Patient Centered Health Technology Medication Adherence Program for African American Hypertensives

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ABSTRACT/SUMMARY

Efforts to improve medication non-adherence (MNA) and blood pressure (BP) control in patients with hypertension (HTN) have met with limited success. Innovative approaches are needed that are acceptable, sustainable, efficacious, and easily disseminated. There have been no randomized controlled trials (RCTs) evaluating the application of theory-driven, patient centered, mobile health (mHealth) technology programs among African Americans (AAs) with MNA and uncontrolled HTN. The proposed research will test and refine the Smart phone Medication Adherence Stops Hypertension (SMASH) program. SMASH includes multi-level components: 1) automated reminders from an electronic medication tray; 2) tailored text message/voice mail motivational feedback and reinforcement guided by self-determination theory and based upon adherence to daily medication and BP monitoring and 3) automated summary reports and direct alerts to providers. A 6-month, 2-arm (SMASH vs. enhanced Standard Care [SC]) efficacy RCT will be conducted in 192 AAs (21-59 years old) with electronic monitor derived MNA and repeated clinic and 24hr BP verified uncontrolled HTN. Evaluations will occur at baseline, months 3 and 6, and post-trial follow-ups at months 12 and 18. Specific aims are to test the hypotheses that, compared to the enhanced SC cohort, the SMASH cohort will demonstrate significantly improved and sustained changes in: 1) **Primary Outcome Variables**: a) Medication adherence: % with electronic monitor-derived adherence scores >0.90; b) BP control: % meeting JNC8 guidelines for BP control (resting BP <140/90 mmHg). 2) **Secondary Outcome Variables:** a) % reaching and sustaining 24-hr ambulatory BP<130/80 mmHg; b) % of provider adherence to JNC8 guidelines as measured by timing of medication changes and c) patient changes in Self-Determination Theory constructs (e.g., competence and autonomous motivation). 3) **Exploratory Outcomes:** a) moderators (e.g., gender, age, income) and mediators (e.g., perceived severity of disease, med side effects, depression symptoms, etc.) of medication adherence and BP control; b) cost effectiveness and c) physical risk factor changes (cholesterol, LDL, HgA1c, blood glucose). After final follow-up evaluations, focus groups with random sample of SMASH subjects (total n=32) and healthcare providers (total n=~12) will assess key user reactions including acceptability, usability, salience and aids/barriers to sustainability. Data from RCT and focus groups will be triangulated to further refine and optimize SMASH and prepare for a multi-site effectiveness RCT. Our long-term objective is to reduce premature mortality among AAs by developing effective and sustainable mHealth chronic disease medical regimen self-management programs including medication adherence, bio-function monitoring (e.g., BP) and timely bidirectional contact with healthcare providers.

NARRATIVE

Interventions that address medication nonadherence among chronic disease patients must be acceptable, sustainable, and easily disseminated by clinicians. We will test and further refine a smartphone delivered, tailored medical regimen self-management program for African Americans with uncontrolled hypertension that will facilitate medication adherence, BP control, and clinician oversight. With demonstrated effectiveness in future trials, the intervention will ameliorate the risk of future comorbidities (e.g., hypercholesterolemia, diabetes), cardiovascular events (e.g., kidney failure, stroke, heart attack) and associated premature mortality.

INTRODUCTION TO REVISED APPLICATION

The thorough reviews guided our new pilot research on Smart Phone Medication Adherence (MA) Stops Hypertension (SMASH) developed for African Americans (AAs).We ran a 3rd feasibility trial (n=24), published 3 articles (2nd mHealth attitudes survey and results of 2 feasibility trials), made SMASH refinements based upon subjects' post trial feedback and made changes in our approach and analyses. **Strengths:** high clinical significance, no RCTs using mHealth in this domain, focus on both MA and BP control, use of 24-hr BP, rigor of using RCT design, time and attention control group and follow-up assessments, intervention theoretically driven, use of cultural tailoring and strategies for low literacy, promising preliminary data, cost effectiveness analyses, excellent environment and investigators. **Weaknesses:** Outlined below with Reviewer (R) comments in *italics* followed by our responses. Text changes are noted by a vertical line in the right margin.

OVERALL IMPACT, SIGNIFICANCE, INVESTIGATOR(S) & INNOVATION: *inclusion/exclusion criteria not in grant* (R1&R2).We apologize for placing too much of that info in Human Subjects. It is now in section D.2 (and Human Subjects [1.a.]) *Unclear how nonadherence due to smartphone service loss will be handled (R1):* In our feasibility trials we observed high BP monitoring adherence via phone app (~88%), nonadherence tended to occur when cellular service was disrupted. We budgeted for 40% to receive a smart phone or data package to cover phone or service loss during the trial (in D.4.) *Justify relatively limited age range (21-59 yrs) (R1):* We are recruiting AAs from a federally qualified health center (FQHC) with sole diagnosis of HTN (n=2,619; mean age ~45.3 yrs). Majority of those ≥ 60 had multiple comorbidities & JNC8 BP control goals differ for patients <60 vs ≥60. *Concern PI may not have time (25%FTE) to devote to project (R1):* Within 2 mos of start date for this grant, Dr. Treiber will be covered 50% FTE on grants (R21 & RO1 will have expired; see bio). He has a long track record of running successful concurrent trials. An experienced full time project manager has been added, Dr. Chandler. *Consider adding someone with usability testing background (R1):* Dr. Ken Resnicow is a consultant with expertise in user centered, iterative design in web/app programs including use of various usability evaluation tactics (e.g., expert heuristic & end user think aloud evals, questionnaires; see bio & letter). *SMASH not highly innovative, been used in other patient groups(R1):* Our patient centered design revealed significant heterogeneity of influence of cultural heritage/acculturation and numeracy of chronic diseases (single vs multi-morbidities) upon MA and other health behaviors within & across ethnic groups. The mHealth program tailored to Hispanics is not culturally attuned for AAs. Our mHealth work with AA renal transplant patients with HTN, diabetes, etc. led to efforts to address poor MA before multi-morbidities develop. Our long-term goal is to prevent common events (e.g., stroke, heart attack) & slow progression of common comorbidities (e.g., chronic kidney disease, diabetes) due to uncontrolled HTN. SMASH for transplant patients required ~2 years of changes to become salient to AAs with solely uncontrolled HTN. We found those with only HTN often have greater MA problems (in C.1.3) & to be more challenging to establish sustained regimen adherence compared to HTNs with multi-morbidities. Experiences during trials & post trial interviews led to an iterative process of identifying highly salient motivational factors (values, beliefs, goals) not needed with multi-morbidity transplant patients (in C.1.5.) Others have observed similar challenges with single vs multi-morbidity HTN patients (in A.2.) This program (nor any earlier iteration) has not been nor is being tested using a fully powered RCT, much less within a low-income population & health system (i.e., FQHC). *No focus on med nonadherence (MNA) mechanisms besides self-motivation or how other diseases & meds affect HTN MA; no lit review on co-morbidities(R2):* We clarified HTNs with comorbidities aren't recruited (in D.2.) Exploratory analyses of MNA mechanisms now include med side effects, stress, depression symptoms, etc. (in D.10.) We added diabetes /CVD risk factor changes (e.g., TC, HgA1c) as exploratory outcomes. Recent trials show some newer HTN meds lower or at least do not increase these risk factors (in A.2.) **APPROACH & ENVIRONMENT:** *Limited description of clinics (R1):* 7 of 8 clinics have similar numbers of AAs with uncontrolled HTN and numbers of primary providers (MD, PA, NP; *M*=2.4). Lead site has 7.3 providers & generates ~45% of patient encounters (in Facilities & Resources). Clinic (=cluster) in our cluster RCT design will be a random effect in the analytic model & account for clinic site differences (in D.10). *More details on SMASH focus group protocol stratification process (R1):* We will identify 2 groups: 16 MA responders &16 partial/nonresponders stratified by clinic, age & sex. We will run 3-4 focus groups separately by group classification (in D.7.) *Measures of numeracy, usability & project evaluation needed; SMASH & control condition descriptions a bit vague (R1):* We added measures (in D.6.) & reworded SMASH & SC protocols for clarity (in D5-7.) *No model to guide analytic approach; how will data be integrated to provide cohesive story (R1):* We clarified in D.10 our conceptual model is built upon Self-Determination Theory with competence & autonomous motivation as primary MA mediators. We now include socio-demographic (e.g., age, income) & biobehavioral (e.g., med side effects, stress, sleep quality, etc.) factors as potential moderators & mediators of MA. Those results will guide an integrated causal model using structural equation modeling that will identify key active ingredients of SMASH to guide future refinements.

SPECIFIC AIMS

Hypertension (HTN), a major risk factor for renal and cardiovascular disease (CVD), affects ~33% of US adults.[1,2] Although blood pressure (BP) control (i.e., SBP/DBP <140/90 mmHg) has improved over the past 20 years, large ethnic/racial disparities continue. African Americans (AAs) have earlier onset and highest prevalence rates compared to all other ethnic groups.[3-6] Poor medication adherence (MA) remains the leading factor in uncontrolled HTN.[7-10] Randomized control trials (RCTs) have found that BP self-monitoring, med reminding tactics and use of case managers each improve adherence, therapeutic inertia and BP levels (see reviews[11-13]). However, only 40-50% reached BP control and BP often deteriorated after trial cessation. Although 24hr BP control is vital for optimal reduction of CVD events,[14] relatively few MA RCTs have evaluated 24hr BP control.[11,15,16] Our work and that of others indicate that HTN patients without comorbidities often experience greater MNA issues than HTNs with multi-morbidities in part due to lower motivation from low perceived disease severity.[5,6,17-26] Culturally sensitive, efficacious and sustainable BP control programs are needed, especially for AAs with sole diagnosis of HTN before comorbidities ensue. To our knowledge, no RCT has monitored, in real time, MNA and resting and 24-hr BP control in this high-risk population.

Formative Research: Our research with AAs with HTN found a high rate of cell phone use and high receptivity to mobile health (mHealth) technology.[20,21] We found poor planning and forgetfulness as leading contributors to MNA. Health literacy, values and beliefs (e.g., “skipping meds ok if feeling good”, “Gullah root medicine works the best”; “I praise God by taking care of his gift of life”) were influential in medical regimen adherence.

Feasibility RCTs: Feedback from AAs with HTN and their health care providers guided development, pilot testing and refinement followed by repeated feasibility RCT testing and refinements of a culturally tailored mHealth MA and BP control program for AAs called Smartphone MA Stops Hypertension (SMASH).[20-26] SMASH consists of multi-level components: Patient level components include: a) sequential automated reminders from an electronic med tray (blinking light, audio chime, automated call) and b) tailored SMS/voice mail that addresses: 1) motivational and social reinforcement to enhance and sustain adherence; 2) BP monitoring reminders; 3) HTN education and functional health literacy, tips on talking with doctor, etc. Provider level components include: a) weekly summary reports of subjects’ MA and BP levels with JNC8 stepped care guidelines and b) phone alerts to clinic nurse managers when verified out of range BPs occur. Our 3 feasibility trials (3 mos; 6 mos) with AAs with uncontrolled HTN demonstrated high acceptability, self-efficacy for following medical regimen, improved real-time MA, reduced emergency department use and higher percentages reaching JNC8 standard for BP control compared to standard of care (SC) cohorts.[22-26] SMASH appears promising but requires further evaluation and refinement. *PA-14-334, Practical Interventions to Improve MA seeks testing of novel, theory guided interventions to improve MNA (self-report & objective indices required) and inclusion of a biological indicator (e.g., BP) expected to be effected by changes in adherence.* We propose to conduct a multi-site cluster efficacy RCT with 192 AAs (21-59 years old) with sole diagnosis of uncontrolled HTN and verified MNA randomly assigned to a 6-month intervention with 12-month follow-up. Evaluations will occur at baseline and months 3, 6, 12, and 18.The central hypothesis is, compared to an enhanced SC group, the SMASH group will exhibit significantly improved MA and resting and 24 hour BP control over the active treatment period (primary endpoint).

Specific aims will assess the efficacy of the SMASH intervention on:

AIM 1) Primary Outcomes: a) Medication adherence: % with electronic monitor-derived adherence scores >0.90; b) BP control: % meeting JNC8 defined BP control (resting BP<140/90 mmHg.)

AIM 2) Secondary Outcomes: a) % provider adherence to JNC8 guidelines measured by timing of med changes; b) % meeting 24-hr BP control (BP<130/80 mmHg) and c) increases in self-determination theory constructs (i.e., competence & autonomous motivation).

AIM 3) Exploratory Outcomes: a) moderators (e.g., gender, age, income, etc.) and mediators (e.g., competence, autonomous motivation, perceived disease severity, med side effects, depressive symptoms, etc.) of MA and BP control; b) cost effectiveness and c) physical risk factor changes (total cholesterol, LDL, blood glucose, HgA1c).

AIM 4) SMASH Refinement: A mixed methods approach will be used including post-study questionnaires (e.g., patient/provider satisfaction, usability scales, etc.) and focus groups of 5-6 people with SMASH providers (n≈12) and SMASH subjects (16 responders and 16 partial/non-responders) will assess program acceptability, usability, salience and aids/barriers to sustainability. Data from the RCT and post trial multi-method evaluations will be triangulated to further optimize SMASH and prepare for a multi-site effectiveness RCT.

