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Addressing antihypertensive medication adherence through EHR-enabled teamlets in primary care

Principal Investigator:	Saul Blecker, MD NYU Grossman School of Medicine Departments of Population Health and Medicine 227 E 30th Street, 6th Floor Saul.blecker@nyulangone.org (646) 501 2513
Sub-Investigators:	Devin Mann, MD Department of Population Health NYU Grossman School of Medicine 227 E 30th St., 6th Floor devin.mann@nyulangone.org 212-263-9026 Antoinette Schoenthaler, EdD Department of Population Health NYU Grossman School of Medicine 180 Madison Avenue Antoinette.Schoenthaler@nyulangone.org 646-501-3434
Additional Investigators:	Hayley Belli Department of Population Health NYU Grossman School of Medicine Hayley.Belli@nyulangone.org Tiffany Rose Martinez Department of Population Health NYU Grossman School of Medicine Tiffany.Martinez@nyulangone.org Yunan Zhao Department of Population Health NYU Grossman School of Medicine Yunan.Zhao@nyulangone.org
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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), any other applicable US government research regulations, and institutional research policies and procedures. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
FFR	Federal Financial Report
FWA	Federalwide Assurance
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

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Protocol Summary

Title	Addressing antihypertensive medication adherence through EHR-enabled teamlets in primary care
Short Title	Addressing antihypertensive medication adherence through EHR-enabled teamlets in primary care
Brief Summary	Our research will be conducted in two phases. During Phase 1, we will refine a multicomponent intervention that utilizes linked EHR-pharmacy data to identify patients with medication non-adherence and facilitates EHR-enabled teamlets and health coaching to improve adherence to antihypertensive medications. To do this, we will conduct workflow assessments, stakeholder interviews, observations, and design workshops to generate the initial concepts for integration and workflow of intervention components; perform usability testing; and validate EHR-based rules to identify patients with low medication adherence and uncontrolled hypertension. During Phase 2, we will conduct a cluster randomized control trial in up to 22 NYU primary care practices to assess the effectiveness and implementation of the multicomponent intervention on medication adherence and blood pressure control for patients who are non-adherent to antihypertensive medications. Patient outcomes will be assessed using electronic health records.
Phase	Multiphase: Phase 1: pre-implementation and usability testing, Phase 2: RCT
Objectives	**Phase 1.** Primary Objective: to conduct workflow assessments with stakeholders to identify best fit of the intervention and identify optimization opportunities. This will include assessment of the “usability” of the proposed intervention in clinical practice. Secondary Objective: to develop and validate EHR-based rules to identify patients with low medication adherence and uncontrolled hypertension. **Phase 2.** Primary Objective: to assess the effectiveness and implementation of the multicomponent intervention on medication adherence and blood pressure control for patients who are non-adherent to antihypertensive medications.
Methodology	Phase 1: Interview of key informants and in-clinic observations of primary care providers, registered nurses, licensed practical nurses, and medical assistants, to assess workflows followed by usability testing. Additionally, we will perform chart review to validate our EHR based definitions for hypertension and medication adherence. Phase 2: Cluster randomized control trial in up to 22 NYU primary care practices (1:1 randomization)
Endpoint	**Phase 1.** Primary Endpoint: optimization of the intervention Secondary endpoint: chart review gold standard of definitions for hypertension and medication adherence. **Phase 2.** Primary Endpoint: medication adherence as measured by proportion of days covered (PDC), systolic and diastolic blood pressure Secondary Endpoint: adoption, acceptability, fidelity
Study Duration	Phase 1: 24 months Phase 2: approximately 24 months

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Participant Duration	Interviews with clinical staff: approximately 30-60 minutes Patients with uncontrolled hypertension: up to 24 months (evaluations are conducted using electronic health records (EHR) only
Population	**Phase 1.** Clinicians: Up to 100 clinicians (primary care providers, RNs, NPs and MAs) from practices at NYULH for workflow analysis and usability testing Patients: We will identify a population of approximately 1,300,000 adult patients with hypertension seen in our health system. From these, we will randomly sample about 500 patients for detailed chart review. **Phase 2.** Clinicians: Up to 100 clinicians (primary care providers, RNs, NPs and MAs) across approximately 22 primary care clinics in the NYU Langone Health network Patients: Approximately 100-200 patients per each study site (up to 4400 patients total)
Description of Study Agent/Procedure	Electronic Health Record (EHR) module assessing patient adherence to antihypertensive medications, barriers to adherence, and prompts to provide brief health coaching to the patient care team.
Study Sites	NYU Langone Health
Number of participants	Phase 1: 100 clinicians and clinical data from 1.3 million patients Phase 2: approximately 22 primary care clinics in the NYU Langone Health network, including up to 4,400 patients and 400 clinicians
Statistical Analysis	**Phase 1.** N/A for workflow analysis and usability testing as this is observational. For validation of EHR-based definitions, we will calculate sensitivity, specificity, positive predictive value, and negative predictive value. **Phase 2.** Descriptive and inferential statistics examining changes in proportion of days covered and blood pressure. Implementation outcomes (adoption, acceptability, fidelity), cost-effectiveness (ICER)

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1 Introduction, Background Information and Scientific Rationale

1.1 Background Information and Relevant Literature

Medication non-adherence is a major contributor to inadequate blood pressure control.[1] Among patients with hypertension, medication non-adherence ranges from 30 to 50%, depending on the study and the measure of adherence utilized.[2-5] Nearly half of patients who are newly started on antihypertensive medications discontinue their medications within one year of diagnosis.[6] Furthermore, it is estimated that 33-50% of patients with hypertension have poorly controlled blood pressure due to medication non-adherence.[7] As a result, poor medication adherence has been associated with increased rates of cardiovascular events, hospitalizations, and mortality in patients with hypertension.[8,9] Poor adherence to antihypertensive medications is estimated to incur $100 billion in annual healthcare costs.[1,3]

Medication adherence is poorly assessed in clinical practice. For the healthcare provider, an accurate understanding of patient adherence behaviors is a critical component of effective disease management. However, several studies have demonstrated that healthcare providers inaccurately estimate patient adherence behaviors.[10-13] In a study of patients with hypertension, the sensitivity of providers' estimate of patient non-adherence to their antihypertensive medications was only 27%, suggesting that providers underestimate patients' non-adherence behaviors.[10] Thus, having precise yet practical measures available is essential in order to assist providers in determining whether inadequate responses to treatment are due to patient non-adherence or the need to intensify treatment.

Pharmacy medication fill information is an accessible approach for population-based adherence measurement. A number of approaches currently exist to assess medication adherence in clinical practice. The most specific measures include electronic medication monitors, measurement of medication in blood or urine samples, or use of pills with electronic signals.[3,14,15] While these approaches are frequently used in efficacy trials, they are impractical for use in clinical practice.[3,16] The most common approach for population-based adherence measurement is through use of medication fill data and is typically assessed using the proportion of days covered (PDC).[3] The PDC is calculated as the number of days covered by medication fills in a given time period divided by the number of days in that time period; patients are typically considered to have low medication adherence if the PDC is less than 80%.[17,18] PDC has been shown to have a similar association to clinical outcomes as electronic drug monitoring and is well correlated with medication continuity and clinical biomarkers.[3,19-21] Moreover, *improvements in PDC-measured adherence among patients with hypertension leads to reduction in adverse clinical outcomes such as cardiovascular events.*[22-24] To date, PDC has been assessed primarily through use of insurance claims data or within pharmacy databases, which are generally not available in clinical practice.

