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Protocol Full Title: DASH Cloud: Using digital health to improve adherence to the DASH diet among women at risk for cardiovascular disease

Short Title: DASH Cloud

Purpose of the Study

One-third of women have hypertension (HTN), and the risk of cardiovascular disease (CVD) because of HTN is more serious among women than men. Until recently, however, efforts to reduce CVD mortality focused primarily on men. The DASH diet is a proven behavioral strategy to reduce blood pressure, however, national adherence rates are poor. Using digital health tools may help to improve adoption of the DASH diet. Digital health approaches capitalize on the ubiquitous utilization of mobile technologies and have broad dissemination potential. There have been few efforts to test a DASH intervention via digital health and none directed to women. This proposal will leverage a commercial diet tracking application and our existing intervention technology platform to test the feasibility of DASH Cloud, a digital health intervention for women with pre-hypertension and hypertension. The primary outcome is DASH diet adherence.

Background and Significance

Women need better interventions for hypertension self-management. One-third of and pre and postmenopausal women have hypertension[1] and only half of those women have their blood pressure under control. Uncontrolled blood pressure is the strongest predictors of heart disease – the leading cause of death among women. This is because heart disease is more serious among women than men. After a heart attack, women have lower survival rates and a poorer quality of life. Despite these gender-based differences in outcomes, our understanding is limited about how to address the unique issues that women face in managing hypertension behaviorally. Developing behavioral interventions specifically for women in the pre- and postmenopausal period is critical to alleviating the burden of hypertension and heart disease among women.

Improving diet is vital to managing hypertension. Along with medical management, behavioral interventions can play a pivotal role in the management of hypertension. The DASH (Dietary Approaches to Stop Hypertension) diet is a nationally recognized dietary treatment for hypertension. DASH emphasizes nutrient-rich foods such as fruits and vegetables, whole grains, and low-fat dairy products, and limits sweets and sugar-sweetened beverages, as well as foods high in sodium, saturated fat and cholesterol. Two seminal randomized controlled feeding trials established the blood pressure-lowering effect of the DASH diet. Many subsequent studies and effectiveness trials have validated its effect.[8,9.10] The initial DASH trial was a four-site, randomized, controlled feeding study led by co-investigator, Dr. Laura Svetkey. Compared to a control diet typical of U.S. consumption, DASH produced reductions in systolic and diastolic blood pressure of 5.5 and 3.0 mmHg respectively (each $p<0.001$). Blood pressure changes were evident in subgroups of men, women, racial/ethnic minorities, whites, and in both hypertensive and normotensive participants.[7] DASH was particularly effective for those with hypertension (systolic (SBP) and diastolic (DBP) change: -10.7 mmHg and -4.7 mmHg, respectively), and among blacks (SBP and DBP change: -6.8mmHg and -3.7 mmHg).[11] The follow-up DASH–Sodium trial, also led by Dr. Svetkey, demonstrated that reducing sodium intake while consuming the DASH diet produces larger blood pressure reductions and greater increases in blood pressure control than either DASH or sodium reduction alone.

Digital health approaches are promising intervention channels for improving DASH diet adherence. Almost all Americans own a mobile phone and 97% of mobile phone owners use text messaging. Digital health approaches can capitalize on the ubiquity of mobile technologies and allow us to reach affected populations with highly personalized content at low cost. Despite this ubiquity, interventions using text messaging for hypertension self-management primarily rely on reminders for tracking and medication adherence without diet and physical activity behaviors or feedback. As such, they are less effective. Our work has shown that we can provide obesity treatment to a variety of populations, including women, through

mobile technologies. Our work is unique because we go beyond simply sending tips or reminders. Rather, our interventions prescribe tailored behavior change goals, prompt tracking of these goals via mobile technologies and then send immediate tailored feedback. As a result, we have been successful in achieving high rates of tracking adherence[17,20] I aim to leverage my experience working on digital health intervention trials to improve adherence to the DASH diet among women with hypertension.

This study will have several areas of impact. We will establish the feasibility of a novel digital health-based approach for disseminating the DASH diet for women, using Nutritionix, a commercially available diet tracking app that thousands of Americans are already using. The data from this pilot feasibility trial will set the foundation for a larger, fully-powered R01 grant to examine whether DASH Cloud can improve blood pressure outcomes among women with hypertension. This proposal will focus on the following specific aims.

