medication monitors, and support the logic behind the text message-based EMA and interactive communication (i.e., personalized feedback and goal-setting) with study participants. It has a secure HIPAA compliant database that facilitates data visualization and analysis."

Statistical Analysis Plan

Study Aims

Primary Aim

To compare the effectiveness of DD-Me versus Dulce Digital in improving diabetes clinical control [HbA1c, primary outcome), low-density lipoprotein cholesterol (LDL-c), and systolic blood pressure (SBP)] over 12 months.

Secondary Aim

To compare the effectiveness of Dulce Digital versus Dulce Digital Me (Automated and Telephonic) in improving patient reported outcomes (patient adherence, diabetes distress, patient-provider communication over 12 months.

Statistical Methods

Power and Sample Size

This study will enroll *N* = 414 men and women allocated equally to the three groups. RMASS2 was used to estimate the sample size needed to detect statistically significant differences between any of the 3 groups: (a) Dulce Digital, (b) DD-Me (automated delivery), and (c) DD-Me (telephonic MA delivery). For HbA1c, the study primary outcome, a clinically meaningful change of 0.5% with a 1.3% standard deviation was used to determine power. To transform this estimate into an effect size (*d*=.33), standard deviations (SD) from prior studies in the same and similar populations were used. To determine the minimum sample size necessary, assumptions included: (1) An alpha level of .05 and a power level of .80; (2) a missing data rate of 15% at each time-point or a 30% missing data rate overall, and (3) a stationary autoregressive structure (lag 1) for the variance-covariance matrix of the repeated measures, using an autocorrelation value of .45. Given these assumptions and the estimated effect size from above, 414 participants are needed at baseline (i.e., n=138 in each of the 3 groups). Although power analyses used HbA1c as the primary outcome, N=414 at baseline is adequate to detect a small-to-medium effect size for all physiological and patient-reported outcomes, given a missing data rate of 30% over the course of the study. Allowing for up to 30% attrition, the minimum number of participants required to be retained at 12-months follow-up to ensure adequate power for statistical analysis is 290.

Analytic Plan

All analytic strategies will follow published standards, including intent to treat principles. Preliminary data screening and cleaning will require examination of distributions for normality, outliers, and missing data patterns at both the uni- and multi-variate level. Preliminary inferential statistical testing and effect size consultation will be used to determine if random assignment has resulted in statistical equivalence between groups. Significant covariates will be added to adjust for nonequivalence. Or variables related to missing data Multilevel models using full information maximum likelihood estimation will be conducted to examine changes in the target outcomes for each Aim. Analyses will include the between-subjects factor treatment group and the within-subjects factor time. The cross-level group by time interaction effect will be of primary interest. Within groups changes will also be examined to evaluate

the clinical and statistical significance of relative change. Outcomes assessment will follow the intention-to-treat principle; each participant will be included in between-group comparisons regardless of adherence level and based solely on randomization assignment.