Our **long-term objective** is to develop effective sustainable mHealth programs for HTN and other chronic diseases. Dissemination of such programs will help reduce burden of HTN associated health disparities.

A. SIGNIFICANCE

A.1. HTN and AAs: HTN, the most commonly diagnosed chronic disease in the US, is an independent risk factor for stroke, renal failure, and CVD events.[1,2] Unfortunately, racial/ethnic disparities persist with AAs exhibiting earlier onset, higher prevalence rates than all other ethnic groups (~39% vs 19-28%) and higher rates of uncontrolled HTN(54-70 %) than Whites(47-54%),[3-5,27-30] Risk factors for poor control of HTN include nonwhite ethnicity, poorer socioeconomic status, and residence in rural southeastern United States.[29,30] These risk factors are all prevalent in South Carolina,[30] and support need for culturally sensitive BP control programs for this population at significant risk for stroke, chronic kidney disease, type two diabetes and CVD events.[31-36]

A.2. Medication Nonadherence (MNA) and Uncontrolled HTN: MA is defined as the extent to which a prescribed dose, frequency and timing of a med are followed.[37] Around 20-32% of new prescriptions are never filled with HTN (28.4%) being a leading category.[38,39] Sustained adherence to HTN meds can control HTN & reduce CV events (e.g., stroke, MI).[40,41] Recent RCTs using newer HTN meds included in JNC8 guidelines (e.g., selective beta 1 blockers, lower dose diuretics, ACE inhibitors, etc.) report reductions in future comorbidity risk factors for diabetes and hypercholesterolemia (e.g., total cholesterol (TC), LDL, blood glucose, HgA1c).[42-44] For example, newer selective beta 1 blockers increase peripheral blood flow which increases glucose uptake and disposal and lower dose thiazide diuretics produce less endogenous glucose; both promoting increased insulin sensitivity.[45] Unfortunately, MNA remains the leading modifiable barrier to BP control.[7-10] Around 50% of HTNs stop taking meds <12 mos after diagnosis and <65% remain in care after 3 years.[46] Across chronic diseases including HTN, MNA affects ~50% of patients (range: 20-75%).[22,25,28,39-41,47,48] Findings are mixed with some studies indicating HTN patients experience greater problems due to MNA with increasing number of comorbidities and meds.[49-51] Our work[22-26] and that of others[5,6,17-19] find **MNA is often a greater problem among patients with a sole diagnosis of HTN compared to those with comorbidities.** When timing of dose is taken into account (e.g., meds taken within 3 hr window of designated times), our findings[22,23] and others,[52,53] indicate MNA is even higher. Most previous studies were limited to self-report or med possession ratio (MPR) to identify MNA, strategies that are less sensitive than electronic medication monitoring. For these reasons, electronic medication monitoring is regarded as the gold standard for measuring MNA.[54,55] We will use electronic monitoring as a primary index of MNA, one of our primary outcomes. We will also explore effects of the SMASH program on changes in diabetes/ hypercholesterolemia risk factors (TC, LDL, blood glucose, HgA1c).

A.3. Causes of MNA: World Health Organization distinguishes MA barriers as intentional (forgetfulness, poor planning, regimen complexity, costs, and access issues) or unintentional (adverse side effects, erroneous health beliefs).[7-9,56] Several recent MA reviews found poor planning and forgetfulness to fill scripts/take meds, poor patient-provider communication, affordability, lack of motivation and erroneous health beliefs (e.g., HTN not permanent, can be healed) were common problems.[55,57,58] Our studies indicate that local practice networks (e.g., Federally Qualified Health Centers: FQHCs) which focus upon lower socioeconomic status, underserved populations have reduced or eliminated some barriers (e.g., lowered med costs, decreased regimen complexity, transportation assistance, use low literacy novella based health education materials). However, poor planning and forgetfulness remained primary MA barriers in our studies involving AAs with HTN or additional comorbidities.[20,21] Our recent work involving AAs with sole diagnosis of uncontrolled HTN revealed similar factors associated with MNA including low functional health literacy, poor planning, and forgetfulness, but also the need to more thoroughly explore motivating factors for establishing sustained regimen adherence. These factors will be used in self-determination theory (SDT) guided tailored SMS motivational and reinforcement messages linked to adherence levels to the regimen (in C.1.5; Appx.3). Roles of other known sociodemographic and biobehavioral MNA mediators among AAs and/or HTN patients will also be examined (e.g., age, income, med side effects, perceived disease severity, stress, patient satisfaction with provider, sleep quality, depressive symptoms, etc.)[7-10,59-68] (in D6,Table3;D.10.AIM 3).

A.4. Therapeutic Inertia and Uncontrolled HTN: Therapeutic inertia, the failure of clinicians to appropriately intensify therapy in a timely manner, explains, in part, why among adherent patients, HTN often remains poorly controlled.[69-72] Although therapeutic inertia is a multifactorial problem, provider unawareness of best practice guidelines is a major culprit.[71-74] Okonofua, et al.,[72] monitored for 12 months 7,253 patients with uncontrolled HTN who attended ≥4 clinic visits from 44 primary practice sites primarily in SC. Med changes occurred on only 13% of the visits at which patients exhibited uncontrolled HTN. Additionally, lack of real-time data as to HTNs' BPs at home and their degree of MNA means important medical decisions are often delayed until the next clinic visit that might be weeks or even months away. Thus, the SMASH program includes a practitioner component to reduce therapeutic inertia and follow JNC8 treatment guidelines (see D.5.b).

A.5. RCT BP Control Efficacy Gaps: A number of interventions have addressed MNA among HTN

populations. Reviews of 133 HTN RCTs ([37 RCTs],[11] [78 RCTs],[12] [18 RCTs][13]) concluded MA reminder tactics (often live or automated phone calls), BP self-monitoring (readings brought/mailed/phoned in) and education/counseling, individually and/or in combination, often improved MA and resulted in small but significant BP declines. Unfortunately, only 40-50% reached BP control and improvements often deteriorated after the trial ended. Notably, although 24hr BP is a better predictor of CV morbidity and mortality than clinic BPs,[14,27,75,76] relatively few MA BP control RCTs have included 24-hour BP.[11,14-16] To our knowledge, besides our work, no other patient/practitioner guided program has been developed for AAs involving real time med reminder tactics, BP self-monitoring and HTN health literacy education guided by behavioral change theory using culturally tailored, personalized motivational/reinforcement messages. Although our pilot studies' results are promising (in C1.4), sample sizes were very small and underpowered. In summary, there is a strong scientific premise for the proposed project. A **significant need remains for evidence-based, cost effective strategies that show sustained improvement in MA and BP control among uncontrolled HTNs, especially AAs. Our mHealth intervention package requires testing in a fully powered RCT if this approach is to be adopted, disseminated and eventually reimbursed via CMS and insurance carriers.**

A.6. Role of mHealth in Adherence Enhancement: mHealth, the use of wireless technology in healthcare, is a rapidly growing field in preventive medicine and chronic disease management.[77-80] mHealth capitalizes upon existing mobile technology infrastructure and the ubiquity of the mobile phone. Mobile phones are used by ~ 94% of US adults and ~72% own a smart phone[81] with ethnic minorities (e.g., AAs at 73%) slightly more likely to own a smartphone.[81] Our preliminary work corroborated the high prevalence of standard feature and smart mobile phone usage among AAs and indicated that AAs are very receptive to mHealth programs.[20,21]

Indirect monitoring using electronic devices (pill trays, vials, smart phone apps) provides various med intake reminders (e.g., blinking light, buzzer, SMS, voice mail). These devices have been found helpful among patients who are intent upon but forgetful about taking their meds or only moderately motivated.[10] Research has verified indirect electronic monitoring methods (e.g., MEMS pill vial cap) reflect actual intake in such individuals and do not increase adherence artificially.[82-85] A recent (2014) review of 37 MA electronic device trials (32 RCTs, 5 nonrandomized) involved 14 chronic conditions (e.g., HTN, diabetes, asthma, heart failure, COPD, etc.), and had a median trial duration of 5.5 mos.[86] Compared to control groups, the majority of studies that provided solely reminder signals with or without additional feedback related to pill intake (e.g., LED with pill number to take, time elapsed since last dose, etc.) failed to show statistically greater improvements in MA.[80] Programs which integrated electronic device data with pertinent health related feedback by healthcare providers (e.g., relationship of MNA to physical risk factors) showed greater improvements than control groups (84.8% vs. 68.4 %, respectively). Other programs which focused upon intake reminders/educational information (e.g., phone alerts, SMS messaging), without monitoring med intake have, typically been unsuccessful in enhancing non self-report based MA and/or BP control.[80,87-89] Our 3 SMASH feasibility studies involving AA HTNs included all of these components. All resulted in high acceptability, usability, improved MA and JNC8 BP control (in C.1.4) and if sustained, might ultimately improve long-term clinical outcomes.[22,23] Our proposed 12-month follow-up will address the sustainability of SMASH.

B. INNOVATION

This revised application seeks to challenge and shift current clinical practice for HTN by testing and optimizing a mHealth program that is practical, sustainable and capable of large-scale dissemination. The research is innovative in several ways. To our knowledge it is the first mHealth program for AAs to: 1) focus upon those with sole diagnosis of uncontrolled HTN and poor MA in efforts to curtail HTN's devastating cascade of damage to organ systems and vasculature contributing to future comorbidities and events (e.g., stroke, heart attack, CVD, diabetes, chronic kidney disease, etc.[31-36]); 2) Apply synergistic constructs from behavioral and technology application theories to develop a culturally tailored medical regimen self-management program via an iterative design process involving repeated guidance from AA patients and healthcare providers; 3) use real-time measurements of MA and BP data to facilitate immediate feedback, HTN educational messages, and automated, culturally tailored motivational/reinforcement messages aimed to enhance self-efficacy and sustained motivation for adherence; 4) include both resting BP and 24-hr BP monitoring as outcome variables and 5) provide healthcare providers personally designed, automated streamlined reports to enable faster changes in med regimens and achieve earlier sustained BP control. Since the first submission, we completed the third feasibility trial and further refinements including transitioning from generic SMS messages to an automated system that delivers culturally tailored, individually personalized motivational and reinforcement SMS and voice mail messages based upon degrees of MA with a library enhanced over the past year of >600 messages (see C.1.5.) In summary, our proposal is both novel and timely offering a practical self-management program which will help establish sustained medical regimen adherence and control of HTN rather than waiting

to address the issue of MNA when chronicity of uncontrolled HTN has contributed to stroke, heart attack or diagnosis of other chronic diseases (e.g., chronic kidney disease, coronary artery disease, type 2 diabetes, etc.)[1,2,31-34] It will also prepare those who do develop comorbidities over time (e.g., type 2 diabetes) with the skills and motivation to adhere to regimen changes.

C.APPROACH

C.1.1 Preliminary Studies: Our interdisciplinary team represents experts in BP management, mHealth, health communications, biostatistics, information technology and clinical psychology. We have significant experience in software/server interface and app development, community-based participatory research, and practice-based behavioral RCTs. The PI has worked with each team member on one or more mHealth projects using an iterative design process, ethnicity/race related cultural framework using key informant interviews, focus groups, software developer heuristic and patient think aloud usability evaluations, surveys and progressive phases of clinical trials with AAs. Examples include smart phone delivered stress reduction for pre-HTN (HL114957), tablet delivered educational/motivational video modules and videoconference sessions for transplant eligible patients (NIDDK098777) and our 2 recent feasibility trials involving AAs with sole diagnosis of uncontrolled HTN.(See PI/CO-Is bios for project overviews).

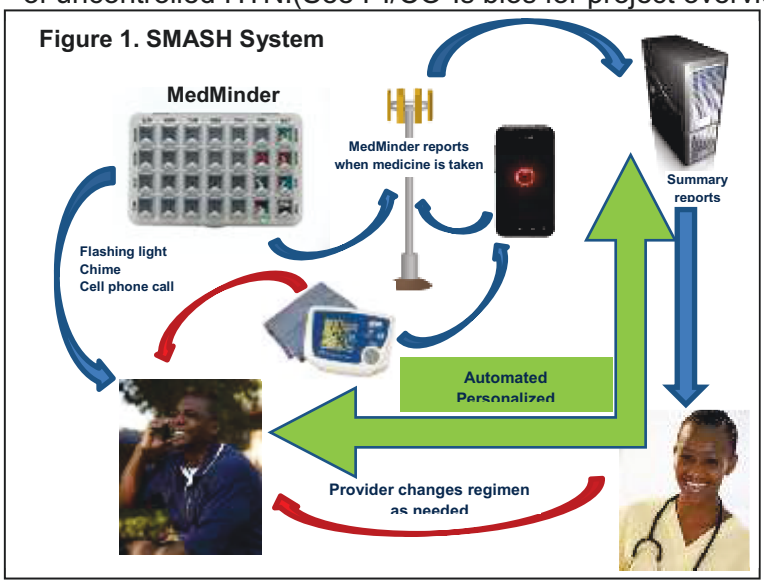


Figure 1. SMASH System

Our Research Pertinent to the Application

C.1.2 Conceptual Model for SMASH: was developed from reviews of the MNA literature including underlying mediators of MNA,[7-10,60-68] theory guided interventions which have shown sustainability of behavioral changes[90-97] and an iterative design which capitalized upon patient and provider input. The SMASH system for AA patients (Fig.1) was developed with a user-centered iterative design process involving socio-culturally preferred and low literacy-based strategies guided by the principles of Self-Determination Theory.[93,95] Initially, ~60 AAs with uncontrolled HTN (and often other CV related comorbidities-e.g., diabetes, stroke, kidney transplant recipients) and their healthcare providers (~10) engaged in key informant interviews. Findings revealed: 1) MDs felt meds need to be taken consistently and within specified time frames (e.g., 90 min before or after designated times); 2) patients reported need for education in HTN literacy or assistance in consistently following medical regimen, especially med timeframes; 3) patients wanted assurance BP self-monitoring data will be used in treatment plan; and 4) patients and MDs desired feedback (brief text responses and summary charts) on how patient is progressing in meeting regimen goals. These findings informed development of a prototype system using an electronic medication tray capable of both encouraging and monitoring med intake in real time, and a Bluetooth BP device for home monitoring that transmits time stamped data encrypted to our secure server. We then performed lab based usability testing including expert (software developers) heuristic and end user (AA HTN patients) think aloud evaluations using established methods for mobile and web based applications.[98-100] After refinements, we conducted several survey studies to better understand AAs with HTN preferences and use of mobile communication and mHealth technology, self-reported MA and attitudes toward the SMASH system (findings in C.1.3.)[20,21] These findings guided further refinements and a subsequent series of 3 feasibility RCTs with further refinement following each trial.[22,23,25,26] (see C.1.4.)

