A Randomized Trial of a BE-EHR Module to Guide the Care of Older Adults with Diabetes

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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.

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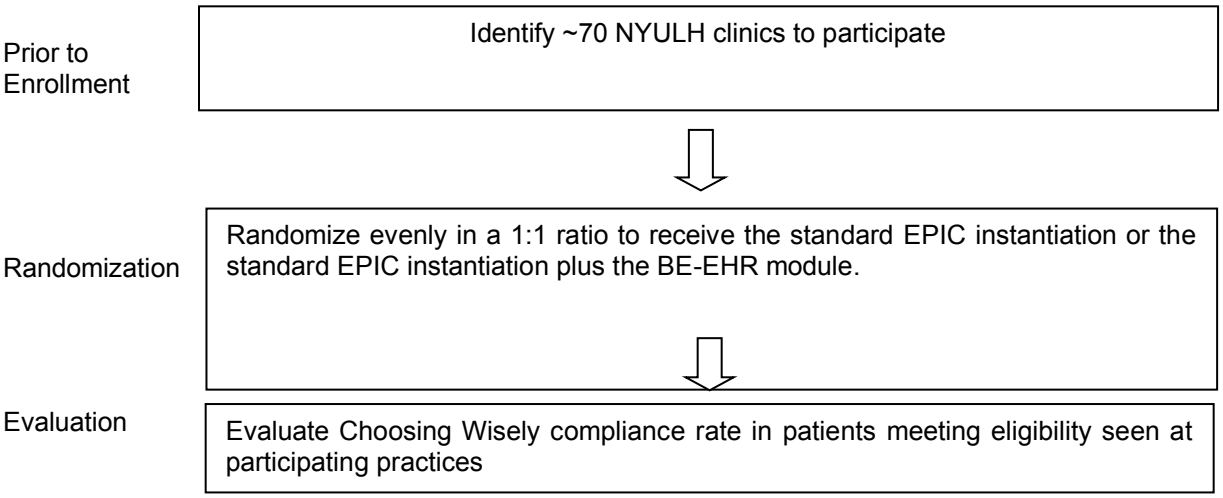
List of Abbreviations

AE	Adverse Event/Adverse Experience
BE	Behavioral Economics
CDS	Clinical Decision Support
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
CW	Choosing Wisely
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
EHR	Electronic Health Record
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
NYULH	New York University Langone 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

Protocol Summary

Title	A randomized trial of a BE-EHR module to guide the care of older adults with diabetes
Short Title	A randomized trial of a BE-EHR module to guide the care of older adults with diabetes
Brief Summary	This RCT will test a new electronic health record module to improve guideline-compliant care of older adults with diabetes. The module incorporates effective behavioral economics (BE) principles to improve the degree to which care of older adults is compliant with Choosing Wisely (CW) guidelines; this generally involves less aggressive targets for HbA1c, and reductions of medications other than metformin. The implementation of the module is triggered by patient scheduling and medication prescribing in EPIC. The BE principles include suggesting alternatives to medications, requiring justification, setting of appropriate default order sets, and incorporation of anchoring and checklists to guide behavior.
Objectives	Primary objective: to test a customized EHR toolkit that applies BE insights to promote appropriate diabetes care in older adults based on the American Geriatric Society's Choosing Wisely guideline, and to assess the acceptability of the resulting module. Secondary objective: to assess the "usability" of the proposed BE-EHR module in clinical practice.
Methodology	Cluster-randomized controlled trial
Endpoints	Primary endpoint: Choosing Wisely guideline compliance Secondary endpoint: medication prescribing patterns
Study Duration	Eighteen months
Participant Duration	Eighteen months
Population	Patients age 75 or older with diabetes
Study Sites	One single site at NYULH consisting of approximately 70 outpatient practices in primary care, geriatrics, or endocrinology
Number of participants	Approximately 5000
Statistical Analysis	We will begin all analyses with descriptive summary statistics and graphical displays of all variables. Primary analyses will utilize Poisson mixed-effects models for the provider-level CW compliance rate, with treatment group as the primary fixed effect of interest and practice as a random effect to accommodate clustering of providers within practices. We will assess whether negative binomial regression is warranted because of overdispersion. We will also explore non-parametric methods such as quantile regression and other rank-based approaches. Although randomization should obviate the need for any additional adjustment, we will explore whether adjustment for provider-level characteristics, such as demographics, panel size, or insurance mix, is necessary.

