HSR&D Data and Safety Monitoring Board
Data Analysis Plan (DAP) v1

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Title: Continuing the Conversation: A Multi-Site RCT Using Narrative Communication to Support Hypertension Self-Management for African American Veterans – (IIR 17-185)

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Background

This is a randomized controlled trial aimed at improving hypertension self-management and lowering blood pressure (BP) in African-American Veterans. In previous HSR&D-funded work, we created video-recorded stories told by African-American Veterans with hypertension, in which Veterans shared strategies for effective self-management. In this study, we 'begin the conversation' by showing these videos to Veteran participants, inviting them to select the peer narrative that is most compelling. We then 'continue the conversation', offering longitudinal support via 6 months of narrative-aligned text messages. Texts will cover key subject areas, providing education, reminders and periodic assessments, and include quotations derived from and aligned with transcripts from the chosen narrative. We will measure the intervention's impact on BP, self-efficacy and self-management behaviors, and conduct a cost analysis.

Rationale for Study Sample Size

We will pilot the process of providing in-person guidance to 20 Veterans as they (a) View the Veteran videos; (b) Select a preferred video narrative; and (c) Sign up to Get texts through the HealtheDialog Texting system. The pilot will contain usability testing and a formative evaluation of the Veterans' experiences. We will purposefully sample 10 Veterans from each site (total of 20) and will aim to include 4 women Veterans (2 per site). We will pilot the process of (1) guiding the Veteran in selection of a preferred veteran storyteller after viewing all stories; (2) using this choice to inform selection of a texting protocol; (3) Receipt of 1 month of texts; and 4) follow-up assessment at the end of 1 month. We will assess feasibility of two options for Veterans to access texts: (a) via regular texting, available on all text-enabled phones; (b) via HealtheDialog 'App' which allows study team tracking of text opening (but is available only on Smart phones). We will assess completion rates (how many Veterans have difficulty or discontinue texts early) and perceptions (e.g. "I felt connected to the storyteller while receiving texts", "the number of texts was: too few, just right, too many"). The formative evaluation will include a qualitative interview with all Veteran participants to understand their experiences with the CTC protocol. Our semi-structured interviews will cover their overall experiences, as well as specific questions about the enrollment process, frequency and content of messages. Interviews will be audio-recorded with brief, descriptive field notes. We will then Test CTC by conducting a randomized controlled trial with the following setting and sample: 600 African-American Veterans with poorly controlled hypertension. Veterans will be recruited from two VA healthcare sites with known disparities in hypertension control.

Data Collection

We will seek a HIPAA waiver from the IRB for data access in order to identify potential participants. • We will include Veterans who have been receiving care at the recruiting VA site for ≥1 year prior to recruitment, with 2 or more visits documented over the past year. We will include Veterans who have documented HTN (ICD10 diagnosis codes: I10-essential HTN) during this 1-year period. We will include only patients who self-identify as African American or Black. In addition, participants must be on at least one medication for BP. Eligible participants will need to have access to their own or a family member's cell phone or smart phone for participation and they must be willing to use this phone for receipt of text messages over a 6-month period. We will exclude Veterans who participated in our previous VA Stories study.

We will exclude patients based on responses from the screening questionnaire conducted during the initial phone call, which screens for cognitive disabilities that might prevent them from

actively or reliably participating in the interviews. We will include both women and men in the study; given that 5% of the VA patient population is women, we plan to oversample for women in order to expect a similar proportion of women to participate in the study. Based on our response rate in previous studies we are confident that approximately 70% of patients will agree to participate. We will track demographics and co-morbidities and BP level, as well as reasons for refusal for those who decline participation. We will delete PHI on potential participants who decline or who do not respond from our analytic database.

For each potentially eligible patient, the RA will contact the patient by telephone, explain the study and ask several eligibility screening questions including the patient's race/ethnicity. We will include only patients who self-identify as African-American or Black. Then the RA will ask if the patient wishes to participate and will schedule a time for the patient to come to the clinic. We have had success in multiple prior studies using this procedure.