Medication non-adherence is not well addressed in clinical practice. Because most patients have an established relationship with their primary care provider (PCP),[25] PCPs have repeated opportunities to deliver patient-centered counseling for medication adherence over the course of multiple visits. Despite potential benefits, 40% of primary care visits do not include discussions about medication adherence among patients with elevated cardiovascular risk.[26] When these conversations do occur, our research shows that they account for only 5% of the total encounter.[27] *Thus, an ideal opportunity to address non-adherence is being missed, especially among patients with elevated cardiovascular risk.* Lack of resources, inadequate skills, and insufficient system-level supports are the most common barriers expressed by PCPs for the lack of integration of behavioral counseling into their routine practice.[28] In order to mitigate the problem of non-adherence in clinical

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practice, sustainable strategies that leverage the multidisciplinary nature of the care team are required.

Teamlets that utilize medical assistants (MAs) as health coaches have the capability to address barriers and improve medication adherence, but scalability has not been demonstrated. Teamlets in primary care settings typically consist of a PCP and an MA who serves as a health coach.[29,30] Health coaching is an approach to enable patients to become active participants in their health; the American Medical Association has endorsed health coaching as part of practice redesign.[31] A number of studies, including our own, have demonstrated that health coaching can improve medication adherence in hypertension and other chronic diseases.[32-36] However, the scalability of MA-led health coaching has been limited in these studies for a number of reasons: they involved individual patient recruitment into research studies creating a highly selective group; health coaches delivered much of the intervention through phone calls, which are outside of typical clinical workflow; adherence was measured by self-report, which can be unreliable and is not always measured at a population level; and recruitment was not typically based on baseline medication adherence meaning resources are not focused on patients who would have the greatest benefit.[32-36]

Single session interventions are effective for promoting behavior change: Brief single session interventions are an efficient and effective way of delivering evidence-based interventions. Practice-based single session interventions have been demonstrated efficacious for smoking cessation; reducing harmful alcohol intake, substance abuse, risky sexual behaviors; and promoting dietary change.[37-40] In a prior trial of patients with hypertension, we established that a single session lifestyle counseling intervention led to a meaningful reduction in systolic blood pressure (9.4 mmHg) that was comparable to that of a multicomponent lifestyle intervention with multiple office visits (6.6 mmHg reduction).[41,42]

In summary, medication adherence is a major contributor to morbidity and mortality among patients with hypertension but is under-recognized and inadequately addressed in clinical practice. Pharmacy fill information has the opportunity to help PCPs recognize and address medication adherence at the point of care, although evaluations of interventions built on these data have been limited. Furthermore, engagement of clinical team members serving as health coaches has demonstrated improvement in medication adherence. We propose to refine an intervention to have health coaching delivered by MAs. The intervention will utilize prior pharmacy fill data to focus efforts on hypertensive patients with low medication adherence, with the intervention sufficiently integrated into workflow to eventually be useful for all clinic patients with low medication adherence.

1.2 Rationale

The proposed project will fill a critical gap in the evidence base to identify whether an intervention can be refined to best address medication adherence in a usable, meaningful, personalized, and timely manner. The intervention being developed is innovative because: 1) We will incorporate user centered design principles to maximize its incorporation into workflow, and 2) We will measure and validate adherence using pharmacy fill data available in the EHR for use in real-time clinical interventions

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1.3 Potential Risks & Benefits

1.3.1 Known Potential Risks

The risk is not greater than minimal risk (i.e. risk encountered in daily life or in the course of usual clinical practice).

For workflow assessment and usability testing, there is risk that clinicians will be made uncomfortable by qualitative questioning about their practice or observations in clinical; however, they can choose not to participate or respond to questions, and will be informed that all questions and participating in observations are voluntary and will not affect employment. Additionally, there is risk of loss of confidentiality. To mitigate the risk and maintain the privacy and confidentiality of clinician information, we will take particular importance to making sure that no one outside of the study personnel and a HIPPA-compliant transcription service has access to sensitive identifiers. Clinicians' names and e-mail addresses will be removed from transcripts and recordings. All interviews will be given a unique study ID that is not linked to sensitive identifiers. To minimize the risks, none of the people who are involved in employment decisions or evaluation of an employee's performance will be involved in recruiting and consenting them for this study.

Patients might also be uncomfortable with being observed during their clinical encounters. However, they may choose not to participate, and will be told that participation is voluntary, participants can withdraw consent for observations at any time, and participation will not influence their clinical care.

For validation of clinical of definitions, we will use existing data collected for other purposes. The primary risk involved in this study is a potential breach in confidentiality for patients. Our research team will take extreme precaution to maintain privacy and confidentiality during and after the study. To mitigate the risk and maintain the privacy and confidentiality of the patient information, we will take particular importance to making sure that no one outside of the study personnel has access to any sensitive identifiers.

1.3.2 Known Potential Benefits

The research will provide much needed guidance on optimal refinement of an intervention that can address medication adherence in clinical practice.

Clinicians will learn more about clinical decision support and their use. The project will increase understanding of the role of various clinicians to care for patients with uncontrolled hypertension and if successful represent a method for monitoring and improving medication adherence for patients with hypertension. If shown to be successful, this multicomponent, clinic-based intervention can be scaled to ultimately improve cardiovascular outcomes for millions of patients with hypertension.

2 Objectives and Purpose

2.1 Primary Objective

Phase 1: The primary objective is to conduct workflow assessments with stakeholders to identify best fit of the intervention and identify optimization opportunities. This will include assessment of the "usability" of the proposed intervention in clinical practice.

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Phase 2: The primary objective is to assess the effectiveness and implementation of the multicomponent intervention on medication adherence and blood pressure control for patients who are non-adherent to antihypertensive medications.

2.2 Secondary Objectives

Phase 1: The secondary objective is to validate EHR based rules to identify patients with low medication adherence and uncontrolled hypertension.

3 Study Design and Endpoints

3.1 Description of Study Design

Phase 1: Pre-implementation evaluation

To adapt the previously developed intervention components and refine workflows redesign to the unique needs of the teamlets promoting antihypertensive adherence in primary care we will employ our user-centric, agile implementation approach that integrates principles of design thinking, lean development and agile implementation to efficiently gather and incorporate feedback systematically from users to design, prototype, test, iterate and optimize the intervention.[43-45] We will do this as part of our first objective, which consists of three components

- **Workflow analysis**. We will conduct a workflow assessment of MAs, LPNs, RNs, and PCPs. This will include an interview of clinicians. Additionally, we will conduct observations in up to 22 selected clinics. These observations will involve seeing the clinicians' interactions with their patients in their usual setting and documentation of existing workflow. The workflow assessments will be used to inform the group adaption and optimization phase.

- **Clinical decision support (CDS) optimization**. Guided by these insights, the investigators and informants will partner with designers, informaticians and implementation science researchers in a design thinking workshop to generate a wide range of potential CDS adaptations that will optimize the integration of the intervention.

- **Multi-Phase Usability Testing.** Once the prototypes have been developed and initially tested, the CDS system will be programmed into a test environment for additional, more realistic usability testing. We will first conduct 2-3 rounds of think-aloud testing, during which a clinician test subjects will be asked to narrate their thoughts, experiences, and reasoning which will be audio recorded and their CDS interactions screen captured for analysis and review. Following testing, we will conduct semi-structured interviews with clinicians. When feedback from the think-aloud usability sessions has reached saturation (typically 2-3 sessions), the "near-live" usability phase will begin, in which the study team will strive to simulate real world use of the CDS tools. Near-live usability testing involves clinicians interacting with simulated data and patient actors to model clinical use of the CDS tools in a more realistic environment. We have planned for 1-2 near-live usability testing rounds, which also take approximately 2-4 weeks and involve approximately 4-6 end-users.