SMASH Conceptual Framework Guided by SDT: Our intervention is guided by SDT which focuses on developing competence (akin to self-efficacy in Social Cognitive Theory[90]) and autonomous regulation**.** Consistent strong effects of these SDT mediators have been observed for various health behavior changes (e.g., smoking cessation, diet, physical activity) including MA.[91,92,94,95] SDT conceptualizes a continuum of human motivational regulation, ranging from fully external to fully internal.[91-94] External regulation, a form of controlled motivation, includes extrinsic rewards and punishments. Common examples are financial incentives/constraints and pressure from others to change (e.g., family members, friends, healthcare providers). Whereas external regulation may motivate short term change, such change is less enduring and stable. The most powerful form of motivation is **autonomous motivation**. Here one not only sees importance, but also links the change(s) with their other core values, beliefs, and life goals. Autonomous motivation in SDT relates to our need to feel independent in our actions rather than feeling controlled or coerced. We will promote

autonomous motivation by linking subjects' behavioral changes (i.e., increased MA) to their personal values, beliefs and goals, including culturally specific drivers such as faith, family and community. Autonomously motivated individuals exert more effort and persistence in their behavior change, which is vital for managing chronic diseases due to lifelong nature of the medical regimen behaviors. The patient must devote daily time and effort (e.g., taking correct meds on time, self-monitoring biofunctions) and exhibit persistent vigilance to sustain these efforts the rest of their life. Numerous studies have shown that, behavior changes rooted in autonomous motivation are more likely to be sustained than change stemming from controlled motivation via external or negative internal pressures.[95-97]

There are reliable and valid instruments to measure SDT constructs that we will be using.[97,101] Our health communications consultant, Dr. Ken Resnicow, has expertise in development of SDT messages and use of SDT measures[102-104], as well as user centered, iterative design in development of web enabled programs and apps. This includes use of mixed method approaches such as expert heuristic and patient think aloud usability evals, key informant interviews, focus groups and questionnaires. He assisted us in the last 2 trials in these evaluations and subsequent refinements including expansion of our tailored motivational messages library. He will continue to do so and aid in analyses of potential moderators and mediators of adherence to SMASH (see biosketch and support letter).

C.1.3 Mobile Phone and mHealth Technology Attitudes: We gave a brief survey to 3 groups of AAs with HTN (kidney transplant patients, FQHC patients, recent stroke patients).[20,21] It assessed use of mobile devices and attitudes and preferences toward mHealth. As shown in Table 1, across the 3 groups, an average of 91% owned a cell phone and 50.6% owned a smart phone with internet activation, which mirrored the U.S. adult population at times of administration. They were facile in use of cell phones (i.e., collectively, 67% sent /received SMS, 36% browsed internet, 34% sent/received email,42% downloaded apps). Poor planning and forgetfulness were leading contributors to MNA; med side effects were not reported as a common cause of MNA.[20,21] Only 69% reported 100% MA over previous 2 weeks using the Modified Morisky Scale,[105] a scale we will use in this study (Appx. 1). **Importantly, self-reported MNA progressively decreased as greater negative impact of uncontrolled HTN increased (e.g., MNA 4% among kidney transplant patients with HTN, chronic kidney disease, diabetes, etc. vs. 64.4% among Fetter FQHC HTN patients without history of CV related events)**.The groups also received a demo of the SMASH program (see Fig.1). Although only 10.8% had a priori knowledge of mHealth, 86% were receptive to using SMASH, especially if it was free. Most (79%) had someone at home who could help them use the system if needed. Most felt SMASH would help them follow their doctor's directions (86%) and enable their doctor to make more rapid adjustments to their regimen (88%).[20,21] Based on above findings and additional guidance from AAs with HTN and healthcare providers, we further refined the SMASH prototype guided by tenants of SDT to enhance competence and autonomous motivation for sustained adherence with med intake and BP monitoring. We then conducted 3 feasibility trials, each followed by post-trial interviews or focus groups with subjects and providers for refinement guidance.

Table 1. African American mHealth

Demographic	Transplant (N=46)	Stroke (N=27)	FQHC (N=66)	Average
Age (avg.)	54.2	52.9	53.4	53.5
Own Mobile Phone (%)	97.8	92.6	87.0	91.1
Own Smart phone (%)	47.8	51.8	51.3	50.6
Help at home (%)	82.2	81.5	77.1	79.5
SMS Text (%)	65.2	77.8	60.0	67.7
Email (%)	32.6	29.6	40.0	34.1
Internet surfing (%)	34.8	40.7	32.5	36.0
Download apps (%)	43.5	40.7	42.5	42.2
Medication Adherence Self-Report				
Missed dose in last 2 weeks (%)	4.0	25.0	64.4	31.1
mHealth opinion				
Receptive to using (%)	80.4	85.2	92.5	86.0
Knew of mHealth (%)	8.7	7.4	16.2	10.8
Follow Dr.'s orders (%)	76.0	92.6	90.0	86.2
Dr. make more timely med change (%)	84.8	88.9	90.0	87.9

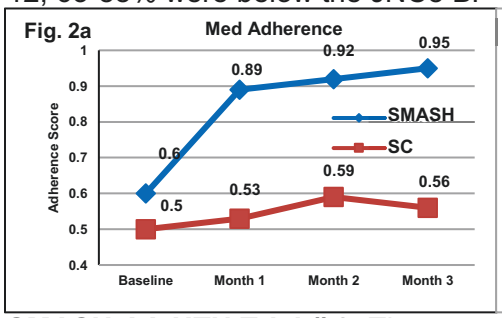
C.1.4 SMASH Feasibility RCTs:

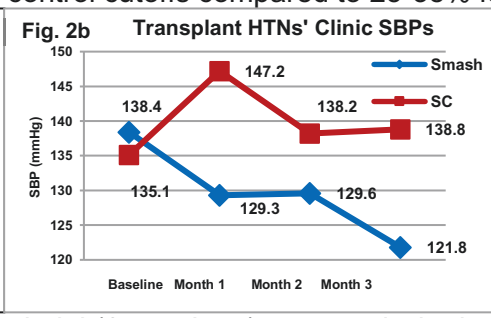
SMASH AA Kidney Transplant Patients with HTN Trial #1: We first ran a 3-mo feasibility RCT in 20 AAs with uncontrolled HTN who were also kidney transplant recipients. They were verified as having uncontrolled BP from clinic records followed by a BP screening. Majority had med possession ratios (MPRs) >0.85. Thus, we identified patients as nonadherent (i.e., adherence score <0.85) to their med regimen based on a month-long screening using an electronic med tray (Maya MedMinder™) with reminder functions disabled. We used a modification of Russell et al.'s algorithm[52] [see Appx. 2]) which considers dose timing in addition to dose taking, especially important when taking meds with especially short half-lives.[20,21] We modified the algorithm to allow for dosing schedules other than twice daily. Subjects were instructed that to be fully adherent, their meds had to be taken within a 3 hr window centered on the prescribed dosing time (within 90 min before or 90 min after designated time.) A dose taken within the 3 hr window resulted in a full score for that dosing time; a dose taken outside the 3 hr window but within 6 hr window resulted in a half score for that dosing time; a missed dose resulted in a score of 0. Each subject received a score from 0-1.0 per day and scores averaged over the month. Despite self-reporting high MA, having MPRs often ≥0.85 for previous month and knowing their exact times of intake were being monitored, they had a mean adherence score of 0.63 (range 0.26-0.94.) Seventy-

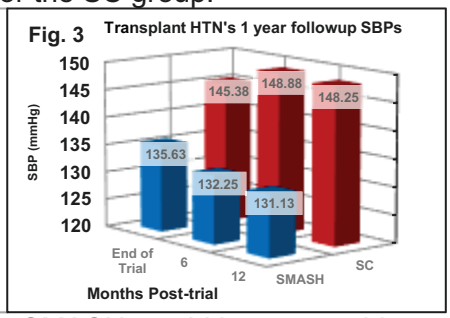
nine % of those screened were deemed non-adherent (i.e., MedMinder adherence score <0.85).[22,23]

Eligible participants were randomly assigned to either standard care (SC) or SMASH. The SMASHers had the reminder functions of their med tray **enabled** and received a Bluetooth enabled BP monitor (see section D.5a). A smart phone received and sent encrypted BP data and delivered automated SMS reminders to measure BP. SMASHers received reinforcement/motivational phone calls from the project manager. These calls aimed to improve MA by increasing the SDT construct of competence for MA and identifying subject's beliefs, values, and short-term life goals and linking them to desirable behavior change. Providers received weekly summary reports of patient MA and BP readings. The SC cohort continued to use the MedMinder with reminder functions **disabled**. Participation rate (% approached who agreed to engage in 1-month med intake screening) was 75% and recruitment rate (% who were eligible following screening who enrolled in trial) was 91%. The SMASH group reported a high degree of overall satisfaction with the mHealth system (4.8/5 Likert Scale) and perceived SMASH to be easy to learn (4.7/5) and use (4.8/5.) HTN med adjustments occurred more often and within ~24 hours of clinic visit (or weekly report) in the SMASH cohort vs the SC cohort. All occurred in the trial's first month. The prototype SMASH system appeared safe and highly acceptable to patients and providers. As shown in Figs. 2a and 2b the SMASH cohort exhibited clinically relevant improvements in time-stamped MA and SBP compared to the SC cohort.[22,23] At 3 months, 90% of SMASHers met JNC8 BP guidelines compared to 25% in the SC cohort.

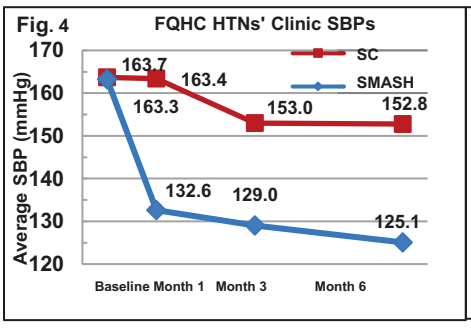
Since the initial grant submission we published a 12 month follow-up using clinic BP readings 6 and 12 months post-trial completion.[24] Clinic nurses took the BPs. They were unaware of patients' previous involvement in the study nor did they use a standard BP protocol as used in our trial. Nevertheless, as shown in Fig.3, the SMASH group maintained significantly lower SBPs compared to the SC group. At months 6 and 12, 63-88% were below the JNC8 BP control cutoffs compared to 25-38% for the SC group.