Aim 1: To modify existing technology platforms and develop content for the DASH Cloud intervention for women with hypertension or pre-hypertension.

Aim 2: To test the feasibility of the DASH Cloud intervention compared to education control among women with hypertension or pre-hypertension (n=up to 65) via a 3-month randomized controlled trial.

- Utilization of intervention components – daily diet tracking rates, and clicks to skills training materials.
- Change in dietary patterns– 3-month change in DASH diet adherence score (as measured from 24-hour recalls)
- Acceptability - patient satisfaction and intention for continued use as measured by surveys.

Aim 3: To evaluate the preliminary efficacy of the DASH Cloud intervention relative to education control on blood pressure, weight, and medication adherence at 3 months.

Design and Procedures

Study Design

We will enroll up to 200 adult women aged 21-70 with pre-hypertension or hypertension in order to qualify up to 65 to be randomized in a 3-month randomized controlled trial to test the initial feasibility of *DASH Cloud*, a digital health intervention for women with HTN. More details are described below.

Selection of Subjects

Setting: We will recruit community participants from the Durham, NC area. Using designated space at the Sarah W. Stedman Center for Nutrition and Metabolism at Duke and Duke Digital Health, participants will complete baseline and follow-up visits where they will complete physiological and survey-based data collection.

Sample: We will randomize participants to either the DASH Cloud intervention or to DASH Light education control and follow up at 3 months.

Inclusion/Exclusion:

Inclusion: ages 21-70 years; BMI >18.5 kg/m^2; on self-reported use antihypertensive medication or self-reported systolic blood pressure 120-159 mmHg and/or diastolic blood pressure of 80-99; current use of a smartphone with an updated operating system, data plan, willingness to be texted daily or weekly; an active email account; spoken and written English fluency.

Exclusion: CVD event in prior 6 months; active malignancy; active psychosis or recent psychiatric institutionalization; current pregnancy or lactation; current participation in a similar trial.

Subject Recruitment and Compensation

We will recruit participants using a multi-pronged strategy: 1) we will distribute flyers at local gyms, community centers, grocery stores, and health and wellness stores; 2) we will collaborate with Duke Early Phase Clinical Research (formerly DCRU) and the Duke Primary Care Research Consortium (PCRC) to request that they query their database for subjects who fit the inclusion/exclusion criteria and email them information about the study, including a link to the study websites (dashcloud.org or dashcloudstudy.com). These URLs do not contain study information, rather they just redirect participants to the REDCap screening survey; 3) we will use social media (Twitter and Facebook) to advertise the study and direct interested subjects to the study web site, and; 4) we will email community organizations, including local health departments and churches, information about the study, including a link to the study web site. 5) We will use the contact list for participants who were ineligible for Study D0822 Comparing Self-Monitoring Strategies for Weight Loss (Campus IRB) that acknowledged they were interested in being contacted for other studies. 6) We will use ResearchMatch.org to connect with potentially eligible subjects. We have used these methods successfully in many of our team's previous studies.

Those who respond to study marketing will undergo preliminary eligibility screening via a REDCap eligibility survey linked from our study website. Those who are deemed potentially eligible will be given a link to a video outlining study participation (https://www.youtube.com/watch?v=4UW23zTuaZQ). Interested participant will then be asked to complete an online consent form. After the consent form is signed, participants will be sent a REDCap link to fill out questionnaires asking about sociodemographic and behavioral characteristics. Participants will be asked to complete 2 dietary recalls on the ASA-24 website. Study staff will send instructions to the participant to download and setup the Nutritionix app before their initial baseline visit. If needed, participants will be provided assistance from study staff to download and setup the app at the initial baseline visit. They will then be asked to take part in an initial baseline study visit at the Sarah W. Stedman Center for Nutrition and Metabolism at Duke or Duke Digital Health. At the first visit, the study staff will complete physiological data collection to confirm final eligibility. Participants with a blood pressure outside the upper range of eligibility will be told they can no longer participate. At this visit, study staff will provide instructions for how to use the app. We will ask women to track their diet for one week. After one week, if they successfully tracked at least 4 of 7 days, they will be asked to attend a 2nd baseline visit where they will be randomized and enrolled in the study. At this visit, participants will also receive a 30-minute in-person, individual orientation to the DASH diet to learn what is required in each study group. Participants who do not qualify based on non-inclusion, exclusion, or non-consent will be tabulated, noting the reason for non-participation. All subjects who attend the two baseline visits will receive a Duke ClinCard with a value of $25. Enrolled subjects will receive another $25 via their ClinCard after attending the 3-month follow up visit.