Additionally, our second objective is to validate EHR-based rules to identify patients with uncontrolled hypertension and low proportion of days covered (PDC, a measure of adherence). To do this, we will perform manual chart review to ensure accurate identification of patients who would meet inclusion for an intervention. We will then iteratively review and adjust definitions. We expect this to take about 4-5 rounds, for a total of approximately 200 charts reviewed. We will then perform validation of the final definition by calculating sensitivity, specificity, and positive and negative predictive values based on sampling of 300 charts from the complete dataset of all patients with hypertension; in total, 500 charts will be reviewed (200 in the iterative development process and 300 in validation)

Phase 2: Cluster randomized control trial

Randomization of clinics: NYU Langone Health has ambulatory care sites in the five boroughs of New York City (NYC) as well as in the suburbs of New York and New Jersey. Sites include academic practices, many

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community-based practices and Federally Qualified Health Centers (FQHC); many are multispecialty. Physicians in these practices form the NYU Faculty Group Practice (FGP) consisting of 351 total practices, including 113 primary care practices. The study trial will utilize a practice-level cluster-randomized design, with 1:1 randomization of up to 22 clinics. We will recruit these sites from 113 primary care practice in the NYU Langone Health network. The primary care practice will be the unit of randomization and allocation will be programmed directly into the EHR system. Randomization will be stratified by clinic size to ensure even distribution of different size clinics to the study arms. We will use block randomization of up to four practices every month for six months to stagger the intervention roll-out across the network. One study arm will receive the intervention while the other arm will receive the usual care CDS tools available.

Intervention Group PCP orientation and training:
Prior to implementation of the intervention, PCPs at the clinics allocated to the intervention will receive a brief orientation to the intervention via targeted emails. PCPs will also have the opportunity to attend an orientation (delivered at the practice site standing monthly meeting) and/or receive orientation material online (such as via Focus). The online orientation materials will be available through Focus and will last approximately 10-15 minutes. For any in-person orientation sessions, a study team member will join the practice's standing provider meeting and deliver the same information available on Focus. We expect in-person orientation sessions to last approximately 30 minutes. Given the automated, low burden nature of the intervention, no training beyond the orientation is required; however, ongoing support for intervention related questions will be provided via a study-specific email address. Orientation sessions will consist of three basic components: 1) an overview of medication adherence; 2) orientation to the screening tool for reasons for non-adherence and the MAs role in addressing specific responses; and 3) on-screen walk-throughs of PCP-facing tool components available within the electronic health record. PCPs will also have access to a "Health Coaching Course" available through Focus. This online training video consist of an overview of basic motivation interviewing techniques, self-management support, action planning, and problem-solving strategies for hypertension and medication management. We expect this course to be approximately 10-15 minutes.

Control Group PCP orientation and training:
Control PCP training will consist of an email with a brief review of the available PDC tool as well as an online resource (via Focus) containing information on medication adherence and common barriers to medication non-adherence will be made available to them.

Intervention Group MA/RN training:
Prior to implementation of the intervention, MAs and RNs at the clinics allocated to the intervention will receive a brief orientation to the intervention via targeted emails. MAs and RNs will also receive training that includes: 1) an introduction to the facilitators and barriers of medication adherence in patients with hypertension and 2) a demonstration of how to screen for medication non-adherence using the validated screening tool. Trainings may occur in-person and/or online/distanced learning to accommodate clinician schedules. The online materials will be available through Focus and will consist of one module: a "Teamlet Intervention Group Course." We expect the module to take approximately 10-15 minutes. For any in-person orientation sessions, a study team member will coordinate with practice leadership and administration staff to join standing MA or RN "huddles" to deliver the same information available on Focus. We expect in-person sessions to last approximately 30 minutes.

Control Group MA/RN training.
MAs and RNs in the control group will not receive any training or orientation information.

Intervention: The intervention consist of three components: 1) patients with hypertension will be automatically screened for low medication adherence using linked EHR-pharmacy data at the time of a PCP encounter; 2) MAs will deliver a validated, rapid, survey of common causes of non-adherence to patients identified as non-adherent to anti-hypertensive medication(s) and who have elevated blood pressure at the time of the visit ; 3) PCPs will address specific barriers to adherence based on survey response.

Patients who meet inclusion criteria will be "enrolled" to be included in the analysis if seen in one of the intervention or control primary care clinics in the first six months after implementation of the intervention into that clinic. Patients will be evaluated for the outcome 12 months after the index clinic visit. The research

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support staff will support intervention implementation at each site for up to a total of 24 months to ensure complete 12 month follow up for all included patients. The 12-month period will be followed by a 6-month period to asses sustainability of the teamlet model once the active intervention has ended and there is no additional support by the research staff.

We will collect and analyze data about the use of each element of the intervention during patient visits, including which elements of the intervention were used and how often. We will also collect data from the site EHRs about medication adherence and blood pressure from all clinics participating in the trial, both Intervention and Control groups.

During Phase 2, we will also invite participants from both the control group and intervention group to interviews to assess their experiences with managing high blood pressure, including their medication adherence, the challenges they face, and their interactions with healthcare providers. Additionally, the interviews aim to explore the tools and strategies patients use to manage their hypertension and how these tools assist them in medication adherence.

During Phase 2, we will also collect assessments and interviews from various clinicians (MAs, PCPs, and RNs) to assess the impact on their workflows from the study intervention, and implementation outcomes. We will reach out to clinicians (MAs, PCPs, and RNS) from the intervention group via email to invite them to participate in interviews. A study team member will conduct the semi-structured interview using the “Phase 2 Interview guide.” Interviews will last approximately 45-60 minutes.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

Phase 1: optimization of the intervention
Phase 2: proportion of days covered (PDC), systolic and diastolic blood pressure

3.2.2 Secondary Study Endpoints

Phase 1: chart review gold standard of definitions for hypertension and medication adherence
Phase 2: adoption, acceptability, and fidelity

4 Study Enrollment and Withdrawal

4.1 Inclusion Criteria

Phase 1.
For the first objective (workflow assessments and usability testing), an individual must be:

- A clinician from an NYULH ambulatory practice location.
    - Eligible clinicians include physicians, medical assistants, licensed practical nurses, and registered nurses.
- Adult patients during appointments with eligible clinicians
- Age>18 years
- Able and willing to provide consent

For our second objective, we validate EHR-based rules to identify patients with uncontrolled hypertension and low adherence. We will perform review on a set of all patients with hypertension to assess true and also positive and negative rates as well. In order to be eligible, an individual must meet all of the following criteria:

1. Age>18 years
2. Presence of Hypertension as defined by either:
    a. Blood pressure≥140/90
    b. Hypertension diagnosis

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    c. Prescription for at least one antihypertensive medication
3. Outpatient clinic visit in NYULH between 1/1/2019 and 1/31/2021

Phase 2.
For the first objective, we will examine patients' electronic health records to identify changes in medication adherence and blood pressure. In order to be eligible, an individual must meet all of the following criteria:

1. Age>18 years
2. Presence of Hypertension as defined by either:
    a. Blood pressure≥140/90
    b. Hypertension diagnosis
    c. Prescription for at least one antihypertensive medication
3. Outpatient clinic visit in the NYULH between 06/01/2022 and 12/31/2025

For our second objective, we will collect assessments and interviews from various clinicians (MAs, PCPs, LPNs, and RNs) to assess the impact on their workflows from the study intervention, and implementation outcomes. In order to be eligible, an individual must be:

- A clinician from an NYULH ambulatory practice location.
    - Eligible clinicians include physicians, medical assistants, licensed practical nurses, and registered nurses.
- Adult patients during appointments with eligible clinicians
- Age>18 years
- Able and willing to provide consent

4.2 Exclusion Criteria

We will exclude clinicians who decline participation. We will also exclude observing clinicians during encounters with patients who decline to be observed.

We have no specific exclusion criteria for patients in chart review.

4.3 Vulnerable Subjects

We will include NYULH employees in our study, as our goal is to understand workflow and usability from the perspective of clinicians (primary care providers, registered nurses, licensed practical nurses, and medical assistants) working at NYULH. We will notify potential clinicians that choosing not to participate or choosing not to answer questions that make them uncomfortable will have no bearing on employment status. No other vulnerable populations will be included. Further methods of protection include that no one involved in an employee's hiring/firing and performance evaluation will be involved in their recruitment or consent process nor will they have access to information about the employee's study performance.