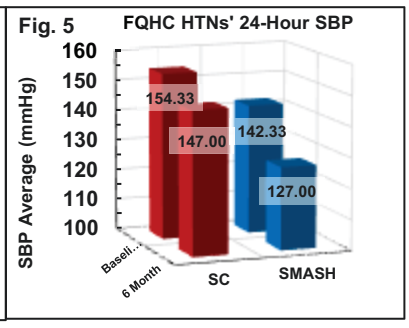




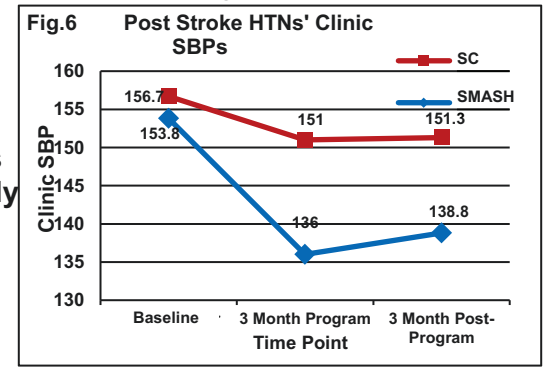


SMASH AA HTN Trial # 2: The second trial (6 mos long) assessed whether SMASH would be acceptable and exhibit similar signals of clinical benefit in a **population from our 4 county FQHC** that had not yet experienced the devastating impact of years of MNA to the silent killer of HTN. **These patients had HTN with no history of other CV or chronic kidney disease related events (e.g., stroke, heart attack, dialysis, transplant, etc.)** The same protocol was delivered with the exception of refinement with delivery of the motivational/reinforcement messages using SMS rather than solely live phone calls. This was a common suggestion from the post-trial interviews with SMASHer kidney transplant patients from the first trial. We obtained 24-hr BP at baseline and the 6-month time point. **Interestingly, as opposed to the first feasibility trial with kidney transplant patients with multiple comorbidities, during our BP screenings, we found that the overwhelming majority of AAs with verified uncontrolled BP had medication possession ratios (MPRs) for the last 3 months well under the cutoff of 0.85**. We bypassed the 1-month electronic tray screening. Since the initial grant submission, we published results from this feasibility trial.[25] In the first 2 weeks, phone calls were made to subjects each day following an MA score of 0 (~30% of subjects). Calls were guided by the values, beliefs, and goals (VBG) questionnaire (in C.1.5) to help the subject identify and rectify MA barriers and identify VBGs to link with MA to foster sustained motivation for adherence . We again found high acceptability (93% recruitment rate; 95% retention rate), satisfaction with SMASH (4.5/5 Likert Scale) and usability (e.g., easy to learn and use; both scores ≥ 4.5/5). The SMASH group exhibited large clinically meaningful reductions in both resting SBP and 24-hr SBP compared to the SC group (see Figs 4 and 5, respectively). At both 3 and 6-mo time points, 90-100% of SMASHers were below JNC8 BP control





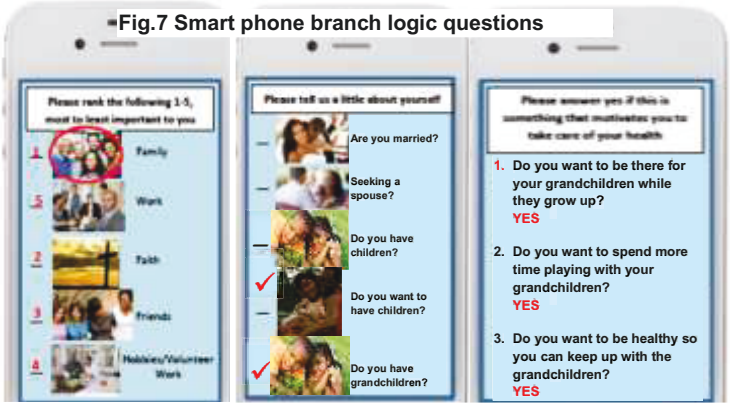
cutoffs compared to 25-40% for the SC group. They also showed significant increases in MPR (mean of 0.90 across trial) compared to the SC group (mean of 0.50 across trial). We also examined emergency department (ED) utilization rates during the 6-mo periods prior to and during the trial.[25] The SMASH group showed a 57.5% reduction (7 vs 3 ED visits) whereas the SC group showed a 5.7% reduction (13 vs 12 ED visits). This equated to a savings of $23,692 in the SMASH group compared to $5,923 in the SC group compared to the previous 6 months. We will assess cost effectiveness in the proposed trial as an exploratory outcome. **Our proposed trial will use patients from this FQHC.**



SMASH Post Stroke AAs with HTN Trial # 3: After the initial grant submission, we completed a 3-mo trial with 3-mo follow-up with AAs just released from hospital following a first incident stroke. **Their only pre-existing diagnosis was HTN.** We used the SMASH program described in trial #2. These findings were recently published and noted high acceptability (90% recruitment rate; 96% retention rate), usability (e.g., easy to learn and use; both scores ≥ 4.25) and satisfaction with SMASH (4.5/5 Likert Scale).[26] The SMASH group showed clinically meaningful reductions in resting SBP compared to the SC group (see Fig 6). At both 3 and 6-mo time points, 57-86% of SMASHers were below JNC8 BP control cutoffs compared to <25% for the SC group. We examined ED rates during the 6-mo periods prior to vs during and following the trial (6-mo period) the trial. The SMASH group showed an 87.5% reduction compared to a 20% reduction in the SC group.[26]

C.1.5 Post-SMASH Trial Refinement: Since the original grant submission, our experiences with the last two feasibility trials with AAs with just uncontrolled HTN resulted in significant refinements of the SMASH program. **We found subjects with a sole diagnosis of HTN vs multiple comorbidities (e.g., transplant recipients with HTN, diabetes, etc.) were often more challenging to establish sustained MA and BP self-monitoring.** After functional health literacy was established, we found a consistent set of values,beliefs and short-term life goals influential in motivating adherence to SMASH. These were primarily identified from their answers to the VBG questionnaire[106] and further clarified when phone contact was required due to MNA during the first several weeksof the trial. Three primary VBG domains from both trials influenced engagement in subjects' medical regimen: family, faith and friends. For example, God was often linked to having guided them to a "good doctor" or "pills that work and don't make me have stomach aches or pass water so much." Power of prayer was often noted in conjunction with "praising God and showing thanks for the gift of life by doing what the doctor says". Family and community cohesiveness and support, especially activities with friends and family members were primary adherence motivators related to short term life goals (e.g., increase time gardening, fishing, playing with grandchildren, attending church functions, etc.) Finally, folk medicine, primarily Gullah root doctors, was noted among some FQHC and post stroke patients as being an adjunct to their medical regimen.

Responses to the questions were placed into a tree-structured algorithm to generate tailored motivational and positive reinforcement SMS messages that can be delivered automatically. We have expanded the SMS messages used in our last two trials and now have a library of >600 SMS messages. The FQHC and stroke patients who received SMS messages and audio and visual graph feedback also suggested having the VBG questions presented in a web-based app via audio delivery and/or photos, noting that this would easily allow them to refresh their goals over time. We have now done this. An example of branch logic questions on the family domain is presented on a smart phone in Fig 7. (See Appx. 3 for examples of branch logic questions). A common combination of relevant values, beliefs and goals responses involved the belief construct of religiosity in which subjects had strong faith and believed God has a plan for them that included helping their family sustain itself. In the life goals category, their primary short and long-term goals often involved engaging in church activities and spending more time with their grandchildren. Two relevant examples of SMS feedback for a MA score of 1.00 are: "*Way to go! Every day of pill taking keeps you on track for…":* 1) *"many more years watching your grandkids grow up"*; 2)*" attending many more prayer meetings".* If one is partially or completely nonadherent, he/she might receive: "*Remember taking your pills on time is one way of giving thanks to God for his blessing of life" or "You must have been really busy yesterday. Get back on track taking your pills on time*



today and plan some special time with your grandkids". For further examples of personalized messages based on patient responses, see Appx. 4. Positive feedback from SMS messages and phone delivered graphic representations of adherence patterns and BP control over time, intends to increase SMASHer's perceived competence in engaging in the program and link their adherence behaviors with their values, beliefs and goals.

D. Research Design and Methods

D.1. Design and Randomization: Subjects will be drawn from Fetter Health Care Network (FHCN). It is the sole FQHC center in the 4-county area (8 clinics)and provides ~60% of routine AA healthcare in the 4 county area.[107] A support letter from the FQHC network is included. EMR files indicated they have ~2,619 AAs (21-59 yrs old; mean age=45.3yrs) with sole diagnosis of uncontrolled HTN. We will use the 8 practice sites in a 2 arm RCT design (n=192) with clinic as unit of randomization and patient as unit of analysis. All primary healthcare providers across the 8 clinics have agreed to participate if selected. Each clinic has a minimum of 2 primary providers (at least 1 MD and 1 or more NPs and/or PAs per clinic).Thus, 2 providers per site will be recruited. Each will have 12 of their patients recruited (24 per clinic). Given our ~90% participation rate in previous FQHC studies[25,108,109] and 93% SMASH participation rate, we anticipate no recruitment problems.The Medical University of South Carolina Family Medicine and Internal Medicine clinic population will be an additional recruitment resource if needed.

D.2. Participants: With consideration of the relevant biological variable of gender, we will recruit 192 AA 21-59 yr old uncontrolled HTNs with equal numbers of males and females that meet the following inclusion/ exclusion criteria: 1) SBP ≥140 mmHg on most recent clinic visit over last 12 mos and at BP screening and recruitment visits; 2) MPR <0.85 over last 3 mos; 3) 24-hour SBP ≥130mmHg (HTN cutoff) to help rule out white coat HTN.[76,110] SBP used as selection variable since most AA HTNs <60 have systolic or combination systolic/ diastolic HTN and for most patients, controlling SBP also results in DBP control;[27,111,112] 4) no other known chronic diseases (e.g., diabetes, chronic kidney disease (GFR <50ml/1.7 m2/min),cancer, renal dialysis, heart attack, coronary artery bypass, arterial stent, substance abuse (e.g., >21 drinks/week), psychiatric illness, Beck Depression Inventory[113-115] >13, able to speak, hear and understand English; take own BP and meds; 6) owns smart phone with current data plan; 7) primary care MD's assent patient able to participate and 8) no planned pregnancy or vulnerable population (e.g., pregnant or nursing women, prisoners).

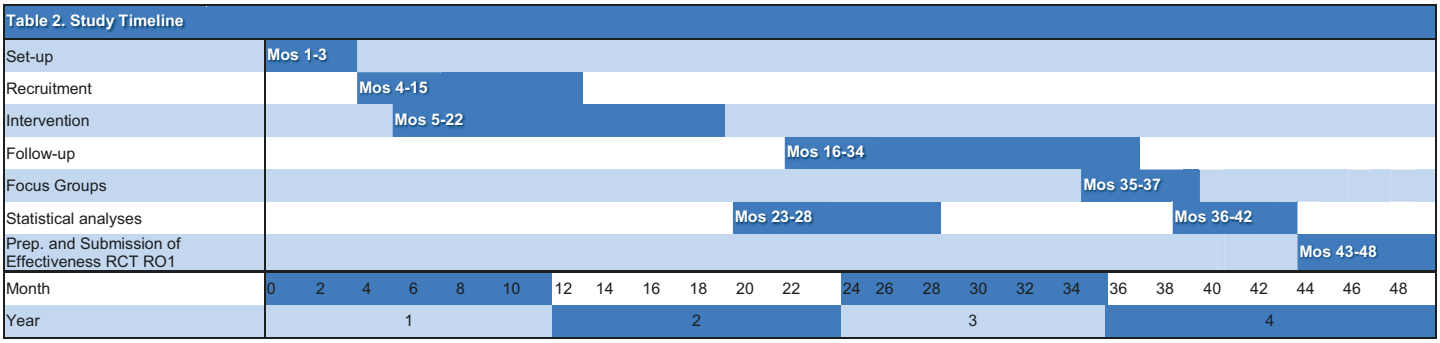
D.3. Recruitment: Proposed procedures were successful in our SMASH pilot trials.[22,23,25,26] Practice sites will prepare a list of eligible patients and Dr. Chandler (project manager) will contact them, explain the study and, if interested, schedule the screening/recruitment visit. As part of **design rigor**, other MUSC staff will conduct the evaluations below using established protocols. They will remain blinded as to patients' group status throughout study (i.e., baseline, 3 and 6 months, and post-trial follow-ups at 12 and 18 months).Subjects who develop any comorbidities over the study period will remain in the trial and all meds will be monitored.

D.3.a. Resting and 24-hr BP screening: After obtaining informed consent, resting BP protocol will be conducted using our established protocol with the previously validated BpTRU device.[116] **If SBP≥140 mmHg** from last 2 readings of 10 min protocol, **they will continue with screening**: height, weight and waist/hip ratio will be recorded (BP and anthros protocols in Appx. 5 and 6). Based on their preference, a set of **questionnaires will be given** orally or read on their own (see D.6 Measures; Table 3; copies in Appx. 7-21). They will have the option of using their smart phone, TACHL provided tablet, or paper copy version. They will **then wear** the previously validated[117] **SpaceLabs 90207 BP monitor for 24 hrs** using our established protocol.[118-120] Protocol and criteria for acceptable readings, generating 24-hr averages, etc. are in Appx. 22. **Only those with 24hr SBP ≥130 mmHg will proceed to the MNA identification phase below.**

D.3.b. MNA Identification Phase: Subjects will be shown how MedMinder™ works and demonstrate proficiency in loading and activating the device. They will be told their doctors will receive summary reports on their med intake patterns. The tray plugs into a standard 110v outlet, has 28 compartments allowing up to 4 dose times per day for 7 days, and is capable of providing escalating reminder signals (described in D.5.a**). Reminder functions will be disabled for the 1-month screening phase**. The nurse manager (or project manager, Dr. Chandler) and subject will program the MedMinder for dosing times (example of subject's 24-hr MedMinder activity in Appx. 23). Subject will receive written and oral instructions on MA criteria (i.e., all meds taken within 180 min window centered on prescribed dosing time).SMASH app has auto call feature for TACHL service line for technical issues. Time and date stamped opening and closure of the tray's compartments are relayed via GSM wireless cellular transmitter/receiver to MedMinder™ server for processing. The encrypted data are sent to a HIPPA-compliant server database housed in the TACHL center. The MA formula will be used to calculate MA scores.[22,23,52,121](see Appx. 2) **Only subjects with MA score <0.85 over the 4 week screening and whose subsequent resting and 24-hr SBP evaluations reconfirm uncontrolled HTN will be eligible for enrollment into the RCT.** Dr. Mueller will randomly assign the 8 sites to either SMASH or

enhanced SC conditions.