As listed in the table below, we will collect 7 data elements: (1) Veteran characteristics; (2) Intervention dose/exposure; (3) Narrative Communication measures; (4) Social Cognitive-Theory-based measures; (5) Hypertension management behaviors; (6) Blood Pressure (BP) (blood pressure will be checked by RA at in-person visits at baseline and at 6 month follow up); and (7) Implementation Data including Process Measures and measures of Fidelity. We will gather these elements through initial data collection (CDW), over-the-phone screening survey, baseline visit and follow-up visit observations and surveys, texting system and phone calls to participant.

• **Table 8. Seven Key Data Elements**	Timing	Source
1.Veteran Characteristics		
Participant Demographics	1	S,C
Comorbidities, VA Utilization	1	C
2. Intervention Dose/Exposure		
Number of videos watched and time spent viewing	2	S
Which was selected video?	2	S
3. Narrative Communication		
Video Transportation Scale	2	S
Homophily (personal relevance)	2	S
4. Social Cognitive Theory		
Beliefs About Medications (BMQ)	1,4	S
Self-efficacy for hypertension (e.g.: MASES-R, PEPPI)	1,4	S
5. HTN management behaviors		
Avoid Salt, Be Physically Active, Monitor your BP(H-SCALE, PEMH)	1,4	S
Talk with your doctor (H-SCALE)	1,4	S
Take Your Medicines: Morisky ; and administrative data adherence (MPR)	1,3,4	S, C
6. Primary Outcome (H1)		
Measured BP (systolic/diastolic)	1,4	BP, C
7. [**Implementation Data/ Process Measures/Fidelity**]	3,4	RA, S, T
Text message opening (subgroup)	3	T
Responses to text assessment	3	T
Confirmation of text receipt	4	S
Phone calls for texting assistance	3	RA
Staff time spent for implementation	3	RA
Persistence/Early Discontinuation of Texting Protocol	3	T
Reasons for discontinuation	5	P
1=Baseline, 2=Immediately post-Video Viewing; P, 3=Repeated throughout 6-month study period, 4 = six-month follow-up; 5= phone call to drop-out. Source: S = Survey; C = CDW data; RA=Research assistant; T=Texting System; P=phone call to participant; BP = Blood pressure cuff, standard protocol		

Randomization

Random allocation to CTC or control will be stratified by site, and within each site, we will stratify by sex (women/men). Our statistician will create a randomization table with randomization blocks varying between 5 and 10 subjects.

Interim Data Analysis

We do not plan to conduct interim data analysis

Missing Data/Subject Dropouts

Missingness not at random may introduce bias. Advance planning through sound data collection and quality control will be used to minimize this bias. We will use all available data regardless of whether a patient has a complete record. Group means will be reported as least-squares means, the predicted marginal mean values, or those that would be expected with a balanced design. Participants with missing data will be compared to those without. Inverse probability weight in and pattern-mixture modeling using the longitudinal data structure, for non-ignorable missing data, will be considered.

Covariates for Adjustment Models

We will look at the balance of randomization and adjust for demographics and behavioral variables if imbalanced.

Data Transformations

N/A

Analytical Sets

We intend to include all patients in intent to treat analysis.

Monitoring Adverse and Serious Events

Because this is a low-risk trial of an educational DVD, we do not expect SAE's or AE's. We will plan to report any SAE's defined as death of participant or hospitalizations reported at 6-month follow-up.

At the time of recruitment, patients experiencing hypertensive urgency, as defined by JNC as Blood Pressure Systolic >= 180 OR Diastolic >= 120, regardless of symptoms, will be referred to urgent care and a notification letter will be sent to their primary care physician. If a patient reports symptoms related to the hypertensive urgency, even if before viewing the intervention DVDs, this will also be reported as an AE. AE's also include stress related to watching the DVD. All AE's reported at baseline and 6-month follow-up will be recorded and submitted at Continuing Review.

Analysis Plan

We will first identify key distributional features for all variables of interest (non-normality, skewness, ceiling or floor effects, presence of implausible values, outliers, etc.) and calculate descriptive statistics. We will document recruitment and retention with a CONSORT diagram. Following best practice, baseline differences between intervention and comparison groups will be based on standardized differences, not simply tests of statistical significance. All primary hypotheses will be tested by intent-to-treat; secondary analyses will account for important covariate imbalances between groups, levels of adherence to the intervention protocol, and missing data. All analyses will be two-sided, with alpha error = 0.05.