4.4 Strategies for Recruitment and Retention

Phase 1.
We will recruit clinicians from ambulatory practices at NYULH. We will send emails to clinicians practicing within the NYULH system using attached email template. Interviews will be conducted in person or via WebEx, as appropriate due to COVID restrictions. After clinicians are consented for observations, their patients will be asked whether they would be willing to have their encounter observed and will be asked for verbal consent. Clinicians will be compensated ($50 gift card) for participating in the interviews and usability testing sessions.

Phase 2.
Recruitment – Clinic Health Care Providers (PCPs/MAs/RNs): We will recruit up to 22 clinics from clinics from 113 primary care practices in the NYU Langone Health network. Verbal consent will be obtained at the practice-level from the medical director in addition to the ambulatory system and enterprise EHR leadership.

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As consent is provided at the clinic level, all clinicians at the research clinics will be part of the study, unless explicitly requesting to opt-out or withdrawal. Prior to the implementation of the intervention clinic health care providers will receive a brief orientation to the intervention via targeted emails with a Key Information Document attached.
For clinician interviews, we will obtain verbal consent from MAs, PCPs, and RNs. We will send emails to clinicians inviting them to participate in interviews using the attached email template. For clinician surveys, providers will be emailed a redcap link that includes the consent as the first page of the survey and their decision to complete the survey will be their consent. MAs, RNs and Providers will be asked for completion of interviews and assessments. We will need to collect assessments from MAs, RNs and PCPs to assess the impact on their workflows from the study intervention and implementation outcomes. Clinicians will be compensated ($50 gift card) for participating in the interviews.

Recruitment – Patients at Control Clinics: We will collect EHR data on any patient seen at the participating clinics to assess clinical outcomes including medication adherence (as measured by PDC) and blood pressure. We are requesting a waiver of informed consent to access these data. We are requesting a waiver of informed consent and HIPPA authorization for all retrospective and prospective EMR data collection.

Recruitment – Patients at Intervention Clinics: We will collect EHR data on any patient seen at the participating clinics to assess clinical outcomes including medication adherence (as measured by PDC) and blood pressure. We are requesting a waiver of informed consent and HIPPA authorization for all study procedures including retrospective and prospective EMR data collection, and for the single item survey question as it is embedded in the EMR and is consistent with questions frequently asked in regular clinical care. We will obtain a waiver of informed consent and HIPPA authorization for patients seen at participating intervention clinics to acknowledge their participation at a clinic level. The risks to subjects are exactly equivalent to the risks experience in the standard setting of patient care. The new module to be activated in EPIC relates only to guidance for physician decision-making regarding hypertension care, and has no impact on disclosure or treatment of PHI. Subjects will receive care from their providers in the usual way. The only difference is the interface with the electronic health record that is used by the physician during the course of the patient encounter. The autonomy of the provider to make decisions about patient care will not be affected. It is impracticable to obtain consent from patients for receipt of standard medical care by their usual providers. It is unclear what they would be providing consent for, since they will receive care as usual from their providers. Patients will not be provided with additional information. They will be treated as usual by their providers and the providers' experience with the module is irrelevant to their patient experience.

For patient interviews, patients will be recruited by Epic MyChart message research request and via phone call. The Epic MyChart research request will include an option to allow patients to respond that they are or are not interested in participating. If no response is received after two messages, an opt-out letter will be sent to the individual's home address on file. The letter will notify them of the study and will include a telephone number to call if they wish to have no further contact. This letter will be submitted via modification to the IRB for approval prior to use in the study. If not patient does not opt out, we will contact them through their primary telephone number to have a recruitment conversation. The study team will also reach out to potential participants via phone call using the attached verbal script. Potential participants will contacted by phone two times. If the individual does not answer, a study team member will leave a message notifying them of the study and will include a telephone number to call if they wish to have no further contact. Participants who express interest using the Epic MyChart message or inform the study team via phone call will be contacted to schedule a time to interview. If the participant would like to proceed, a copy of the key information sheet and verbal consent form will be emailed via SendSafe and reviewed with the patient during the call. The patient will be consented and interviewed over a phone or video call based on the patient's preference.

	Physicians	**MAs/RNs**	**Patients**
Intervention	- Study intro email - Attached key information document - Waiver of documentation of informed consent	- Study intro email - Attached key information document - Waiver of documentation on informed consent	- HIPPA authorization waiver and waiver of informed consent for all study procedures including retrospective and prospective EMR data collection, and for the single item survey question as it is embedded in the

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	- Orientation/training on tool + motivational interview training	- Orientation/training on tool	EMR and is consistent with questions frequently asked in regular clinical care
Control	- Study intro email	- N/A	- HIPPA authorization waiver and waiver of informed consent for retrospective and prospective EMR data collection.

Retention: The multicomponent intervention being delivered by teamlets consisting of MAs, RNs, PCPs, and LPNs will be adapted from the workflow developed during prior work and refined through group adaptation sessions during Phase 1. This user-centered approach to the intervention design is specifically geared toward enhancing engagement and is expected to support retention of the study participants. All CDS components of the intervention will be integrated into the MAs, RNs, and provider facing workflow of the EHR, thereby requiring minimal additional effort in engagement. We will use ongoing training and organizational peer support to continuously improve acceptability and adoption of the intervention, as well as provide additional teaching support, and trouble-shooting for participants.

4.4.1 Use of DataCore/Epic Information for Recruitment Purposes

Although we will not be using EPIC for recruitment, we will use Epic/DataCore for retrieval of the dataset we will be using for objective #2.

4.5 Duration of Study Participation

Phase 1.
Individual subjects will be consented for workflow and usability testing interviews lasting 30-60 minutes. Individuals may be contacted again for follow up in the process of iterations. Patients' participation in observations will last for the duration of their clinical encounter. The exact schedule of visits will depend on the information obtained and the requisite number and timing feedback/iteration cycles. The entire process of workflow analyses and usability testing is expected to take approximately 18 months although subjects do not need to be followed longitudinally through them.

Phase 2.
Practice-level and clinician participation will span 18 months.

4.6 Total Number of Participants and Sites

Phase 1.
Up to 100 clinicians (primary care providers, MAs, RNs, LPNs) from practices at NYULH will be recruited for workflow analyses and usability testing. This number will be determined by reaching thematic saturation. We will observe up to 72 patient encounters.

For data validation, we will identify a population of approximately 1,300,000 adult patients with hypertension seen in our health system. From this population, we will identify patients who meet criteria and do not meet rules for low medication adherence. We will perform stratified sampling of approximately 500 patients for detailed chart review.

Phase 2.
Phase 2 will involve total cumulative recruitment of up to 22 clinics across the participating primary care clinical sites, up to 4,400 patients, and up to 400 clinicians.

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4.7 Participant Withdrawal or Termination

4.7.1 Reasons for Withdrawal or Termination

Clinicians who wish to opt out of participation may do so at any time. Patients who wish to opt out of participation during observations can do so at any time.

4.7.2 Handling of Participant Withdrawals or Termination

If many clinicians withdraw from participation, we will recruit additional clinicians until we reach thematic saturation.

4.7.3 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Dr. Saul Blecker, the NIH, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor and/or IRB.

5 Study Schedule

5.1 Screening

Eligible participants will be identified through each clinical practice, based on inclusion and exclusion criteria provided at the onset of the study.

5.2 Enrollment/Baseline

At the initial visit for each clinic, the Principal Investigator will describe the purpose of the study, address questions by clinicians, and identify particular personnel for inclusion in study activities.