D.4. Time Table (Table 2) Based on our SMASH trials, we will recruit 16 subjects/mo beginning mo 4 and finish recruiting by mo 15. We will provide a smart phone and/or service plan for ~40 SMASHers we project might lose phones or service plans during the trial.[20,21,25,27] Post-trial data collection will finish in mo 34. Post study focus groups and subsequent qualitative analyses will end in mo 43. Table 2 presents a timetable for the study.



D.5. SMASH Protocol:

D.5.a. **Patient Level**: Subjects whose practice site is randomly assigned the SMASH condition are termed **SMASHers**. The nurse manager or Dr. Chandler will confirm with the doctor and patient the med regimen and times meds will be taken daily (example of subject's 24-hr MedMinder activity in Appx. 23). **SMASHers will have MedMinder's reminder functions activated.** (Enhanced SC care group will not receive reminders, see D.5.c.) Initially, the designated pill compartment on the tray (28 compartments for up to 4 doses/day for 7 days) emits a bright white blinking light for 30 minutes when it is time to take the meds. If the compartment is not opened, cup removed and emptied within that time, an intermittent chime ensues for 30 minutes. If the cup is not opened, removed, emptied and returned during that time period, the subject receives an automated SMS or voicemail according to his/her preference. They will be provided and instructed on use of the validated Bluetooth-enabled UA-767 Plus BP monitor.[122] The SMASH app will be installed on their phone that includes audio, text and graphic step-by-step instructions with countdown timers for the 3 readings over the 10 min protocol, and a 1-min refresher training video. BP data are securely received on the phone and sent to the TACHL-housed server. SMASHers will receive written and oral info on adherence criteria: 1) take all meds within 180 min window (90 min before or after dosing times); 2) take BP every 3 days in morning and evening (protocol in Appx. 24). They will correctly load and operate the tray, use the app and BP monitor before leaving the clinic.

Smashers will complete the values, beliefs and life goals questionnaire (VBG; see Appx. 14). Responses are used in a tree-structured algorithm to select tailored motivational and positive reinforcement SMS or voicemail messages based on previous day's MA levels. Examples of motivational messaging based upon patients' responses are provided in C.1.5 and Appx. 4. After 2 consecutive weeks of 100% MA (typically first 2-4 weeks), messages are switched from daily to a variable interval schedule averaging 2 messages/week. Cumulative MA graphs will be sent on their phones weekly during the 6-month trial (MA rate algorithm in Appx. 2). Automated SMS messages will remind subjects to self-measure BP every 3 days. After each BP session, the SMASH app provides audio and visual BP feedback, and opportunity to see BP averages charted over time and against JNC8 guidelines (screenshot example in Appx. 25).

SMASHers will receive 30-45 sec audio or SMS messages 2x/week on HTN facts (e.g., HTN is permanent, uncontrolled HTN is silent killer), importance of timely, consistent MA, tips on expressing questions /concerns with MD (e.g., side effects; examples in Appx. 26). SMASHers will have auto dial feature on their app for Dr. Chandler (or TACHL service techs if needed) to address technology related issues should they arise.

D.5.b. Provider Level: SMASH primary providers will receive summary reports, designed by them, using patient ID#s every week based upon their preference (e.g., email; NexGen EMR with email reminder to view it; example in Appx. 27).They will receive email reminders for viewing generated reports as needed every 6 hrs for 24hr period. They (and the SC MDs) will receive the same summary charts of JNC8 BP management guidelines used by us in other studies[22,23,25] (Example in Appx. 28). If a SMASHer's mean BP exceeds thresholds (e.g., BP >180/ 105 or <100/75 mmHg) during a session, Dr. Chandler will receive an SMS alert, call the patient and conduct the BP protocol again. If BP still exceeds thresholds, FQHC providers have requested their nurse managers be called to do a follow-up with the patient.

D.5.c. Enhanced Standard Care (SC) Protocol: Subjects whose practice site is randomized to the SC group will continue to use the tray with reminder functions disabled for another 6 months. To **help maximize rigor**

(internal validity) we will control for attention exposure by sending SC subjects automated SMS messages on topics related to healthy lifestyle behaviors (diet, physical activity) but not related to MA or HTN functional health literacy. Message length and frequency will be of same length as the personalized messages delivered to SMASHers. To account for time SMASHers measure their BP, the SC subjects will receive, every 3 days, an automated SMS directing them to different 2-3 minute video/YouTube™ clips on healthy lifestyles. For those who prefer hard copy material, brochures (esp. novella format) will be mailed weekly across the 6-month trial (examples of SMS, voice mails, video clip links and brochures can be found in Appx. 29).

D.6. Measures: Table 3 presents all outcome variables, questionnaires and timing of administration. Most scales have been used with 21-59 yr old AAs and have established psychometrics. We provide brief psychometric information (e.g., internal consistency, test-retest reliability) (see Appx.1, 7-21, for copies and additional psychometrics). We will assess SDT constructs (competence/self-efficacy; MA Self-Efficacy Scale [Appx. 7]) [101,123,124] & autonomous motivation [Treatment Self-Reg. questionnaire; Appx. 8],[97,125] cultural values, beliefs and life goals,[106] (Appx. 14), self-reported MA (Morisky scale, Appx. 1),[105,126,127] and MPR (formula in Appx.30).[128] We will assess sociodemographic, biobehavioral and disease attitudes/knowledge variables which have been identified as potential mediators of MA[7-10,60-68] including HTN knowledge (Appx. 9),[129,130] health literacy and numeracy (Test of Functional Health Literacy scale, Appx.10),[131-133] med side effects (Appx.11),[134] quality of life (SF-8, Appx 12),[135] depression symptoms (Beck Depression Inventory, Appx.13),[113-115] stress (Perceived Stress Scale, Appx.15),[136,137] sleep quality (Pittsburgh Sleep Quality Index; Appx 16),[138,139] perceived disease severity (Illness Perception Questionnaire, Appx.17),[140] and patient satisfaction with MD (Quality MD/Patient Interaction, Appx.18).[141] These questionnaires will be given at baseline and mos 3, 6, 12 and 18. Satisfaction and usability scales will be completed at mo 6 (System Usability Scale, Telemed. Satisfaction and Usability Scale, Mobile App Rating Scale, Appx. 19-21).[142-147] All intervention tactics cease for both groups at end of 6-mo trial. Follow-up visits will occur at mos 12 and 18. Per SC, all subjects will have blood drawn for bioassays including TC, LDL, HgA1c and blood glucose at baseline, mos 6, 12 and18.

D.7. Post-Trial Follow-up Focus Groups: Focus groups will be run after the final follow-up evaluations by Drs. Nemeth, Chandler & Treiber. To help ensure robust and unbiased results, purposive sampling will be used to recruit 32 SMASHers based upon MA, termed responders (MA score >.90) or non/partial responders (MA score <.90) based upon their cumulative adherence score (MedMinder 6 mo score & MPR level across follow-up). Groups will also be stratified by sex, age group (<40; >40) and practice site (4 per site). The 16 subjects from each group will be divided into groups of 4 to 5 (i.e., 3-4 focus groups). A semi-structured interview guide with topic area probes will cover expectations, experiences, adherence, motivation, SMASK system usability and overall satisfaction. We will explore suggestions for improving the SMASK app content and features, tray/BP device usage, quality of SMS, and possible future use of motivational interviewing booster calls, etc., especially among non/partial responders.

The 8 SMASH primary providers and 4 nurse managers from the 4 SMASH sites will engage in a focus group (1 for providers; 1 for nurses). We will assess attitudes, beliefs, aids/barriers to use, feedback on retention, impact on therapeutic inertia and other practice considerations. Focus groups will be audio recorded and field notes written to note any reflexive findings and initial impressions. Recordings will be professionally transcribed, verified for accuracy and imported to NVivo 11.0 (QSR International PTY, Doncaster, Victoria Australia) for analysis.

Table 3. Outcome Variables & Measurements/Instruments Used

Outcome Variables	Measurements/Instruments Used (Cronbach's α)	Time points
Primary Outcomes		
MA	MedMinder (time-stamped) primary measure.	Daily for 6 mos
	Self-report (Morisky Medication Adherence Scale [.76-.83] (**Appx.1**)).	Baseline,3,6,12,18 mos
	Med Possession Ratio [MPR] (**Appx.30**).	
BP	Resting SBP (**Appx.5**).	Baseline,3,6,12,18 mos
Secondary Outcomes		
Therapeutic Inertia	Provider adherence to JNC8 goals: Timely med changes (date of med change following MA & BP feedback).	weekly SMASH reports (SMASHers) and from clinic visits for all subjects
Ambulatory BP	24-hr Ambulatory BP with SpaceLabs 90207 (**Appx.22**).	Baseline,3,6,12,18 mos
SDT constructs	TSRQ Autonomous Self-Motivation (α.81-.84)(**Appx.8**)[97,122]	Baseline,3,6,12,18 mos
	Perceived Competence Scale (MASES-R) (.92, test-retest [3 mos.] .51) (**Appx.7**).[101,123,124]	
Exploratory Outcomes		
Cost effectiveness	Costs of additional personnel time, SMASH devices, ED visits, unplanned outpatient visits & hospitalizations, workdays lost.	First 6 mos of trial & through post-trial follow-ups
Physical Risk Factors	TC, LDL, HgA1c, blood glucose from FQHC standard care via MedCorp (intra-assay variations all <5%; inter-assay variations 3.3% to 6.6%)	Baseline,6,12,18 mos
Potential MA Mediators	HTN Knowledge (.70) (**Appx.9**);[129,130] Short Test of Functional Health Literacy (S-TOFHLA)(.68) (**Appx.10**);[131-133] SF-8(α.87) (**Appx.12**);[135] Med Side effects (**Appx.11**);[134] Adverse events; Pittsburgh Sleep Quality Index (sleep quality) (.83; test-retest [1mo,12 mo] .85, .68) (**Appx.16**);[138,139] Beck Depression Inventory (BDI) (0.82-0.92); (**Appx.13**);[113-115] Perceived Stress Scale (PSS) (.84-.86; test-retest [2 day] .85)(**Appx.15**);[136,137] Illness Perception Questionnaire (IPQ-R; perceived disease severity);.84, test-retest [3 weeks,6 mos].74,.74)(**Appx.17**);[140] Questionnaire on Quality of Patient & Physician Interaction (QQPPI)(**Appx.18**).[141]	Baseline,3,6,12,18 mos
Values/Beliefs/Goals	Values, Beliefs, Goals (test-retest [1 mo].85) (**Appx.14**).[106]	Baseline,3,6,12,18 mos
Anthropometrics	Ht./Wt./Girth (**Appx.6**).	
Sociodemographics	Age, education level, income, type of healthcare insurance	Baseline
Feasibility	Recruitment and Retention rates.	End of trial
System Usability	System Usability Scale (**Appx. 19**);[146,147] Patient/Provider SMASH/SC Treatment Satisfaction & Usability Scale (TSUQ) (α.82-.96, test-retest [1wk] .98) (**Appx.20**);[144,145] User Version of Mobile App Rating Scale (uMARS) (.90, test-retest [2, 3 mos] .66, .70) (**Appx.21**).[142,143]	At 6 mos (All subjects) After all subjects complete 6 mos trial (Providers)
Process/uptake	Patient level (e.g., connection/reloads of MedMinder, BP uploads via phone & opening of messages /education info) & provider level (e.g., opening of patient summary reports & phone alerts).	First 6 mos of trial

D.8. Sample Size Justification & Power Calculations: For AIM 1: Sample size/power calculations were based on two-sided

Cochran-Mantel-Haentzel chi-square tests of differences in % of patients being >0.90 med adherent and % of patients within JNC8 guidelines for BP control (<140/90 mmHg) at the 6 month visit (primary endpoint) between the two groups (SMASH; enhanced SC). Type I error rate was 0.05 (two-sided). Sample size was adjusted to account for the cluster randomization scheme, using variance inflation factor (VIF) method.[148] Power and sample size estimates were performed for within-clinic sample sizes of 22 subjects for 4 clinics per group, assuming ICCs ranging from 0.0 to 0.05.The ICC from our feasibility trials for primary outcomes of electronic med tray based MA and SBP was estimated at 0.04. For an ICC of 0.04 the proposed sample size of 22 per clinic and 4 clinics per group provides at least 90% power to detect a difference in the assumed 6-month MA/BP control rates between the 2 groups (difference of ≥30% between SMASH and SC based on feasibility trials' results).[22,23,25,26] For the proposed study, for calculation of the VIF we used the conservative absolute ICC value of .04 for a final sample size 176. We inflated that by 10% (N=192) to account for greater than expected attrition across the trial. Conservative estimates for expected MA (or BP control) proportions were used for power calculations; proportions observed in our SMASH feasibility studies were 89% vs.0%, N=19 for MA based upon MedMinder[22,23] and for resting SBP, an average of 90% vs. 10% for the three trials lasting 3 and 6 months and the recent 12-month follow-up (n=19,[22] n= 22,[25]n= 24,[23,] n=19,[22]).For secondary continuous outcomes of 24-hr BP (and MPR derived MA scores) for longitudinal analyses [assuming 4 intervention time points (months 3, 6, 12, and 18), level of significance = 0.05 (two-tailed), correlation among repeated measures (ICC ≤ 0.5)], we will have 90% power to detect a 0.48 standardized effect size (i.e., Cohen's d effect size). A standardized effect size of 0.48 sd is equivalent to a raw effect size ranging from 2.4 to 4.3 mmHg (raw scale units) for difference in SBP change from baseline between the groups for a range of sd from 5.0 to 9.0 mmHg, based upon our SMASH feasibility data.[22,23,25,26] For resting DBP based upon our SMASH findings, this equates to a difference of 1.3 to 3.3 mmHg assuming sd ranging from 2.0-5.0 mmHg. SMASH findings for the tray derived monthly MA scores revealed a difference in MA score changes between the groups from baseline to 3 month of 28% (sd=6.2).[22,23] Assuming similar adherence in both groups through the 6-month trial, we will have at least 94% power to detect differences in adherence change scores as small as 10% (with sd up to 15).