Schematic of Study Design



1 Key Roles

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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

2.1.1 Intensive glycemic control is of unclear benefit and carries increased risk for older adults with diabetes. A number of randomized controlled trials, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[1] the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial,[2] and the Veterans Affairs Diabetes Trial (VADT)[3], found that intensive glycemic control was not protective for macrovascular complications of diabetes including myocardial infarction or stroke. Although the United Kingdom Prospective Diabetes Study (UKPDS) did find a reduction in myocardial infarction in the long term after intensive glycemic control, this study enrolled middle-aged patients at time of diabetes diagnosis.[4] ACCORD,[5] ADVANCE,[2] and UKPDS[6] all suggested improvements in microvascular complications with tight glycemic control, but these often take years to develop. In total, these trials suggest that tight glycemic control is primarily beneficial to patients with newly diagnosed diabetes and a long life expectancy; these characteristics do not apply to most older patients, many of whom have been living with diabetes as a chronic disease.[7] Furthermore, these trials demonstrated the potential for harm with tight glycemic control, notably

increased risk of hypoglycemia,[1,2] as well as a suggestion of increased all-cause mortality.[1] Indeed, older adults are particularly susceptible to harms related to hypoglycemia in diabetes, including emergent hospitalization and neurologic complications.[8-12] Intensive glycemic treatment may also lead to increased risk of polypharmacy and adverse medicine interactions for older adults with multiple chronic conditions.[13]

2.1.2 The American Geriatric Society's Choosing Wisely guideline recommends moderate glycemic control. The third Choosing Wisely recommendation from the American Geriatric Society is: "Avoid using medications other than metformin to achieve hemoglobin A1c<7.5% in most older adults; moderate control is generally better."[14] Furthermore, as shorter life expectancy and greater comorbidity burden may decrease the benefits and increase the risks of tight glycemic control, the Choosing Wisely campaign suggests using these markers of health status to identify glycemic targets for older patients with diabetes. Glycemic target HbA1c ranges are provided for older adults in three categories: 7.0-7.5% for healthy adults with a long life expectancy, 7.5-8.0% for patients with moderate comorbidity and a life expectancy of less than 10 years, and 8.0-9.0% for patients with multiple comorbid conditions and a shorter life expectancy.[7,15] These recommendations build on work by Co-investigator Dr. Caroline Blaum on categorization of older adults with diabetes into three clinical groups based on health status;[16] this has been endorsed by numerous expert panels and guidelines.[11,17,18] The target ranges for glycemic control are similar to HbA1c values that have been associated with the best outcomes for older adults with comorbid conditions in observational or modeling studies.[19-21] Additionally, the American Diabetes Association (ADA) and others have recommended similar health status categories related to HbA1c targets in older adults.[11,17,18] Although the ADA guidelines do not identify lower targets for HbA1c,[11] other societies including the American Geriatric Society recommend similar lower thresholds for glycemic control.[18,22-24] Unfortunately, despite these recommendations, a substantial number of older adults have intensive glycemic control that may not be necessary.[25-27] Additionally, older patients with intensive glycemic control generally do not undergo de-intensification of therapy, suggesting opportunity for improving appropriate care.[28]

2.1.3 Behavioral economic approaches offer promise in influencing hard-to-change behavior. The field of behavioral economics (BE) seeks to combine principles of standard economics and psychology to recognize the limitations of the classical economic framework that views human decision-makers as purely rational actors who make decisions by maximizing the outcomes of available choice sets (sometimes termed *Homo economicus*).[29] In reality, humans are predictably irrational,[30] making common decision errors that are explicable through a set of psychological principles, and are therefore *predictable*. The field of behavioral economics posits that these decision errors, once recognized, can be harnessed to encourage desired behaviors rather than inhibit them.[31]

2.1.4 Decision errors fall into a typology of recognizable classes with known mechanisms. Traits contributing to decision errors include loss aversion, anchoring, overweighting of small probabilities, present bias, regret aversion, sensitivity to defaults, and the power of social comparisons.[32] Once recognized, each of these decision errors can be harnessed and overcome, often in the form of gentle "nudges" that make a desired behavior more likely.[33-36] Loss aversion occurs when a loss is more distressing than a gain of equivalent value;[37,38] thus, presenting rewards using a loss rather than a gain frame can be an effective motivator. Anchoring occurs when the decision-maker compares potential outcomes to some specified or implied reference level;[39] responses can be heavily influenced by the first information presented, so adjustment of the scale and/or starting point of a choice set can influence the resulting decisions. Present bias, also called hyperbolic discounting,[40] occurs when outcomes occurring in the near future carry much more weight than those occurring further into the future.[41] Human beings tend to overweigh small probabilities, one feature that contributes to the popularity of lotteries.[42,43] Regret aversion can be a highly motivating force in determining future actions.[44-46] Regret lotteries are a behavioral economic intervention simultaneously targeting probabilistic errors, present bias, and regret; in this approach, rewards are contingent on a desired behavior and participants are informed that they *would have won* if they had only completed it.[47,48] Defaults are a powerful driver of decisions, carrying implications of superiority or endorsement and taking advantage of decisional inertia; examples exist in such diverse domains as participation in retirement plans[49] and organ donation[50] that demonstrate dramatic differences in participation as a result of the chosen default option. Social comparisons have