5.2.1 Enrollment/Baseline Visit

Verbal consent will be obtained at the practice-level from the medical director in addition to the ambulatory system and enterprise EHR leadership. As consent is provided at the clinic level, all clinicians at the research clinics will be part of the study, unless explicitly requesting to opt-out or withdrawal.

Phase 1 Baseline

- Verify inclusion/exclusion criteria
- Provide study overview to potential clinician participants
- Obtain verbal consent from participating clinicians
- Collect basic information about clinical functions and workflows

Phase 2 Baseline

- Verify inclusion/exclusion criteria
- Provide study overview to potential clinician participants

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- Obtain verbal consent from participating clinicians that choose to participate in interviews

5.3 Intermediate Visits

Phase 1. Intermediate Visits

Potentially eligible clinicians, i.e. providers, RNs, LPNs, MAs working in primary care, will be emailed to see if interested in potential enrollment. Emails will be sent either directly from or on behalf of three principal investigators. Research coordinators will then explain risk and benefits and obtain consent. Coordinators will not have a supervisory role over potential subjects. Patients having a clinical encounters will be asked to see if they are willing to have their clinical encounter observed.

Workflow Analysis Stage. We will ask clinicians who agree to be enrolled in the trial questions about typical workflow. We hope to conduct the workflow analysis at clinical sites to directly observe of consenting clinicians and patients in the usual setting and document of existing workflow.

Usability Stage. This stage clinicians will be asked to work with the CDS to simulate workflows. Initially this will be through think aloud usability assessment based on laboratory assessment. Once saturation is reached, the “near-live” usability phase will begin, in which the study team will strive to simulate real world use of the CDS tools. Near-live usability testing involves clinicians interacting with simulated data and patient actors to model clinical use of the CDS tools in a more realistic environment.

Phase 2. Intermediate Visits

Potential eligible primary care practices will be emailed to see if interested in potential enrollment. Emails will be sent either directly from or on behalf of three principal investigators. A principal investigator will then explain the study and obtain verbal consent at the practice-level from the medical director in addition to the ambulatory system and enterprise EHR leadership. As consent is provided at the clinic level, all clinicians at the research clinics will be part of the study, unless explicitly requesting to opt-out or withdrawal.

Potentially eligible clinicians, i.e. providers, RNs, LPNs, MAs working in primary care, will be emailed to see if interested in potential participation in interviews to assess the impact on their workflows from the study intervention, and implementation outcomes. Emails will be sent either directly from or on behalf of three principal investigators. Research coordinators will then explain risk and benefits and obtain consent. Coordinators will not have a supervisory role over potential subjects.

Eligible patients from the entrolled practice sites will be identified electronically and automatically within EPIC. We will obtain a waiver of informed consent to collect EHR data on any patient seen at the participating clinics to assess clinical outcomes including medication adherence (as measured by PDC) and blood pressure.

Month 1-12: Follow-up Assessment of Study Endpoints and Safety

- Medication adherence as measured by Proportion of days covered (PDC) at 6 and 12 months.
- Diastolic and systolic blood pressure
- Implementation outcome measures will collected at various time points:
    - Adoption: Number of completed surveys addressing reasons for non-adherence, documented instances of health coaching among intervention patients, use of clinical decision support tools, documented instances of discussion of medication adherence among intervention patients will be measured through extracted EHR data.
    - Acceptability: Clinicians from all participating clinics will be email a validated survey to measure acceptability of the intervention.
    - Fidelity: Live usability sessions will be conducted to directly observe MAs using the survey and delivery health coaching at approximately 1, 6, and 12 months after initial implementation.

5.4 Final Study Visit

Phase 1.

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There is no final visit for Phase 1.

Phase 2.
Month 18: End of Study Assessments

- Proportion of days covered (PDC) at 18 months.
- Diastolic and systolic blood pressure
- Sustainability will be measured through conducting semi-structured interviews with medical directors, primary care providers, registered nurses, medical assistants, licensed practical nurses, and other key stakeholders post-intervention.

5.5 Withdrawal/Early Termination Visit

In the event that involuntary withdrawal, data collection will cease at the time of withdrawal. Data up until the point of withdrawal will be used in the analysis.

5.6 Unscheduled Visit

Not applicable.

6 Study Procedures/Evaluations

6.1 Procedures/Evaluations

There are multiple phases. The general steps are outlined below:

6.1.1 Study Specific Procedures

Phase 1.
Objective 1 will include the following three components, all of which will either be conducted by study staff in-person or over WebEx. We expect each step to take 30-60 minutes of study subject time. Clinician interviews will be recorded, transcribed, and the interview audios will be deleted. We may use an outside HIPPA-compliant transcription service.

- **Workflow analysis**. We will conduct a workflow assessment adapted from the Agency for Healthcare Research and Quality.[46,47] The research team will interview key informants of MAs, LPNs, RNs, and PCPs. We will conduct observations in up to 22 selected clinics. These observations will involve seeing the clinicians' interactions with their patients in their usual setting and documentation of existing workflow. The workflow assessments will be used to inform the group adaption and optimization phase.

- **Clinical decision support (CDS) optimization**. Guided by these insights, the investigators and informants will partner with designers, informaticians and implementation science researchers in a design thinking workshops to generate a wide range of potential CDS adaptations that will optimize the integration of the intervention. The workshops will incorporate the constraints of primary care workflow gleaned from the workflow mapping and interviews with a goal of building the simplest approach to rapid identification of poor medication adherence, assessment of common barriers to adherence, and potential health coaching by MAs, RNs, LPNs when appropriate. In the workshops, the participants will also explore the development of enhanced CDS tools, which will allow PCPs to take more specific actions, such as leveraging order sets with common antihypertensive alternatives, prescribing blood pressure tracking sheets via the patient portal or prescribing tailored education accessible via the patient portal or text messaging. Candidate CDS tool components and workflows will also be assessed by the clinical informatics and operations teams to vet their sustainability in real-world settings prior to prototype development. The products of the workshop will be synthesized with all of the other gathered data to produce potential journey maps and ultimately a rough concept for prototyping

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- **Multi-Phase Usability Testing.** Once the prototypes have been developed and initially tested, the CDS system will be programmed into a test environment for additional, more realistic usability testing. The objective of this phase is to optimize the interactions between MAs, LPNs, RNs, PCPs, their respective workflows, and the CDS system. Our approach to rapid-cycle usability testing prioritizes pragmatic over academic needs.[48,49] We will first conduct up to 5 rounds of think-aloud testing, during which a clinician test subjects will be asked to narrate their thoughts, experiences, and reasoning which will be audio recorded and their CDS interactions screen captured for analysis and review. Following testing, we will conduct semi-structured interviews with clinicians. Clinicians will be asked about the acceptability (including usability and usefulness), barriers and facilitators associated with adopting the CDS into routine care, and issues of feasibility (compatibility with workload and workflow, practicality). Additionally, providers will be asked their suggestions for improvement of the interventions in these domains. To maximize the rapid-cycling, comprehensive field notes are created to synthesize findings and these memos are used to drive rapid iterations of the tools. More comprehensive qualitative analysis of the recordings will be performed to search for more subtle but less urgent insights as well as for general research knowledge. The data gathered from each round is summarized and reviewed during multi-disciplinary workgroup reviews that will refine the CDS prototypes and improve their integration into the primary care workflow.[50] Each of these cycles will take approximately 2-4 weeks and involve approximately 4-6 end-users (MAs, RNs, LPNs and PCPs). When feedback from the think-aloud usability sessions has reached saturation (typically 2-3 sessions), the “near-live” usability phase will begin, in which the study team will strive to simulate real world use of the CDS tools. Near-live usability testing involves clinicians interacting with simulated data and patient actors to model clinical use of the CDS tools in a more realistic environment. We have planned for 1-2 near-live usability testing rounds, which also take approximately 2-4 weeks and involve approximately 4-6 end-users.