For AIMs 2: secondary outcomes (changes in SDT constructs [i.e., competence & autonomous motivation], % reaching & sustaining 24-hr BP control [<130/80 mmHg], therapeutic inertia (i.e., % making med change in patient's EHR & script delivery to patient or pharmacy within 24 hours of subject's clinic visit and/or receiving BP info report)[72] and **AIM 3:** exploratory outcomes (cost effectiveness; changes in TC,LDL,HgA1c, blood glucose) in the intent-to-treat sample, we have 80% power to detect a difference of 0.53 sd between the 2 groups assuming α = 0.05 (Type I error rate), two sided; independent sample t-test comparison of means; equality of variance between groups. For 24-hour BP, we will have > 85% power to detect a 30% difference in % reaching 24-hr BP control between groups. Our 24-hr BP data from a subgroup (N=12) of FQHC AAs in the feasibility trial found 85% of the SMASH group vs 25% of the SC group achieved 24-hr BP control at 6 mos.

D.9. Data Management & Quality Control: Quality control checks of anthropometrics/BP evaluations & 24-hr BP protocol delivery will be run on random selection of 10% of subjects per mo & protocol retraining conducted as needed. Questionnaire data will be directly captured via REDCap (HIPAA compliant, web-based app) & overseen by Mr. Patel and Dr. Mueller. Clinic data (e.g., anthropometrics, BP) & EMR derived data (e.g.TC, HgA1C) will be double entered with discrepancies resolved by Mr. Patel. Data will be reviewed on twice-monthly basis. Outlying, inconsistent data values, as well as missing data, will be targets of the data quality review. Issues will be communicated to Drs. Treiber, Chandler and Mueller for resolution.

D.10. Quantitative Analyses: AIM1 Primary outcome measures are % of subjects with >0.90 MA from MedMinder and % within JNC8 clinic resting BP guidelines (<140/90 mmHg). Secondary analyses will assess resting & ambulatory BP levels (e.g., 24-hr, daytime/nighttime BP level changes) & MA indices (i.e., MPR score changes). Intent-to-Treat (ITT) sample analyses will be used along with multiple imputation methods for missing end-of-study outcomes.[149,150] To assess relationships between intervention outcomes and intervention status (SMASH or SC) at end of the active trial period (6-mo visit, primary endpoint), two-sided Cochran-Mantel-Haentzel chi-square tests for unadjusted differences in proportions will be used. Adjusted differences in proportions at the 6-mo visit will be compared using logistic regression. To assess relationships over time, we will use a generalized linear mixed models (GLMM; generalized estimation equation [GEE]–type models) analytic model with group (SMASH vs SC) & time (3, 6, 12 &18 months) included as fixed effects and FQHC practice site as a random effect to account for clustering within FQHC practice site/MD.[151-153] In the first set of models, baseline measurement of the dependent variables (e.g., MA or BP levels) will be included as adjustment variable. The test of primary interest is F-test for the treatment x time interaction, which will reflect a difference in change between the 2 groups over the study. If a statistically significant treatment x time

interaction is found, we will obtain odds ratios for SMASH vs SC groups at each of the study time points.

A mixed effects model (MEM) will be used to compare the primary continuous outcome measures (e.g., tray or MPR derived MA scores or BP levels) for the two groups over the study period. Modeling will be carried out as described above. We will estimate resting and 24-hr BP changes and MA (MPR) changes for each subject over the trial (baseline, 3, 6, 12 &18 months) and the within subject longitudinal trajectories (e.g., slopes) and summarize as the mean longitudinal trajectory within each group. ICCs and variance estimates will be obtained of efficacy outcomes and covariance structure of the longitudinal scores for determination of sample size (and hence adequate power) for a future effectiveness RCT.

AIM 2 Secondary outcomes of changes in SDT constructs competence & autonomous motivation, % provider adherence to JNC8 guidelines (med changes based upon JNC8 guidelines made in EHR & script delivery within 24 hrs) & 24-hr BP will be assessed using GLMM with these outcomes as separate dependent variables, group as independent variable & primary outcomes (resting BP & MA) & clinical & sociodemographic factors included as adjustment variables. Modeling will be carried out as described above.

AIM 3 Exploratory outcomes of **changes in metabolic syndrome /CVD risk factors** (TC, LDL, blood glucose and HgA1c) in relation to intervention group with type of med (low vs high dose diuretics; old vs new selective beta1 blockers, etc.) as covariates will be assessed using MEM as described above in AIM1.

Cost-effectiveness analyses will be run using established methodology for economic evaluation of electronic drug monitoring for MNA.[154] Data will be collected on incremental direct and time cost SMASH program adds to enhanced SC for facilitating MA and BP control. This includes personnel costs for referral & BP/ MA screening, all supplies and equipment used (MedMinders, BP devices, smart phones/ data packages) and costs of additional meds beyond SC. Value of project manager's time will be included in attending to patient assistance calls, verification of out of range BPs, etc. Sensitivity analyses will estimate cost changes related to different types of personnel time needed to perform her tasks. We will define benefits as difference in cost of health services use and lost worked days between SMASH and SC groups. We will compare costs of emergency department (ED), outpatient and hospital visits during the 6-month trial and most importantly, the 12 months following trial completion. We will use estimates from the Healthcare Cost and Utilization Project[145] for ED and hospitalization and the Medical Expenditure Panel Survey[144] (for outpatient and individual out-of-pocket costs) to value healthcare use costs in each group. Thus, healthcare costs will be evaluated at institutional provider, third party payer and individual level and all costs adjusted using inflation adjustment from Bureau of Labor Statistics.[155] We will estimate cost of lost worked days during the 6-mo trial and12-mo follow-up and reported baseline income. We will assess differences in means, medians and quartiles based on distribution of the variables. As we did in another telehealth project, we will use GLM with appropriate distribution to examine association of SMASH with patient level healthcare costs and patient lost income adjusting for patient demographics and comorbidities.[156] We will conduct sensitivity analyses by estimating different healthcare costs and income models while adjusting for clinical outcomes (e.g., % with JNC8 BP control; % with 24-hr BP control). We will do the same for healthcare utilization and lost workdays using a count model (Poisson or Neg Bin if over dispersion occurs or zero-inflated if many zeros are present). We will perform a comparison of SMASH cost with changes in clinical outcomes to provide cost-effectiveness ratios for clinical outcomes.

Exploratory Moderator Analyses: Our conceptual model will guide moderator analyses of MA and BP control using logistic regression with >90% MA or BP control at 6 months as dependent variable and the GLMM/GEE model over the entire study (measurement times 3, 6, 12 and 18 months). Modeling will be carried out in a sequential fashion. Initial set of models will first be adjusted for sociodemographics (age, gender, education, marital status, income), autonomous motivation and biobehavioral factors (e.g., stress, sleep quality, depressive symptoms, med side effects, etc.).If needed, models will be further adjusted for new comorbidities (e.g., diabetes) and associated additional meds. Effect modifications of covariates (moderators) will be examined through inclusion of a covariate-by-group (SMASH vs SC) interaction term in the multivariable models.[67] We are especially interested in the interaction of treatment by gender, as well as SES and autonomous motivation.

Exploratory MNA Mediation Analyses: Potential mediators will be examined individually and subsequently in a multivariable model. Exploratory analyses will follow modifications suggested by MacKinnon, Fairchild and Fritz[157] of the causal steps approach developed by Baron & Kenny.[158] Analyses will be guided by our conceptual model framed upon change scores in SDT constructs (competence & autonomous motivation) followed by MNA mediators identified in the empirical literature including biobehavioral (e.g. stress, med side effects, depression symptoms, sleep quality, perceived disease severity, doctor-patient relationship, quality of life, HTN knowledge/beliefs) and process /uptake features (e.g., opening of motivational/reinforcement messages/education info, BP graph uploads via phone, patient SMASH (or SC) usability and satisfaction scale

scores, mobile app usability scale score). These results will be used in exploratory structural equation modeling with outcomes of sustained MA and BP control. Those findings will further guide SMASH refinement for a future effectiveness RCT. Dropout rate is an important issue. We will assess reasons for dropout and compare groups for missing outcome measures using logistic regression modeling. If >10% of data are missing, we will likely add an intermediate evaluation point in a future RCT to provide more data for use in endpoint imputation. Frequency distributions of adverse events & serious adverse events will also be obtained. Proportions within categories of AEs/SAEs for the SMASH vs. SC will be compared via chi-square analyses.

D.11. Qualitative & Mixed Methods Analyses: As in our other recent studies,[159-163] we will use the constant comparative method of qualitative analysis derived from constructivist grounded theory.[164,165] This approach acknowledges researchers' prior knowledge and influence in the process, supports and provides guidelines for building a conceptual framework to understand interrelations (e.g., what and how) between constructs. NVivo 11 will be used to identify common themes constructs regarding MA, BP self-monitoring, etc. Iterative coding will be conducted by Dr. Chandler to identify thick descriptors of informants' responses, refine theme classifications, and impose a data-derived hierarchy of nodes. Interrelations between individual classifications (e.g., gender, age, responder vs partial/non responder) and themes will be examined for relationships. To evaluate reliability and validity of the conclusions, Dr. Nemeth will code a random selection of 20% of these cases and conduct member checks to ensure validity of the findings. Drs. Chandler and Nemeth will use reflection and a process of immersion and crystallization[166] to reconcile any differences and reach consensus. Once no new themes emerge, thematic saturation will have been reached,[167] We will compare and contrast themes from participants and providers. The quantitative and qualitative data sources will be analyzed in a mixed methods sequential triangulation approach.[168] We will refine SMASH content, delivery format and feedback mechanisms for initial and sustained use, based on participants' adherence data, responses to feedback, providers' responses and other variables that might influence optimal use of SMASH.[169,170]

D.12. Potential Problems, Pitfalls & Solutions: **A potential problem for any RCT is subject recruitment & retention.** The FQHC network identified 2,619 21-59 yr old AAs with uncontrolled HTN (mean age=45.3 yrs) who meet initial prescreening inclusion criteria. Using a 75% participation rate for screening, as experienced in the FQHC feasibility trial, we project access to ~1,964 AAs with sole diagnosis of uncontrolled HTN. Our SMASH trial which used electronic pill monitoring found 79% had 1 mo adherence score <0.85.[22,23] Given our 91% minimum acceptance into randomization on our feasibility trials involving AAs, a conservative estimate would give us ~1411 patients. Multiple tactics will be used to foster high retention including obtaining full contact info for subjects' immediate family members and ≥ 2 friends at enrollment and updating every evaluation. Transportation will be provided when needed; project evaluations will be scheduled, whenever possible, on subjects' scheduled clinic visits. Birthday and holiday cards will be sent out and non-study related telephone calls made. **A second issue may be subject "tech-phobia".** Our research with AA HTNs,[20,21] found little concern regarding use of an electronic tray or automated BP monitor, as they operate similarly to instruments they use (e.g., pill trays; digital BP devices).Our SMASH feasibility trials found high acceptability, satisfaction and adherence to the MedMinder and BP self-monitoring protocols.[22,23,25,26] Patients will be provided auto call numbers in their SMASH app should they experience technical problems. **A third issue is possible post-trial adherence deterioration.** We elected not to include a booster program or other post trial intervention (e.g., motivational interviewing) as our intent is to determine whether 6 mos of SMASH results in persistent improvements in MA and BP control resulting from increased competence and autonomous motivation. SDT-based behavioral change programs that are typically 3-6 mos have led to lasting changes 1-2 yrs later.[92,95-97] Tentative support was recently published suggesting sustainability of SMASH program's impact upon MA with a 12-mo post-trial eval of AA kidney transplant patients' medical records.[24] Former SMASH patients sustained lower BP levels and better JNC8 designated BP control compared to the SC group. Whether such can be achieved with the SMASH program adapted for a more challenging group of patients, AAs with sole diagnosis of uncontrolled HTN, requires evaluation. If reductions are observed, the future effectiveness RCT will include booster sessions guided by participants' suggestions. **A fourth issue is the MedMinder does not detect pill ingestion**. Although the gold standard for med intake monitoring is biosensor pills (e.g., Proteus), these are not commercially available or financially feasible. Further, a 12-wk trial using the Proteus Digital Health ingestible sensor system verified 99-100% accuracy of pills ingested, but 40% of patients dropped out during the first month due to side effects (i.e., diarrhea, erythema & rash from the on-body sensor patch).[171] During weeks 8-12, 61% of the remaining patients required SMS reminders to take their pills. In our feasibility trials, increased BP control mirrored increases in MA suggesting AAs with uncontrolled HTN do not fake pill intake. The proposed efficacy RCT will determine whether this is replicable and if improvements in MA and BP control are sustained over the 6-mo intervention and subsequent 12-mo follow-up. **Finally, we**

will have a wealth of data to address important issues not detailed which will guide our future work. For example, we will use triangulation of Morisky MA self-report scale, MPR, pharmacy record information and MedMinder data to develop an effective algorithm for MA measurement.