Consent Process

INFORMED CONSENT

The informed consent process for this study involves several components.

- First, participants will hear about the study from one of the previously-described recruitment methods.
- Next, participants will complete an online screening questionnaire. If preliminarily eligible, participants will then be shown a video that provides an overview of study participation and risks. Once they watch the video (script and link uploaded into full protocol section), participants will review the online consent form via REDCap. If they have any questions about consent before signing, participants can ask for a followup in the REDCap survey. The study team will receive a prompt via REDCap and follow-up via phone with the participant. If there are no questions and/or

after the participant has had their questions answered by research staff, participants will provide a signature in the online consent.

- Once they sign the online consent, a pdf version of the consent is sent to the participant via secure email. Each participant's signed informed consent form will also be kept on file by the investigators for possible inspection by regulatory authorities.

The mobile health intervention involves a potential risk of loss of confidentiality of the subject's mobile device number and the self-reported lifestyle habits regarding nutrition only. The data collection stored on REDCap involves a minimal risk of loss of protected health information. We will use the language in the consent form to inform patients of these risks.

Subject's Capacity to give legally effective consent: see above, "consent"

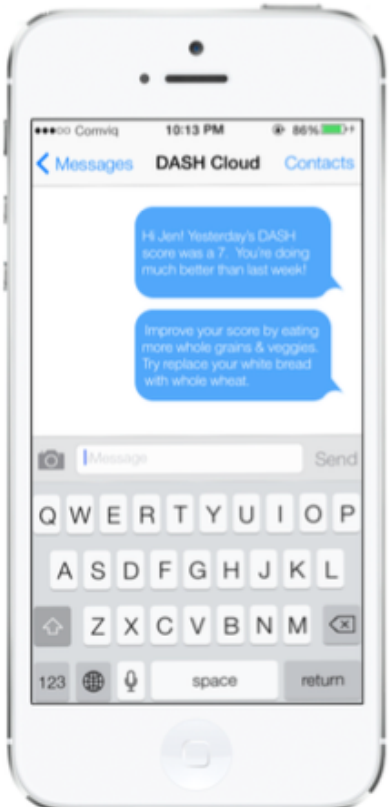
Study interventions:
Participants will download and install the Nutritionix application ("app") onto their smartphone and study staff will setup the study-specific account to send data to Duke's software system called Prompt. Participants will be instructed to input their dietary intake daily for three months using the Nutritionix app. *DASH Cloud* will access participant's dietary intake data through the Nutritionix application programing interface (API) for three months. Participants' data will automatically be uploaded from the Nutritionix app via the API that links the device with *DASH Cloud*. This secure system will store participant ID, email and password credentials for logging into Nutritionix, phone number, and all tracking data. *DASH Cloud* will run an algorithm and send a daily or weekly feedback text message with a score reflecting DASH adherence for the prior days or week's food consumption using a previously validated scoring system.

Each week, we will also deliver a link via text to a video that displays content about a topic related to the DASH diet (e.g., how to get more potassium and less sodium - https://www.youtube.com/watch?v=gUbKisHsC6k&feature=youtu.be).

Control participants will be asked to use the Nutritionix app daily and receive publicly available written materials on the DASH diet at the baseline visit. After baseline, they will receive no other feedback via text message. Each intervention component is described in more detail below.

Tailored feedback texts. With DASH Cloud, as in several of our center's previous studies, we will provide tailored feedback about a participant's DASH adherence via fully automated daily or weekly text messages (see separate document with sample text messages). These feedback messages will describe both an individual's absolute performance and change over time (see Figure 2 for example). As shown, we also include theory-driven tailored content that reinforces successes, offers motivational strategies, and offers short behavior change tips. We will take this content from the extensive feedback library (insert link to box here) used in our other studies (PI Bennett: Shape - 2628 (Campus IRB); Track - B0033 (Campus (IRB)). The library contains verbiage options with major categories (e.g., user is improving, stable, declining) and subcategories (e.g., motivational messages, validation, reinforcement, challenges). We will recommend that individuals self-monitor their dietary intake daily and we will prompt users with engagement messages when they don't track. In our past several trials, we have become adept at developing messages that are appropriate for the constraints of text messaging.