Our second objective is to validate EHR-based rules to identify patients with uncontrolled hypertension and low proportion of days covered (PDC, a measure of adherence). To do this, we will perform manual chart review to ensure accurate identification of patients who would meet inclusion for an intervention. First, we will perform an electronic query, e.g. through DataCore, of the EHR to identify patients who meet the definition for hypertension, i.e. blood pressure≥140/90 or a listed diagnosis. From this cohort, we will then identify patients who electronically meet the definition of low adherence (PDC<80%). We will then randomly sample 50 charts, which will be reviewed by a clinician to determine whether the identification is accurate. If there are errors in the pull or definition, the clinician will provide feedback with suggestions for definition refinement. We will then iterate the definition and repeat the procedure of sampling patients who meet the new criteria, perform chart review, and obtain feedback for improvement. This iterative process will continue until we reach “saturation” in our review of charts; i.e. no additional errors are noted. We expect this to take about 4-5 rounds, for a total of approximately 200 charts reviewed. We will then perform validation of the final definition by calculating sensitivity, specificity, and positive and negative predictive values based on sampling of 300 charts from the complete dataset of all patients with hypertension; in total, 500 charts will be reviewed (200 in the iterative development process and 300 in validation) This approach is based on our prior work of accurate cohort identification using EHR data.[51-53]

All Data will be pulled from EHR data, which was initially collected as part of routine clinical care. DataCore will perform data extraction. Only study team members listed on the IRB will have access to these data.

PHI to be included will be medical record numbers and dates of service.

Data from EPIC will include: age, race, ethnicity, sex, insurance, office visits, hospitalizations, laboratory results, vital signs, chronic conditions, medication prescribed, medications filled, and adherence measured.

Data will be searched with each iteration of the definition; as noted we expect that this will occur 4-5 times over the study period.

All data will be destroyed upon study completion.

Phase 2.

In Phase 2, we will roll out the clustered RCT. We will also assess implementation outcomes during this time. Activities include:

- Screening potential clinics by inclusion and exclusion criteria
- Obtaining clinical leadership approval and verbal consent
- Present study to PCPs, MAs, RNs, and administrative clinic staff
- Administering online and in-person trainings to clinicians at participating clinics
- 1:1 randomization of clinics into intervention or control groups
- Periodic assessment of trial protocols with clinicians
- Periodic assessment of primary and secondary outcomes with clinicians
- Retrospective-prospective data assessment of patients seen at clinics with uncontrolled hypertension
- Assessment of secondary outcomes with patients via interviews

7 Safety and Adverse Events

7.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

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All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

7.1.1 Investigator reporting: notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report Promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:
The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using a Reportable New Information submission and will include a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution, and need for revision to consent form and/or other study documentation. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

8 Statistical Considerations

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8.1 Study Hypotheses

This study does not involve any hypothesis testing. We are performing qualitative analysis to understand workflow and improve CDS and validating EHR-based definitions.

8.2 Sample Size Determination

The sample size of approximately 40 clinician participants is based on our past experience with workflow analysis and module development, but we may need to interview or observe up to 100 clinicians in total. The additional participants may be needed for design workshops that will develop and refine clinical decision support tools. We expect to conduct up to 72 patient-clinician observations. The final number will ultimately be based on thematic saturation and number of iterations needed in refinement.

8.3 Statistical Methods

The first objective will employ qualitative analytic approaches. The process of tool suite demonstration, observation, clinician feedback, and module refinement is highly iterative and responsive. Formal statistical analyses will not be relevant.

For data validation, the first portion of developing an accurate algorithm will also involve iterative review and qualitative assessment. Specifically, we will then randomly sample 50 charts, which will be reviewed by a clinician to determine whether the identification is accurate. If there are errors in the pull or definition, the clinician will provide feedback with suggestions for definition refinement. We will then iterate the definition and repeat the procedure of sampling patients who meet the new criteria, perform chart review, and obtain feedback for improvement. This iterative process will continue until we reach “saturation” in our review of charts; i.e. no additional errors are noted. There will be no formal statistical analysis

We will then validate the final definition. For this, we will randomly sample 300 charts from those not previously sampled. We will used detailed chart review as the gold standard and compared to results of the algorithm. We will test performance characteristics, including sensitivity, specificity, and positive and negative predictive values, in this validation set.

9 Ethics/Protection of Human Subjects

9.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46.

9.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

9.3 Informed Consent Process

9.3.1 Consent/Assent and Other Informational Documents Provided to Participants

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Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and verbal informed consent is required prior to starting intervention.

9.3.2 Consent Procedures and Documentation

For workflow analysis and usability testing with clinicians, a study team member will provide a printed “Key Information and Verbal Consent” document to study participants or share an electronic copy via email (e.g “Email invitation to Clinicians” and/or prior to the interview) or via a RedCap link (e.g. shared using the Webex chat feature prior to the start the interview). Verbal consent will be obtained from participants either in person, through Webex or over the phone.

For observations of clinicians’ interactions with their patients, patients will be provided a printed “Key Information and Verbal Consent” document. Verbal consent will be obtained in person.

Informed consent is a process that is initiated prior to the individual’s agreeing to participate in the study and continues throughout the individual’s study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participants may withdraw consent at any time throughout the course of the study.

Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

For the validation of algorithms using EHR data, we are requesting a waiver of informed consent for this secondary analysis of data being collected for other reasons, in this case related to clinical care. The study meets the four conditions for waiver of consent under Federal Regulation 45 CFR 46.116(d): 1) the research involves no more than minimal risk to the participants; 2) the waiver or alteration will not adversely affect the rights and welfare of the participants; 3) the research could not practicably be carried out without the waiver or alteration; and 4) whenever appropriate, the participants will be provided with additional pertinent information after participation.

9.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

10 Data Handling and Record Keeping

10.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the study staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Any data collected will be kept on the MCIT-managed network drive approved for storage of study data (“R drive”). All approved study team members will have access to this data.

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10.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close out or 5 years after final reporting/publication. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.3 Protocol Deviations

A protocol deviation is any noncompliance with the study protocol or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to NHLBI Program Official. Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

11 Study Finances

11.1 Funding Source

This study if financed through a grant from the US National Institute of Health/NHLBI

11.2 Costs to the Participant

There are no costs to participate in this study.

11.3 Participant Reimbursements or Payments

Participants will be compensated ($50 gift card) for participating in interviews and usability testing sessions. Patients will be compensated ($25 gift card) for participating in interviews.

12 Study Administration

12.1 Study Leadership

Dr. Saul Blecker, as the PI of the study, take full responsibility for the study. He will meet monthly with sub-PIs Drs. Mann and Schoenthaler to govern the conduct of the study.

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12.2 Study Monitoring

The Data Safety Monitoring Board (DSMB) will be responsible for monitoring the study. The purpose of the DSMB is to ensure the safety of participants and the validity and integrity of the data. Personnel involved in the monitoring activities will include:

- The Co-Principal Investigators
- DSMB (see details below)

The DSMB will be made up of professionals in the field who are willing to participate, and will include at least one individual with statistical expertise and two individuals with expertise in related fields such as pragmatic trials, health services research, and hypertension management.

The DSMB will perform the following activities:

- Review the research protocol and plans for data and safety monitoring.
- Evaluate the progress of the interventional trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome.
- Monitors will also consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study. For example, if there is a systematic trend showing decreasing, rather than improving medication adherence or patient communication, in the II vs. the control condition.
- Make recommendations concerning continuation or conclusion of the trial(s).
- Protect the confidentiality of the trial data and the results of monitoring.