been shown in a number of settings to be effective in influencing behavior,[24,51] as people tend to be heavily motivated by their perception of how their performance compares to those around them;[52,53] the phenomenon of social desirability bias is well documented.[54,55]

2.1.5 Substantial evidence shows the benefits and limitations of clinical decision support on clinical care. Electronic health records (EHRs) now dominate the landscape, influencing nearly every clinical decision, workflow, and order placed by health care providers. While EHRs have been successful in standardizing documentation, facilitating data sharing, and improving safety, their impact on clinical decision making has been mixed. Clinical decision support (CDS) is the primary EHR tool for influencing clinical decision making and promoting adherence to clinical guidelines. CDS entails providing clinicians, patients, and other healthcare stakeholders with pertinent knowledge, templates, and/or person-specific information, intelligently filtered or presented at appropriate times, to enhance health and healthcare.[56] CDS is an effective tool for improving provider performance and patient outcomes;[57] a meta-analysis of 25 randomized controlled trials found strong evidence that CDS improves care (odds ratio 1.42, 95% confidence interval 1.27 to 1.58).[58] Moreover, best practices for optimizing CDS effectiveness have been identified.[59,60] Successful CDS must deliver accurate information in the right clinical context at the point of care, and must be integrated into the relevant provider's workflow.[61] CDS can take many forms; to date, alerts and reminders have been the dominant CDS tools.[62] Large systematic reviews of CDS have demonstrated a moderate ability to reduce morbidity, utilization, and costs.[63,64] These modest improvements, however, are undermined by the well-documented problems of alert fatigue and poor workflow integration, which together blunt the potential impact of EHRs and CDS to improve healthcare outcomes.[62]

2.1.6 New studies indicate that combining behavioral economic and EHR clinical decision support tools offers promise for improving guideline adherence. Integrating behavioral economics and electronic health records using various CDS tools is a novel approach to improving adherence to guidelines that also seeks to minimize negative impacts on clinical workflow and cognitive load. For example, Meeker et al. integrated three BE concepts (suggested alternatives, accountable justification, and peer comparisons) into the EHR at 50 primary care practices to significantly (~5-7%) reduce inappropriate antibiotic prescribing for upper respiratory infections.[51] New approaches like these are needed to complement the traditional alerts, reminders, and other CDS tools that disrupt clinical workflow, increase cognitive load, and stress the limited capacity of clinicians to rationally process and evaluate the diverse and competing demands on their attention.

2.1.7 Innovation. This study will evaluate an innovative tool, implementing behavioral economic principles within the electronic health record, to promote clinician adherence to the Choosing Wisely guideline for diabetes management in older adults. Specific areas of innovation include:

- ***Minimal impact on clinician workflow or cognitive workload***. Unlike most new CDS systems, the proposed BE-EHR module will have limited negative impact on clinical workflow and cognitive load. BE tools inherently bypass the central processing route that requires clinicians to actively think about decision making.[66] Instead it leverages the peripheral route, which uses contextual cues and other influencing tools to nudge clinicians to choose actions consistent with stated guidelines.

- ***Extending the power of BE by combining modalities using the EHR.*** Several BE approaches have demonstrated efficacy. By combining multiple BE approaches and packaging them in a customizable EHR module, we will amplify the potential impact of BE on clinician guideline adherence when treating older people with diabetes*.*

- ***A flexible, scalable, modular intervention***. The creation of the BE-EHR module serves as a highly scalable platform for embedding BE-based CDS into any EHR system. The proposed module will guide other EHR users through a menu of customizable options that can switch on (or off) various BE-derived CDS tools to replicate our intervention for improving clinician adherence to diabetes management guidelines in older adults. More importantly, this module can be easily applied to many other conditions in older adults and other populations where combining BE with EHR-based clinical decision support will be useful for improving guideline adherence.

- ***A scalable, interoperable, standards-based solution***. The BE-EHR tool will follow standards-based development approaches, enabling widespread adoption across healthcare systems and diverse EHR platforms.