Figure 2. Sample feedback texts



Behavioral skills training. We will include behavioral skills training content in video format created by our study staff, drawn from materials about DASH available from the National Institute of Health, National Institute of Lung, Blood and Health (https://catalog.nhlbi.nih.gov/pubstatic//06-5834/YourGuideLowBloodPressureBrief.pdf). The skills training lessons cover a wide range of topics (food labels, recipe modification, reducing fat, sodium, etc.). We will send links to this content in weekly texts. A sample video can be found here: http://bit.ly/2q0Hvxd.

Measures

Engagement: The primary feasibility outcome is utilization of intervention components at 3 months.
1) Diet tracking: proportion of participants completing daily dietary self-monitoring
2) Review of skills training: number of clicks to skills training via video tracking software.

DASH adherence: Dietary intake data will be collected using NCI's Automated Self-Administered 24-hour Recall tool (https://asa24.nci.nih.gov/). Participants will be prompted via email by study staff to complete the ASA-24. We will collect 2 dietary recalls at baseline and 3 months. To determine DASH adherence, we will use a previously determined index based on 11 food groups (e.g., fruits) and nutrients (e.g., sodium). We have experience using the ASA-24 in a previous trial with much success.

Patient satisfaction: We will use measures that we have delivered successfully in prior studies.

Blood pressure: Blood pressure will be measured at baseline and 3 months in the upper arm in triplicate at 1-minute intervals. Measurements will be obtained by trained study staff using the validated Omron HEM-907XL blood pressure monitor.

Sociodemographics: We will collect self-reported age, race/ethnicity, health insurance, income, employment status, education, current health status, household size, and marital status at baseline only.

Risk/Benefit Analysis

The primary risk to the subject is loss of confidentiality. The mobile technology carries a higher risk of this than the other stored data due to the nature of mobile technology and the servers used to deliver the intervention. We will follow data security plans used in our previous and current studies, which were developed with the guidance of Duke Office of Information Security. The details are explained below in the data and safety monitoring section.

Potential benefits for study participants include improved blood pressure and consequent reduction in cardiovascular risk. An additional benefit for some participants may be personal satisfaction in being part of a study that may have major public health implications for the community. No benefit from participation can be guaranteed. Potential benefits to others include the possibility that this research will help researchers evaluate the feasibility and efficacy of the DASH Cloud system in promoting DASH diet adherence. The minimal health risks to participants listed above are offset by the potential benefits to them and to society.

Cost to the Subject

No costs are incurred by the subject, unless the subject is charged for receiving text messages or data usage for watching videos. This is very uncommon, and if it occurs, the cost is typically less than 3 cents per text received.

Data Analyses and Statistical Considerations

We will perform descriptive analyses to determine engagement and feasibility. Linear mixed modeling will be used to test for across group differences in DASH adherence and other secondary outcomes. Our model will

include group, time, and a group by time interaction, and will be fitted with a full maximum likelihood method using all data. As this is a feasibility study, we have estimated sample size from our previous text messaging trial where we saw strong engagement; 50% texted daily and 85% texted at least 2 days/week.

Data and Safety Monitoring

Study records that identify patients will be kept confidential as required by law. All data will be marked with a unique code number for storage at Duke University Health System in accordance with Duke's Institutional Review Board's guidelines and policies. All data collection will occur in private settings where patient survey responses cannot be seen or heard by others. Patients can refuse to answer any of the questions or stop participation in this study at any time.

Mobile technology: Information collected by Nutritionix mobile app is subject to the terms of use. Many apps make claims that they are secure, compliant with federal privacy regulations, and used and tested by other academic centers. However, any mobile app that is downloaded carries potential security risks, and Duke cannot guarantee that these mobile apps are free of risk. Some apps may be able to perform hidden functions or may have security flaws that allow unauthorized access to information. We are unable to fully tell participants what information these mobile apps can access or change on their phone or what information from their phone may be stored outside of Duke. Participants will be encouraged to limit personal identifiers entered into mobile applications only to those that they wish to voluntarily share with others.