PROTECTION OF HUMAN SUBJECTS

This Human Subjects Research meets the definition of a clinical trial.

1. Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

This will be a two-arm RCT design that will assess efficacy of the SMASH mHealth program compared to an enhanced standard care (SC) program. Participants will be drawn from Fetter Health Care Network (FHCN), the sole FQHC center in the 4-county area (Charleston, Dorchester, Colleton and Berkeley counties). The Medical University of South Carolina Family Medicine and Internal Medicine clinics will be available if needed for recruitment of participants. Collectively,this offers a unique opportunity to recruit underserved, at risk patients without extensive screening protocols. We will recruit 192 AAs with uncontrolled HTN (no other comorbidities) and MNA according to the inclusion and exclusion criteria below and the methods described in Section D.2. Participants. The Fetter Health Center Information Technology Department will provide a list of potentially eligible patients to the SMASH project manager, Dr. Chandler. She will make the initial phone contact with potential subjects. She will inform them about the study and that they will have an equal chance of being randomized to either the enhanced health education (i.e., enhanced standard care [SC]) or SMASH cohort if they are found eligible at the conclusion of the screening period. Following a successful BP screening (SBP ≥140 mmHg), a battery of questionnaires are completed and then 24-hour BP monitoring will occur. Likelihood of white coat hypertension in these patients is low.[30,75,76] We found no case of white coat hypertension in the FQHC feasibility trial involving AAs. If the participant's 24 hour SBP is ≥130mmHg, he/she will proceed to the next phase of screening involving use of the Maya MedMinder for one month with reminder signals deactivated. If MA score < .85, they will again complete the baseline clinic BP evaluation and 24-hr BP monitoring to reconfirm uncontrolled SBP HTN.

The practice sites will have been randomly assigned to SMASH or SC. The MDs and nurse managers at each site will have received an orientation in the SMASH study and refresher on the JNC8 Guidelines for HTN management. **As in our feasibility trials, the project research technicians responsible for conducting all evaluations will remain blinded to the subjects' status for the entire duration of the study and follow-up.** To help prevent contamination, the SMASH and SC subjects will be reminded by phone the night before study evaluations by Dr. Chandler and again in clinic by the nurse manager, not to discuss their involvement in the trial with the technicians. Subjects will also be instructed not to discuss their treatment regimen with other individuals excepting those in their household. **The SMASH project manager, Dr. Chandler, will not be directly involved with data collection, as she will be a phone contact for SMASH subjects and will not be blinded**. This same approach was successful in the 6-month FQHC feasibility trial.

Primary clinical outcome variables are 1) fraction of subjects reaching JNC8 guidelines for BP control (i.e., resting BP <140/90 mmHg), and 2) fraction of subjects with medication adherence score >0.90, as measured by electronic medication tray. Secondary clinical outcome measures include provider adherence to JNC8 guidelines, as measured by timing of medication changes, % reaching 24-hr ambulatory BP control (BP<130/80 mmHg) and changes in subjects' SDT constructs of competence and autonomous motivation. Exploratory outcome variables will include cost effectiveness, other MA indices (i.e., pharmacy record based medication possession ratio [MPR] and self-report [Morisky scale]) and examination of potential moderators (e.g., gender, age, income, etc.) and mediators (e.g., competence, autonomous motivation, perceived disease severity, med side effects, depressive symptoms, sleep quality, etc.) on MA and BP control. We will also explore impact of SMASH program (i.e., increases in MA) upon changes in physical risk factors of TC, LDL, HgA1c and blood glucose. All data will be evaluated on an intent-to-treat basis.

Inclusion Criteria:

1. 21-59 years old; male or female; African American or Black
2. Prescribed medication(s) only for HTN;
3. Medication possession ratio (MPR) <.85 for last 3 months;
4. uncontrolled HTN (SBP ≥140 mmHg) based upon last clinic visit within previous 12 months, initial clinic screening and subsequent recruitment evaluation following one month med intake screening with score of <.85 ;

5. 24-hour SBP ≥ 130 mmHg on clinic screening and subsequent recruitment evaluation;
6. Ability to speak, hear and understand English;
7. Able to take their own BP and self-administer medications;
8. Owns smart phone with data plan;
9. Primary care provider's assent that patient is able to participate

Exclusion Criteria:

1. No other known chronic disease (e.g.,chronic kidney disease (GFR<50 mL/1.7 m2/min;diabetes (type one or two);renal dialysis ;cancer diagnosis or treatment in past 2 years;prior cv event such as heart attack, congestive heart failure, arterial stent, coronary artery bypass graft ; psychiatric illness
2. Beck Depression Inventory score >13
3. Ongoing substance abuse (e.g., >21 drinks/week);
4. Planned pregnancy;
5. Vulnerable populations such as pregnant or nursing women, prisoners, and institutionalized individuals.

Healthcare Team Focus Groups: The 8 primary providers and their nurse managers whose 4 practice sites are randomly selected to deliver SMASH will be eligible to attend a focus group after all patients have completed the final follow-up. All participants will provide written informed consent before taking part in the focus groups and we anticipate that, as before, all healthcare team members will participate. Due to the nature of this sample, a targeted/planned enrollment recruitment table based on gender, race, or ethnicity was not developed.

b. Sources of Materials

In determining eligibility and subsequent enrollment, participants will have their resting BP measured by a research technician during an initial screening visit.If their average of the final 2 SBP readings ≥140 mmHg and their 24-hr SBP ≥ 130 mmHg, they will be eligible for the 1-month MA screening using the electronic medication tray with its reminder functions disabled. If, at the end of the 1-month MA screening, the adherence score is <0.85, they will participate in a baseline study evaluation that will again include measurement of resting BP and 24 hour BP. Those who again have uncontrolled HTN (resting SBP ≥140 mmHg and 24-hr SBP ≥ 130 mmHg) will be eligible for participation in the trial. Participants will have the resting BP and 24-hr BP monitoring performed again at months 3, 6, 12, and 18. At each evaluation, participants will complete a battery of questionnaires that have been purposely selected as having established psychometric properties for AAs and the age range of our cohort (see Appx 1, 7-21 for copies of questionnaires and additional psychometric properties than those presented in Table 3). Questionnaires will include measures of self reported MA, competence, autonomous motivation, health literacy, HTN knowledge, adverse events, med side effects, depression, sleep quality, stress, quality of life, patient satisfaction with provider). They will also complete several scales scale that assesses degree of satisfaction with study implementation and study/home evaluations, usability of the SMASH protocol ,app and wireless BP device or the enhanced SC group's educational materials, and potential barriers/facilitators of adherence. As part of standard care, all participants will have blood drawn at baseline and months 6, 12 and 18 to include TC, LDL, HgA1c and blood glucose levels. All subjects will wear an ambulatory BP monitor for 24-hr on several occasions over the course of the study. The combination of anthropometric evaluations, resting BP measurements, ambulatory BP measurements, and the majority of the questionnaires has been used in prior studies (e.g., HL 05662, HL 078216, and SMASH feasibility RCTs) and was not considered a burden by the subjects. All study materials will be de-identified so that only the subjects ID number will be associated with any collected data.

On completion of the final follow-up evaluation, a random sample of 32 of the 96 SMASH subjects will participate in a focus group (4-5 per group). SMASHers will be stratified by sex, age (<40/>40), practice site and MA responder classification. That is, 16 SMASH responders (MA >.90) and 16 non/partial responders (MA <.90.) based upon their cumulative adherence score (MedMinder 6 mo MA score and MPR level across follow-up period).We anticipate 3-4 groups of responders and 3-4 groups of nonresponders. Topic areas will include perceptions of the SMASH protocol, the MedMinder electronic medication tray, the home BP monitors, smart phone delivery of BP feedback, smart phone-relayed motivational and reinforcement messages. They will provide perspectives on the usefulness of SMASH and suggestions for enhancing its acceptability, usability and sustainability. Qualitative analyses of the focus groups will identify themes using NVivo 11.0 software to analyze audiotape recordings and transcriptions of the group meetings.

c. Potential Risks

Potential risks to the participants are minimal. The only invasive procedures are venipunctures, which are conducted as part of standard care at baseline, months 6, 12 and 18 for blood labs of which we will focus upon TC, LDL, HgA1c and blood glucose. All questionnaires have been purposely selected so that they can be completed in the briefest time possible. Those who prefer will have the forms read to them. Participants will be given an opportunity to discontinue participation in the study at any time for any reason. There are no aspects of the intervention or testing protocol expected to cause physical discomfort with exception of venipunctures.

The two programs presented (SMASH and enhanced SC) are non-invasive and present no more than minimal risks to the participants; the treatment modalities themselves are hygienic and health promoting with no known adverse physical side effects. SMASH medication and BP monitoring adherence will be monitored automatically via HIPAA compliant transfer of encrypted, deidentifed data to our server. Participants' data will not be stored on the cell phone but will be encrypted and sent to password-protected server storage. The study procedures (e.g., resting BP, questionnaires, ambulatory BP) are all non-invasive and present no more than minimal risks to the participants. In the unlikely event that adverse event occurs during a study visit, the participant will be in the healthcare facility where they normally see their treating physician and where the medical team is familiar with their medical history. The situation will be assessed and appropriate treatment will be provided, or if necessary, transportation by ambulance to a nearby emergency department will be arranged. There are no social or legal risks associated with participation in the study. Confidentiality will be maintained. Participant data will be stored in locked files with coded ID numbers.

2. Adequacy of Protection Against Risks

a. Recruitment and Informed Consent

The MUSC IRB has approved the use of SMASH, the various study procedures, and the ICD. The practice site MDs and nurse managers maintain CITI certification. Several Fetter Health Care Network (FHCN) MDs are quite familiar with SMASH, as they jointly participated in the development of the provider portion of the program. They helped design the MD summary report contents and how such a program can best function given the way their FHCN center (and other FQHCs) operate. They will receive training from the PI, Dr. Treiber, project manager, Dr. Chandler, and Co-I, Dr. Diaz, on the rationale for the SMASH efficacy trial and how the programs will operate. The SMASH project manager, Dr. Chandler, will contact potentially eligible patients by phone to gauge their interest. If they express an interest in participating, they will be invited to an initial screening at the FHCN clinic. She will explain the risks and benefits of study participation at the time of their screening visit. Interested participants will have all of their questions answered and will sign a written informed consent document. All participants will be reminded that they are free to contact study personnel or the PI at any time if any questions or concerns arise. They will be provided a copy of the written consent with the SMASH project with contact information for the project manager, the PI, and the MUSC IRB Chair.

b. Protections Against Risks

All the material delivered to the SMASH cohort by smart mobile phone and to the SC cohort either by mobile phone or hard copy mail are hygienic and health promoting and non-invasive with no known adverse physical side effects and present no more than minimal risk to the subject. With exception of standard of care blood draws, the study procedures are non-invasive and present no more than minimal risks to the subject. Subject data will be stored with coded ID numbers and no identifiers will accompany the data files. Confidentiality will be maintained. Dr. Treiber will keep all records in locked storage areas and on encrypted network storage.

3. Potential Benefits of the Proposed Research to Human Subjects and Others

Participants in enhanced SC may learn more about how unhealthy lifestyle behaviors (e.g., high salt/fat diet, smoking, sedentary lifestyle, alcohol intake) contribute to uncontrolled HTN and CVD events. They may learn how to initiate healthy lifestyle changes in such a way that they are likely to be maintained over time. The SMASH participants may benefit by learning better self-management skills related to medical regimens, by having potential misconceptions clarified (e.g., importance of dosing times, that HTN is a permanent condition), by learning the importance of following doctor's orders (especially as it relates to medicine taking), by attending routine clinic evaluations, and by disclosing side effects and the use of any homeopathic/cultural remedies. By doing so, they may not only improve their long-term BP control but also reduce their risk of CV events, chronic kidney disease, stroke, etc. They will also be better prepared and able to successfully engage in additional medication intake regimens that would arise if they develop other comorbidities over time.