Hypothesis 1: (Primary Hypothesis) The difference in blood pressure from baseline to 6 months will favor CTC intervention group by 5mm Hg, compared with the change in control.

H1 postulates a difference-in-differences between study groups. We will use study group, assessment time, and group-time interactions as predictors in regression models. With this parameterization, the coefficient for the group-time interaction represents differential change for intervention vs. comparison. Multilevel mixed-effects generalized linear models will: (1) model the outcome distribution with an appropriate link function; (2) account for clustering of repeated measures within individual; (3) adjust for observed group imbalances as secondary analyses; and (4) support secondary mediation analyses as described below. The most general structure of the mixed model is $\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\boldsymbol{\gamma} + \boldsymbol{\varepsilon}$, where the $\mathbf{y}$ matrix is the observed outcomes, $\boldsymbol{\beta}$ is a vector of fixed-effect parameters with design matrix $\mathbf{X}$, $\boldsymbol{\gamma}$ is a vector of random-effect parameters with design matrix $\mathbf{Z}$, and $\boldsymbol{\varepsilon}$ is a random-error vector. We will assume that $\boldsymbol{\gamma}$ is independent of $\boldsymbol{\varepsilon}$ and has a multivariable normal distribution with mean $\mathbf{0}$. We will examine residuals to seek gross violations of underlying assumptions, and explore approaches to address violations such as variable transformation, outlier trimming, or placing bounds on the extent that extreme observations can affect conclusions.

Hypothesis 2: Self-efficacy and hypertension management behaviors during 6-month follow-up will be greater for those in the CTC intervention group than comparison.

As Self-efficacy and HTN management behaviors (salt intake, physical activity, doctor-patient interaction, monitor BP) will be measured as self-report at baseline and follow-up, we can measure these as differences in change ("difference-in difference") between study groups, and mirror the analysis plan for H1.

In addition to self-report, for "Take your medicines" (medication adherence) we will use administrative data to calculate refill-based measures (ie: MPR) for each HTN medication and average these over six-month periods (before and during intervention). We will again use a repeated measures analysis (like H1).

Secondary Analyses: Covariates to account for substantial imbalances in group characteristics will be added to our main regression models. Secondary analysis will occur for the separate measures of HTN management behaviors and BP change. As in our prior trials, we will also conduct secondary stratified analyses above and below the median mean arterial pressure at baseline (in our prior VA stories, we found the effect greater in those below the median baseline BP (see Section B5.b)). We will also analyze effect by site, by chosen storyteller and by age group. Further, using the administrative data for MPR, we have a pragmatic opportunity to study sustainment of effect after the six-month CTC is completed. For the subset of patients with six-months completed before Year 4, we will also calculate MPR six months after the end of CTC. In a secondary model, three time periods (before, during, after CTC) will be jointly tested using "segmented regression" to account for the three time periods.

Hypothesis 3: The effect of CTC on BP will be mediated by the more proximal measures of (H3a) cognitive and emotional processes (i.e.: emotional engagement with stories, self-efficacy), and (H3b) HTN management behaviors.

For this hypothesis, we will conduct a formal mediation analysis. Initial methods will follow Barron and Kenny's

protocols, with more recent advances developed by MacKinnon. Mediation occurs when an intervention changes the rate of uptake of an intermediate process that directly influences outcome. Mediation analysis can help to disentangle the mechanisms which may contribute to intervention effectiveness. We will estimate the proportion of the intervention effect that is transmitted through each of these mediators and quantify the precision of these estimates with 95% bias-corrected and accelerated bootstrap confidence intervals. Thus, we will be able to quantify the relative proportional mediation for each of the measures listed in Hypothesis 2.