The *DASH Cloud* environment is processed and stored on Heroku, an application server platform. This platform will support the following *DASH Cloud* services: the *DASH Cloud* database, text message (SMS) communications via Twilio, software logging, and file serving. The *DASH Cloud* environment sends and receives data to/from Twilio and stores data on Amazon S3. We will collect names, phone number, study ID, and nutrition information from Nutritionix in this database. *DASH Cloud* will receive nutrition information via the Nutritionix API on ten different nutrients (calories, potassium, magnesium, calcium, total fat, saturated fat, protein, cholesterol, fiber, and sodium). The data will be automatically analyzed weekly according to algorithms we embed. Study staff use a password-protected database to view study ID, name, phone number, and nutrition information for each day for each participant. Staff use multifactor authentication to log into the database. We will use Twilio to send text messages to participants each week. We will use Heroku to process data analysis for the engine. We will use Amazon S3 to store data; data will be encrypted when it is stored. These are companies outside of Duke that will have access to participants' personal information, including name, phone number, and self-monitoring data. If these data are further disclosed by them or their business partners, it may no longer be covered under the privacy protections. Text messaging does not provide a completely secure and confidential means of communication. Participants are made aware of the risks that are inherent in using text messaging.

Participants will complete the ASA-24 measure on https://asa24.nci.nih.gov/. Study staff will create an account and password credentials for participants. The account information will not include any personal identifiers. NCI will not have access to participant information. Study staff will keep a log of ASA-24 accounts matched to study information. This will be stored within a secure Duke box and have access restricted to key study personnel. Information from the ASA-24 will be downloaded from the NCI website and stored in a secure Duke box folder.

Participants' safety will be monitored by maintaining ongoing contact with field staff and convening monthly meetings between the investigators and project team. The study field staff will be trained and provided with a written protocol that instructs them to contact the study coordinator if any reportable AE occurs. The study coordinator will follow-up with participants within 48 hours to ensure that the event has been resolved and document actions taken.

Privacy, Data Storage and Confidentiality

Heroku's configuration obviates the need for physical server protections such as: protections against port scans, firewalls, VPN, vulnerability patches, log rotation, and automated database backups and off-site database backup storage.

In its place, the protections now in place are:

- Multi-factor authentication and strong passwords protect Web, shell, and console access to the Heroku dashboard.
- Application servers are inaccessible. These resources are virtualized and cannot be accessed via SSH or SFTP. The application itself is accessible only via SSL.
- No database configuration parameters (including host address, database name, password, and login) are stored in the application code or in the code repository. This follows the 12-Factor Security Protocol.
- All Amazon services are protected via the provider's IAM and 2FA tools. No identifiable information is stored on Amazon.
- Log files are available only through the Heroku dashboard. Log files do not reveal passwords, IP addresses, or PII. Identifying information is limited to the participant's masking study ID.
- SMS activity is protected by strong passwords and 2FA.

Further, logins to Heroku are severely restricted. Currently, only two people have access to all resources: one is the developer and the other is program manager. Research staff does not have access to any computing resources. The information generated by this study will be kept for seven years after the date of last publication. Then it will be destroyed by shredding the paper copies and by securely deleting the computer files. Data management will take place under the supervision of Dr. Steinberg. Our group has developed extensive quality assurance procedures, including on-going quality control checks. After data analysis, we plan to disseminate the results of the study via journal publications and presentations. We will not collect information about illegal activities. Further, we do not expect that participants will reveal information subject to reporting because the Research Assistant will be instructed to maintain close adherence to a protocol that involves discussing only behavior change efforts related to diet.

Electronic study data storage: A REDCap database will be created and shared with key personnel on this study, and used to store information collected at screening and in the "Measures" section above. Using encrypted study computers, a trained research assistant will send links to REDCap surveys to consented subjects via email. At the time of analysis and after data cleaning, we will export the data from REDCap into secured statistical software as above. All output analyses will be stored on a secure Duke Box folder created for this study and with access restricted to key personnel.

Physical data storage: All hard copies of participant data will be stored in office or lab space at the Duke Global Digital Health Science Center at 310 Trent Dr. in a locked office in a locked file cabinet or in the CRC's office space accessed by badge in a locked filing cabinet on the 10th floor of Erwin Square Plaza 2200 W. Main St.