4. Importance of Knowledge Gained.

Despite tremendous advances in the medical management of HTN, levels of BP control are far from optimal, especially among AAs. Two major contributors to uncontrolled HTN are medication non-adherence (MNA) and therapeutic inertia. MNA is common among HTNs and contributes to patient morbidity and mortality (e.g., renal failure, stroke, diabetes and CV events.) To date, no mHealth RCT has been conducted with AAs that has demonstrated high, sustained, MA and improvement in BP control. Medication regimen and BP control programs are needed which can be sustained over time by HTNs, especially AAs who have not yet developed any other comorbidities. Innovative approaches for improving MNA that are effective, acceptable, feasible, and sustainable are urgently needed. Helping patients develop functional health literacy, self-efficacy and intrinsic motivation for sustained adherence to their medical regimen with their sole diagnosis of hypertension will help curtail the ravages of uncontrolled hypertension upon other biological systems and vasculature leading to additional comorbidities and/or CV events. The proposed research will address these issues by evaluating and refining a theory-driven mHealth-based med reminder and BP monitoring program that utilizes tailored feedback messages to motivate and sustain the subjects' medical regimen related behaviors. The SMASH system will also provide the SMASH primary providers (and their nurse managers) with summaries of subjects' MA and BP alongside JNC8 management guidelines for HTN in an effort to reduce therapeutic inertia and allow more rapid and sustained control of HTN. If the efficacy RCT outcomes are positive, we will have developed a practical, patient and provider friendly, MA enhancement and BP control program that will be ready for a full-scale, multi-site, effectiveness RCT. If sustained control of BP is observed in the full-scale effectiveness RCT, we will have made significant strides in our long-term objective to develop practical, effective, and sustainable primary and secondary prevention programs for AAs with sole diagnosis of HTN. Dissemination of SMASH and other programs as part of best practice models will help curtail the heavy burden of uncontrolled HTN and its associated morbidity and mortality.

5. Data and Safety Monitoring Plan

The MUSC IRB has reviewed this study and determined that this study presents no more than minimal risk to the subjects. Any severe adverse events will be reported to the IRB within 24 hours and all other unanticipated and possibly related adverse events will be reported as part of the annual re-approval process per the IRB policy. Dr. Treiber will monitor the recruitment of subjects, the conduct of the study, and the integrity of data collection. Dr. Treiber and the data manager (Sachin Patel, MS) will continuously monitor adverse events. As PI, he will be responsible for ensuring that adverse events are reported to the IRB in compliance with their requirements. Given the minimal risk associated with the intervention, we will utilize an internal Data Safety Monitoring Board (DSMB) with the addition of two external members. Drs. Diaz and Mueller will comprise the internal members. The members external to the project include Dr. Gaynelle Magwood (nurse behavioral scientist) and Dr. Robert Adams (neurologist who specializes in management of hypertension and stroke.) Both have served on other DSMBs and have significant experience in health-related practice-based participatory research programs. The DSMB will meet twice per year to review study progress (e.g., recruitment, retention, and adverse events) and Mr. Patel will provide monthly administrative reports that describe the study progress including accrual, demographics and subjects' status. The reports will also describe adherence to inclusion/exclusion criteria and study protocol and any adverse events. Drs. Diaz and Mueller will review reports on a monthly basis after the intervention has begun. The adequacy of recruitment and retention will be addressed at those points. Summary reports, void of personal identifiers, will be provided to the NIH annually as part of progress reports. Drs. Adams and Magwood, as well as Drs. Diaz, and Mueller, will be alerted if any unexpected serious (e.g., injury requiring medical treatment) adverse event occurs to determine whether changes in the study protocol (e.g., additional safety measures, change in exclusion criteria) are needed. If, in the unlikely event we encounter any serious adverse events (SAEs), the DSMB will convene and determine whether the SAE was likely a result of participation in the trial. If so, and a consensus cannot be reached regarding preventing reoccurrence of a similar event, the NIH will be contacted to discuss procedures for halting the trial. If any changes to the protocol are needed, Dr. Treiber will notify the IRB and the NIH. Summary reports of interim analyses will be provided to NIH as part of annual progress reports. Ongoing quality control will include regular data verification and protocol compliance checks to be performed by Drs. Treiber, Chandler and Mueller.

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Autonomous Motivation Questionnaire (TSRQ) (Williams GC et al. (1996)

(

Description: (The purpose of TSRQ is to assess the degree to which one's motivation for a particular behavior or set of behaviors is relatively autonomous or self-determined, (of if motivation is externally driven ((controlled). (The responses on the autonomous items are averaged to form the reflection of autonomous motivation for the target behavior and the responses on the controlled items are averaged to form the reflection of controlled motivation for the target behavior. (In those studies where a motivation has also been assessed, (the amotivated responses are also averaged. (These three subscale scores can be used separately, (or a (Relative Autonomy Index can be formed by subtracting the average for the controlled reasons with the average for the autonomous reasons. ((Autonomous: (1,3,6,8,11,13r (Controlled: (2,4,7,9,12,14r (No motivation: (5,10,15)(

(

((

(

1. (Source: ((Williams GC et al. ((1996) (Motivational predictors of weight loss and weight-loss maintenance, (Journal of Personality and Social Psychology, (70, (115-126. (

(

Sample Characteristics: (94 obese individuals who enrolled in a weight loss program. ((27% male (Mean age (43.4 (Range: (20-77)(

(

Psychometric Properties: (Reliability: (

(Test-Retest coefficient ((after (18 months (or more) (Autonomous items: (r (=(.47 ((p (<(.01), (Controlled items (.34 ((p (<.05). (

Validity: (Autonomous items (correlated (with (Autonomy orientation (score (of (General (Causality (Orientations (Scale ((r (=.38, (p<(.001) (and (the (Perceived (Autonomy (Support (of (the (Health (Care (Climate (Questionnaire ((r (=.38, (p<.001). (

Predictive (Value: (Autonomous (items (at (start (predicted (attendance ((r (=.34, (p<.001) (and (BMI ((r (=(-.11, (p<.05). (

(

2. (Source: (Williams GC et al. ((1998) (Autonomous (regulation (and (long-term (medication (adherence (in (adult outpatients, (Health (Psychology, (17, (269-276. (

(

Sample Characteristics: (126 (Adults (taking (at (least (one (prescription (pill ((24.6% (male, (mean (age (56.3 (years, (range: (37-65)(

Psychometric Properties: (Reliability: (

Internal (consistency: (Cronbach's (alpha (score, (Autonomous (items=(.81, (

Controlled (items (=(.84 (

(Validity: (Autonomous (items (correlated (with (the (Perceived (Autonomy (Support (of (the (Health (Care (Climate (Questionnaire ((r (=.24, (p (<.05). (

Predictive (Value: (Autonomous (items (predicted (adherence ((r (=.58, (p<.0005). (

((

Medication Adherence (ASRQ)

(

The following questions relate to the reasons why you would either start to take your medicine as prescribed by your physician or continue to do so.

+

Different(people(have(different(reasons(for(taking(medicine(as(prescribed,(and(we(want(to(know(how(true(each(of(the(following(reasons(is(for(you.(Please(indicate(the(extent(to(which(each(reason(is(true(for(you.(

(

All 15 responses are to the one question:

+

The reason I would take my medicine as prescribed by my physician is:

+

1. Because I feel that I want to take responsibility for my own health.

○	○	○	○	○	○	○
1	2	3	4	5	6	7
Not at all True		Somewhat True		True		Very True

2. Because I would feel guilty or ashamed of myself if I did not take my medicine as prescribed.

○	○	○	○	○	○	○
1	2	3	4	5	6	7
Not at all True		Somewhat True		True		Very True

3. Because I personally believe it is the best thing for my health.

○	○	○	○	○	○	○
1	2	3	4	5	6	7
Not at all True		Somewhat True		True		Very True

4. Because others would be upset with me if I did not.

○	○	○	○	○	○	○
1	2	3	4	5	6	7
Not at all True		Somewhat True		True		Very True

5. I really don't think about it.

○	○	○	○	○	○	○
1	2	3	4	5	6	7
Not at all True		Somewhat True		True		Very True

6. Because I have carefully thought about it and believe it is very important for many aspects of my life.

○	○	○	○	○	○	○
1	2	3	4	5	6	7
Not at all True		Somewhat True		True		Very True

7. Because I would feel bad about myself if I did not take my medicine as prescribed.

○	○	○	○	○	○	○
1	2	3	4	5	6	7
Not at all True		Somewhat True		True		Very True

8. Because it is an important choice I really want to make.

○	○	○	○	○	○	○
1	2	3	4	5	6	7
Not at all True		Somewhat True		True		Very True

9. Because I feel pressure from others to do so.

○	○	○	○	○	○	○
1	2	3	4	5	6	7
Not at all True		Somewhat True		True		Very True

10. Because it is easier to do what I am told than think about it

○	○	○	○	○	○	○
1	2	3	4	5	6	7
Not at all True		Somewhat True		True		Very True

11. Because it is consistent with my life goals.

○	○	○	○	○	○	○
1	2	3	4	5	6	7
Not at all True		Somewhat True		True		Very True

12. Because I want others to approve of me.

○	○	○	○	○	○	○
1	2	3	4	5	6	7
Not at all True		Somewhat True		True		Very True

13. Because it is very important for being as healthy as possible.

○	○	○	○	○	○	○
1	2	3	4	5	6	7
Not at all True		Somewhat True		True		Very True

14. Because I want others to see I can do it.

○	○	○	○	○	○	○
1	2	3	4	5	6	7
Not at all True		Somewhat True		True		Very True

15. I don't really know why.

○	○	○	○	○	○	○
1	2	3	4	5	6	7
Not at all True		Somewhat True		True		Very True

Medication Adherence Self-Efficacy Scale Revised (MASES-R) (Fernandez, et al., (2008)

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Description: (The (Medication (Adherence (Self-Efficacy (Scale ((MASES-R) (consists (of (13 (self-administered (questions, (which measure (situation-specific (efficacy (beliefs (regarding (adherence (to (prescribed (antihypertensive (medications. (Responses (are (Not (at (all (sure (= (1, (A (little (sure (= (2, (Fairly (sure (= (3, (Extremely (sure (= (4. ((

(

1. (Fernandez (S, (et (al. ((2008) (Revision (and (validation (of (the (medication (adherence (self-efficacy (scale ((MASES) (in (hypertensive (African (Americans. (Journal (of (Behavioral (Medicine, (31 (6), (453-462 (
   Sample (Characteristics: (((168 (hypertensive (African (Americans ((14% (male) (mean (age (54 ((±12.4) (years. (
   +
   Psychometric (Properties: ((Reliability: (Chronbach's (alpha (= (.92 (
   Test-Retest ((3 (months) (coefficient (= (.51 ((p<.001). (
   Concurrent (Validity: (With (self-Report (of (adherence, (Non-adherent (Mean (= (3.51 (±(.52, (adherent (Mean (= (3.81 (±(.33 ((p<.001) (
   With (electronic (adherence (measure ((MEMS) (at (3 (months: (r (= (.20, (p (= (.02. (
   Predictive (validity: (Baseline (MASES-R (with (MEMS (at (3 (months: (r (= (.19, (p (= (.02. (
2. (Voils (C, (et (al., ((2012) (Initial (Validation (of (a (Self-Report (Measure (of (the (Extent (of (and (Reasons (for (Medication (Nonadherence. (Med (Care, (50, (1013-1019. (
   Sample (Characteristics: (202 (hypertensive (veterans ((86% (male), (mean (age (64.1 ((±(11) (years, (50% (Black. (
   (
   Psychometric (Properties: (Concurrent (validity: (with (Extent (of (Nonadherence (measure: (r (= (-.42, (p<.0001. ((
   +
3. (Breaux-Shropshire (T, (et (al., ((2012) Relationship (of (Blood (Pressure (Self-Monitoring, (Medication (Adherence, (Self-Efficacy, (Stage (of (Change, (and (Blood (Pressure (Control (Among (Municipal (Workers (With (Hypertension. (Workplace (Health (& (Safety, (60 (7), (303-311. (
   Sample (Characteristics: (149 (hypertensive (municipal (employees ((85% (male), (mean (age (47 ((±(8.4) (years, (69% (Black. (
   (
   Psychometric (Properties: (Concurrent (validity: (with (Morisky (Medication (Adherence (Scale: (r (= (.549, (p<.001. ((
   +
   + +

+

MASES]R+

+

Situations(come(up(that(make(it(difficult(for(people(to(take(their(medications(as(prescribed(by(their(doctors.(
Below(is(a(list(of(such(situations.(We(want(to(know(your(feelings(about(taking(your(blood(pressure(
medication(s)(in(each(of(these(situations.(Please(indicate(your(response(by(checking(the(box(that(most(closely(
represents(your(feeling.(There(are(no(right(or(wrong(answers.(

(

For(each(of(the(situations(listed(below,(please(rate(how(sure(you(are(that(you(can(take(your(blood(pressure(
medications(all(of(the(time.(

(

Items+	Not+at+all+ sure+	A+little+ sure+	Fairly+ sure+	Extremely+ sure+
How confident are you that you can take your blood pressure medications:+				
1.(When(you(are(busy(at(home(	((	((	((	((
2.(When(there(is(no(one(to(remind(you(	((	((	((	((
3.(When(you(worry(about(taking(them(for(the(rest(of(your life(	((	((	((	((
4.(When(you(do(not(have(any(symptoms(	((	((	((	((
5.(When(you(are(with(family(members(	((	((	((	((
6.(When(you(are(in(a(public(place(	((	((	((	((
7.(When(the(time(to(take(them(is(between(your(meals(	((	((	((	((
8.(When(you(are(travelling(	((	((	((	((
9.(When(you(take(them(more(than(once(a(day(	((	((	((	((
10.(When(you(have(other(medications(to(take(	((	((	((	((
11.(When(you(feel(well(	((	((	((	((
12.(If(they(make(you(want(to(urinate(while(away(from(home(	((	((	((	((
Please rate how sure you are that you can carry out the following task:+				
13.(Make(taking(your(medications(part(of(your(routine(	((	((	((	((

(

+ +