12.3 Data Safety Monitoring Plan

The Data and Safety Monitoring Plan will comprise the following elements:

- Data Analysis and Coordination: data analysis will be conducted by Yunan Zhao, MA, working under the direction of Dr. Hayley Belli, PhD, Assistant Professor of Population Health in the Division of Biostatistics. Ms. Zhao will prepare bimonthly reports, for review by Dr. Saul Blecker and the study team, of the number of patients eligible to trigger the CDS tools described above, along with information about each CDS alerts' occurrence and any responses by the provider. This information will be provided by practice and aggregated across the whole sample. This information will be available for provision to the DSMB on request.
- Reporting of adverse events to the IRB and to the NIH: Adverse events will be reported to the New York University IRB, as well as to the Chair of the DSMB. The DSMB has the authority to halt the trial if it perceives that harm is occurring due to the intervention. Summaries of adverse events reports will be made to NIH in the yearly progress or report or, at the end of Year 5, in the final report, unless the nature of a particular event is such that it bears immediate reporting to the NIH.
- The DSMB will meet with the PIs, and the co-Investigator approximately every 6 months and at minimum annually given this is a low risk trial. The DSMB is to review adverse events, senior complaints, if any, and dropout rates. Data will be provided at those meetings by the investigators on key variables that may indicate harm, including hospitalization rates and mortality in each group. The DSMB biostatistician will evaluate the confidentiality and integrity of the database, and the procedures for recording and storing confidential files. The DSMB will also review the elements of the plan to deal with emergencies. Documentation of each DSMB meeting will be kept and submitted to the IRB each continuation.

12.3.1 Use of INSIGHT Information for Data Safety Monitoring Purposes

As well as monitoring hospitalizations and ED visits that occur at NYU Langone, we will use Insight to monitor hospitalizations and ED visits that occur at sites included in the INSIGHT Clinical Research Network (CRN). Safety data for our Data Safety Monitoring Board (DSMB) review will be obtained from INSIGHT and stored as described in Data Core. Data Core is a secure data storage environment hosted by Weill Cornell Medicine (WCM) created to store researcher data in a secure, customizable space. The Addressing Antihypertensive Medication Adherence through EHR-enabled Teamlets in Primary Care study data environment will have access to data limited in accordance with access restrictions from data use agreements, IRB protocols, and

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other constraints relevant to the type of data. Personnel access will be restricted to investigative team members with current HIPAA, Good Clinical Practice (GCP) and human subjects' protection certification. In order to conduct analyses in this environment we will submit a ticket to WCM Data Core to import a file containing the INSIGHT proxy ID, patient study group assignment (de-identified as Group A and Group B), and date of first clinic appointment in this study to use as a start date for analyses. This file will be merged with the INSIGHT data to allow for us to analyze any differences in utilization between intervention and control. This data is all consistent with a Limited Data Set (LDS) and contains no PHI.

The INSIGHT Clinical Research Network (CRN) is an infrastructural initiative that offers users access to a centralized, accessible, robust database with 12 years of longitudinal high-quality research-ready data on over 17 million patients eligible for trial enrollment. The INSIGHT Network also provides important research services, such as patient recruitment and a centralized IRB, to advance and streamline research. The INSIGHT Network is a unique partnership of 6 highly ranked academic medical centers and collaborators: Columbia University Irving Medical Center, Montefiore, Mount Sinai, Weil Cornell Medicine, NYU Langone Medical Center, and New York-Presbyterian. The INSIGHT CRN is characterized by a large, diverse patient population, reflecting the racial, ethnic and socio-economic diversity of New York City's population as well as the extensive set of health care services offered by hospitals across a fragmented healthcare landscape. NYC patients seek care from multiple institutions, requiring unique informatics solutions that includes a centralized process for advanced patient identity management to link individual patient records across sites. The INSIGHT Clinical Research Network has successfully de-duplicated patient records across institutions and standardized data linkages across disparate data sources to provide a broad, unique, and complete view into a patient's pattern of care.

12.4 Study Modification

The study may be modified or discontinued at any time by the IRB, NHLBI, or other government agencies as part of their duties to ensure that research subjects are protected. If any protocol changes are needed, the PIs will submit a modification request to the IRB. Protocol changes will not be implemented prior to IRB approval unless necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB will be promptly informed of the change following implementation (within 10 working days).

12.5 Study Discontinuation

The study may be discontinued at any time by the IRB, NHLBI, or other government agencies as part of their duties to ensure that research subjects are protected. If a serious adverse event occurs as a result of the study, consideration will be given to stopping the study early. In the event of early stopping of the study, the IRB will be promptly notified.

12.6 Study Completion

The estimated completion date of this study is 06/30/2024. At that time, a progress report will be submitted to the IRB and the record will remain open for analysis of study data. Once all research-related interactions with participants are completed and collection and analysis of identifiable private data (as described in the IRB-approved protocol) are finished, the study will be closed with the IRB.

13 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study. The study leadership in conjunction with the NIH/NHLBI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULH investigators will follow the applicable conflict of interest policies.

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14 References

1. Neutel JM, Smith DH. Improving patient compliance: a major goal in the management of hypertension. *J Clin Hypertens (Greenwich).* 2003;5(2):127-132.
2. Chang TE, Ritchey MD, Park S, et al. National Rates of Nonadherence to Antihypertensive Medications Among Insured Adults With Hypertension, 2015. *Hypertension.* 2019;74(6):1324-1332.
3. Kini V, Ho PM. Interventions to Improve Medication Adherence: A Review. *JAMA.* 2018;320(23):2461-2473.
4. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. *Am J Med.* 2012;125(9):882-887 e881.
5. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med.* 2005;353(5):487-497.
6. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *BMJ.* 2008;336(7653):1114-1117.
7. Rose AJ, Glickman ME, D'Amore MM, Orner MB, Berlowitz D, Kressin NR. Effects of daily adherence to antihypertensive medication on blood pressure control. *J Clin Hypertens (Greenwich).* 2011;13(6):416-421.
8. Bailey JE, Wan JY, Tang J, Ghani MA, Cushman WC. Antihypertensive medication adherence, ambulatory visits, and risk of stroke and death. *J Gen Intern Med.* 2010;25(6):495-503.
9. Ho PM, Magid DJ, Shetterly SM, et al. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. *Am Heart J.* 2008;155(4):772-779.
10. Zeller A, Taegtmeyer A, Martina B, Battegay E, Tschudi P. Physicians' ability to predict patients' adherence to antihypertensive medication in primary care. *Hypertens Res.* 2008;31(9):1765-1771.
11. Sidorkiewicz S, Tran VT, Cousyn C, Perrodeau E, Ravaud P. Discordance Between Drug Adherence as Reported by Patients and Drug Importance as Assessed by Physicians. *Ann Fam Med.* 2016;14(5):415-421.
12. Heeb R, Kreuzberg V, Grossmann VJJPCHS. Physicians' Assessment of Medication Adherence: A Systematic Review. 2019;6(202):2376-0419.1000202.
13. Gross R, Bilker WB, Friedman HM, Coyne JC, Strom BL. Provider inaccuracy in assessing adherence and outcomes with newly initiated antiretroviral therapy. *AIDS.* 2002;16(13):1835-1837.
14. Checchi KD, Huybrechts KF, Avorn J, Kesselheim AS. Electronic medication packaging devices and medication adherence: a systematic review. *JAMA.* 2014;312(12):1237-1247.
15. Sutherland JJ, Morrison RD, McNaughton CD, et al. Assessment of Patient Medication Adherence, Medical Record Accuracy, and Medication Blood Concentrations for Prescription and Over-the-Counter Medications. *JAMA Netw Open.* 2018;1(7):e184196.
16. McGrady ME, Holbein CE, Smith AW, et al. An Independent Evaluation of the Accuracy and Usability of Electronic Adherence Monitoring Devices. *Ann Intern Med.* 2018;169(6):419-422.
17. Choudhry NK, Shrank WH, Levin RL, et al. Measuring concurrent adherence to multiple related medications. *Am J Manag Care.* 2009;15(7):457-464.
18. Martin BC, Wiley-Exley EK, Richards S, Domino ME, Carey TS, Sleath BL. Contrasting measures of adherence with simple drug use, medication switching, and therapeutic duplication. *Ann Pharmacother.* 2009;43(1):36-44.
19. Choo PW, Rand CS, Inui TS, et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Med Care.* 1999;37(9):846-857.
20. Mehta SJ, Asch DA, Troxel AB, et al. Comparison of Pharmacy Claims and Electronic Pill Bottles for Measurement of Medication Adherence Among Myocardial Infarction Patients. *Med Care.* 2019;57(2):e9-e14.
21. Pladevall M, Williams LK, Potts LA, Divine G, Xi H, Lafata JE. Clinical outcomes and adherence to medications measured by claims data in patients with diabetes. *Diabetes Care.* 2004;27(12):2800-2805.
22. Dragomir A, Cote R, Roy L, et al. Impact of adherence to antihypertensive agents on clinical outcomes and hospitalization costs. *Med Care.* 2010;48(5):418-425.