Power Calculations

Power is driven by our most distal outcome, Blood Pressure (H1). Our sample size calculations are performed to detect a difference in the change in BP, comparing intervention and control. We carry out the calculations to determine sample sizes that would detect significant effects at the 2-sided 0.05 level, at 80% power. Difference in BP for our video stories alone ranged up to 6mm Hg, and as low as 2.7mm Hg (adjusted difference in systolic BP in VA stories). We have designed CTC to result in a stronger effect, compared with our prior VA Stories. With this rationale in mind, we calculated power to achieve a conservative and meaningful difference of difference in BPs of 5mm Hg. We used a repeated measure power calculation to estimate the group-time interaction for the difference of differences statistical analysis. Derived from our prior work, follow-up rates, within-person correlation of repeated measures of BP and standard deviation of a single BP measurement were used for the estimates. With our recruited sample of 600 (and assuming follow-up rates, over-time within-person correlation, and BP standard deviations from our prior work (85% follow-up, correlation = 0.5, SD = 18 (equivalent to variance of 324)), we have over 80% power (alpha 0.05) to detect a difference of 5mm Hg. In fact, we calculated power for a range of scenarios, and are able to maintain the 5mm Hg detection with a lower follow-up rate of 82%.

Power for H2 & H3: Conceptually, the CTC intervention impact on blood pressure is possible because the intervention will have an effect on more proximal cognitive and behavioral outcomes (H2) that then mediate the main effect (H3). Thus, theoretically, power for group-by-time differences in the scales for H2 will be greater than H1, and thus we should be over-powered for these measures. We calculated H2 power for difference-in-differences analyses. As each of the scales were different, we report minimum detectable differences as effect sizes. For example, Morisky Medication Adherence Scale (MMAS) response categories are yes/no for each item with a dichotomous response and a 5-point Likert response for the last item. The MMAS categorizes low adherence as a score of <6, medium adherence as a score of 6 to <8, and high adherence as a score of 8. In a 2008 publication validating MMAS in a complex patient population (with 75% African American and 54% with an income < $5,000), mean score was 6 (SD 1.6). We found similar mean (SD) in our prior storytelling interventions. A one-point MMAS shift has been reported as clinically important (which translates to an effect size (r) = 0.29 assuming the mean and SD above). Repeating our repeated measures power calculations formulas from Aim 1, with a follow-up of 80%, we have 80% power (alpha 0.05) to detect an effect size of 0.29 with an over-time correlation coefficient as low as 0.3, and each MMAS administration SD as high as 3.0. This estimate is conservative as the SD is over-estimated, and the correlation over time will likely be higher. Thus, we are more than powered to detect an effect size of 0.29 for MMAS, and by extension our other H2 scales.

Further, for H3, our simulation studies (Fritz and MacKinnon) show that a total sample as small as 200 is adequate for 80% power with standardized effect sizes for the mediation paths of 0.29 or larger. Thus, we have considerable power to detect small effects in the mediation analyses.

Cost Analysis

We will conduct a cost-identification analysis (CIA) to assess the cost of providing the CTC, and a budget impact analysis (BIA) to assess impact on costs to a VA medical center of implementing the intervention. To estimate costs and the potential budget impact for a facility implementing CTC, we will obtain cost data from VA Managerial Cost Accounting (MCA) datasets (formerly known as Decision Support System (DSS) National Data Extracts), consultation with the Health Economics Resource Center, and consultation with the study sites. Costs will be tracked for each intervention component: viewing stories, selecting preferred narrative, and delivering text messages. We anticipate that the majority of costs will be related to staff time. In addition, we will also estimate the staff time associated with the control group. To obtain staff time estimates, we will have RAs track the time needed for each intervention component, and also for the control group. RAs will in addition track time spent handling phone calls for assistance with the texting system for both intervention and control (we will maintain a phone line during recruitment and follow-up). Additionally, we will describe the number and types of staff positions required for the intervention and control. We will then estimate wages based on staff positions using data obtained from the facility. We will use a similar process to estimate the training costs related to staff time. In addition to staff time, we will estimate the costs of supplies for showing the videos, training staff, and the toolkit (training guides and Veteran handouts). The Aim 3 economic analyses will be primarily descriptive statistics. Using the cost estimates of supplies, staff time, and the potential savings to the healthcare system that result from the intervention (e.g., decreases in missed appointments, ED visits, or HTN-related hospitalizations), we will calculate the budget impact of implementing the intervention from the perspective of the facility. We will follow the guidelines outlined for best practices in BIA. We will create tables to describe the assumptions of our inputs and outputs, and perform sensitivity analyses to examine how changing the model assumptions impacts the potential costs for the facility.