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23. Choudhry NK, Glynn RJ, Avorn J, et al. Untangling the relationship between medication adherence and post-myocardial infarction outcomes: medication adherence and clinical outcomes. *Am Heart J.* 2014;167(1):51-58 e55.
24. Corrao G, Parodi A, Nicotra F, et al. Better compliance to antihypertensive medications reduces cardiovascular risk. *J Hypertens.* 2011;29(3):610-618.
25. Goldstein MG, Whitlock EP, DePue J, Planning Committee of the Addressing Multiple Behavioral Risk Factors in Primary Care P. Multiple behavioral risk factor interventions in primary care. Summary of research evidence. *Am J Prev Med.* 2004;27(2 Suppl):61-79.
26. Bokhour BG, Berlowitz DR, Long JA, Kressin NR. How do providers assess antihypertensive medication adherence in medical encounters? *J Gen Intern Med.* 2006;21(6):577-583.
27. Tarn DM, Mattimore TJ, Bell DS, Kravitz RL, Wenger NS. Provider views about responsibility for medication adherence and content of physician-older patient discussions. *J Am Geriatr Soc.* 2012;60(6):1019-1026.
28. Whitlock EP, Orleans CT, Pender N, Allan J. Evaluating primary care behavioral counseling interventions: an evidence-based approach. *Am J Prev Med.* 2002;22(4):267-284.
29. Bodenheimer T, Willard-Grace R. Teamlets in Primary Care: Enhancing the Patient and Clinician Experience. *J Am Board Fam Med.* 2016;29(1):135-138.
30. Bodenheimer T, Laing BY. The teamlet model of primary care. *Ann Fam Med.* 2007;5(5):457-461.
31. AMA Steps Forward. Health Coaching. Available at: https://edhub.ama-assn.org/steps-forward/module/2702562.
32. Capoccia K, Odegard PS, Letassy N. Medication Adherence With Diabetes Medication: A Systematic Review of the Literature. *Diabetes Educ.* 2016;42(1):34-71.
33. Schoenthaler A, de la Calle F, Pitaro M, et al. A Systems-Level Approach to Improving Medication Adherence in Hypertensive Latinos: a Randomized Control Trial. *J Gen Intern Med.* 2020;35(1):182-189.
34. Thom DH, Willard-Grace R, Hessler D, et al. The impact of health coaching on medication adherence in patients with poorly controlled diabetes, hypertension, and/or hyperlipidemia: a randomized controlled trial. *J Am Board Fam Med.* 2015;28(1):38-45.
35. Tuluce D, Kutluturkan S. The effect of health coaching on treatment adherence, self-efficacy, and quality of life in patients with chronic obstructive pulmonary disease. *Int J Nurs Pract.* 2018;24(4):e12661.
36. Wu JR, Cummings DM, Li Q, et al. The effect of a practice-based multicomponent intervention that includes health coaching on medication adherence and blood pressure control in rural primary care. *J Clin Hypertens (Greenwich).* 2018;20(4):757-764.
37. McCambridge J. Motivational interviewing is equivalent to more intensive treatment, superior to placebo, and will be tested more widely. *Evid Based Ment Health.* 2004;7(2):52.
38. Diallo DD, Moore TW, Ngalame PM, White LD, Herbst JH, Painter TM. Efficacy of a single-session HIV prevention intervention for black women: a group randomized controlled trial. *AIDS Behav.* 2010;14(3):518-529.
39. DeWalt DA, Schillinger D, Ruo B, et al. Multisite randomized trial of a single-session versus multisession literacy-sensitive self-care intervention for patients with heart failure. *Circulation.* 2012;125(23):2854-2862.
40. Stevens VJ, Glasgow RE, Toobert DJ, Karanja N, Smith KS. One-year results from a brief, computer-assisted intervention to decrease consumption of fat and increase consumption of fruits and vegetables. *Prev Med.* 2003;36(5):594-600.
41. Schoenthaler A, De La Calle F, Barrios-Barrios M, et al. A practice-based randomized controlled trial to improve medication adherence among Latinos with hypertension: study protocol for a randomized controlled trial. *Trials.* 2015;16:290.
42. Schoenthaler A, Luerassi L, Teresi JA, et al. A practice-based trial of blood pressure control in African Americans (TLC-Clinic): study protocol for a randomized controlled trial. *Trials.* 2011;12:265.
43. Chokshi SK, Belli HM, Troxel AB, et al. Designing for implementation: user-centered development and pilot testing of a behavioral economic-inspired electronic health record clinical decision support module. *Pilot Feasibility Stud.* 2019;5:28.
44. Chokshi SK, Mann DM. Innovating From Within: A Process Model for User-Centered Digital Development in Academic Medical Centers. *JMIR Hum Factors.* 2018;5(4):e11048.

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45. Mann D, Hess R, McGinn T, et al. Adaptive design of a clinical decision support tool: What the impact on utilization rates means for future CDS research. *Digit Health.* 2019;5:2055207619827716.
46. Agency for Healthcare Research and Quality. Workflow Assessment for Health IT Toolkit. https://healthit.ahrq.gov/health-it-tools-and-resources/evaluation-resources/workflow-assessment-health-it-toolkit. Accessed October 8th, 2019.
47. Jerome A. Osheroff MDFF, T JM. *Improving Outcomes with Clinical Decision Support: An Implementer's Guide.* Healthcare Information and Management Systems Society; 2012.
48. Mann DM, Chokshi SK, Kushniruk A. Bridging the Gap Between Academic Research and Pragmatic Needs in Usability: A Hybrid Approach to Usability Evaluation of Health Care Information Systems. *JMIR Hum Factors.* 2018;5(4):e10721.
49. Richardson S, Feldstein D, McGinn T, et al. Live Usability Testing of Two Complex Clinical Decision Support Tools: Observational Study. *JMIR Hum Factors.* 2019;6(2):e12471.
50. Bodenheimer T. Health coaching checklist. https://cepc.ucsf.edu/sites/cepc.ucsf.edu/files/Health_Coach_Observation_14-0602.pdf. Accessed March 1, 2020.
51. Blecker S, Katz SD, Horwitz LI, et al. Comparison of Approaches for Heart Failure Case Identification From Electronic Health Record Data. *JAMA Cardiol.* 2016;1(9):1014-1020.
52. Gold A, Sontag D, Rosenman M, Katz S, Kuperman G, Blecker S. Heart Failure Phenotyping: A Set Theory Based Approach to Identify Patients With Heart Failure *Circ Cardiovasc Qual Outcomes.* 2016;9:A162.
53. Weerahandi H, Huynh HL, Shariff A, Attia J, Horwitz L, Blecker S. Diabetes Phenotyping Using the Electronic Health Record. *Journal of General Internal Medicine.* 2018;S:158.

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