2.2 Rationale

This study aims to evaluate a new BE-EHR module to improve adherence to Choosing Wisely guidelines among older adults with diabetes.

2.3 Potential Risks & Benefits

2.3.1 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). Individual case determinations of potential safety gaps will never be released to supervisors of any clinicians whose charts are being reviewed. None of the study investigators has any oversight capacity over any clinicians.

2.3.2 Known Potential Benefits

There may be benefit to individual participants in this pilot study if their care is improved to comport with guidelines. The research will contribute critically to our knowledge of how to integrate behavioral economic interventions into EHR-driven clinical workflows. In the past, our team has successfully identified the potential benefit of connecting interventions with clinical workflows, and will assess a novel BE-EHR module to enable improved, guideline-consistent care of older adults with diabetes.

3 Objectives and Purpose

3.1 Primary Objective

The primary objective of the study is to evaluate a customized EHR toolkit that applies behavioral economic insights to promote appropriate diabetes care in older adults based on the American Geriatric Society's Choosing Wisely (CW) guideline.

3.2 Secondary Objectives (if applicable)

The secondary objective of the study is to continue to assess the usability of the proposed BE-EHR module in clinical practice.

4 Study Design and Endpoints

4.1 Description of Study Design

NYU Langone Health has ambulatory care sites in the five boroughs of New York City (NYC) as well as in suburbs of New York and New Jersey. Sites include academic practices, many community-based practices and a Federally Qualified Health Center (FQHC); many are multispecialty. Physicians in these practices form the NYU Faculty Group Practice (FGP) consisting of 351 total practices, including 81 primary care and 21 endocrinology practices. The NYU Brooklyn Family Health Center (FHC) is the second largest FQHC in the nation and has 9 additional clinics. All have the NYU Epic EHR, connecting all ambulatory visits at FGP clinics and at the FQHC. We will identify approximately 70 practices and conduct a parallel-groups cluster-randomized comparison of standard EPIC to standard EPIC + the BE-EHR module.

4.2 Intervention

The BE-EHR module includes six components: 1) a tailored advisory for patients over 75 with diabetes, 2) medication refill protocol with information on Choosing Wisely guidelines, 3) pre-population of the medication preference list with metformin, 4) lab result protocol with information on Choosing Wisely

guidelines, 5) peer comparisons regarding performance meeting guidelines, and 6) media campaign with information about Choosing Wisely guidelines. The set of nudges is referred to collectively as the BE-EHR module.

To tailor the intervention appropriately, we use a life expectancy algorithm to address different target patient populations with different CW guidelines. The life expectancy algorithm was built into the BE-EHR module to drive timing and content of module firings that incorporate both patient life expectancy (high, medium, low) and target glycemic index per the CW guideline. These categories are defined as follows:

1) healthy older adults with long life expectancy (>10 years): HbA1c target range of 7-7.5%;
2) those with moderate comorbidity and a moderate life expectancy (3-10 years): HbA1c target range of 7.5-8%;
3) those with multiple comorbidities and shorter life expectancy (≤3 years): HbA1c target range of 8-9%.

4.3 Randomization

There are currently 81 primary care practices in our FGP. Practice sites will be randomized using variable block sizes of 4 and 6 to ensure balance, with an even randomization ratio that will result in half of the sites randomized to the BE-EHR module activation (BE-EHR) and half randomized to usual care (UC). Randomization will be stratified by practice size (<= 100 patients vs > 100 patients over 75 with diabetes) to ensure balance. Dr. Troxel will request that the randomization scheme be generated by one of her faculty or staff members in the Division of Biostatistics who is unaffiliated with the project, in order to maintain blinding of assignment by the study team.

4.4 Study Endpoints

Outcomes measured at the prescription encounter level include whether the prescription is for a diabetes medication other than metformin, and whether the patient's most recent HbA1c value is within the Choosing Wisely HbA1c range guidelines for his/her age and morbidity category; these will be combined to classify the encounter as CW-compliant or CW-noncompliant. Outcomes measured at the physician level include these two measures, aggregated as a proportion of total prescription encounters within all eligible patients.

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

- Patient at NYULH primary care or endocrinology practice
- Practices that have patients aged 75 or older
- Practices that have a diagnosis of diabetes in the EHR chart

5.2 Exclusion Criteria

- Under age 75

5.3 Vulnerable Subjects

No vulnerable subjects will be enrolled.

5.4 Strategies for Recruitment and Retention

Eligible patients from the chosen practice sites will be identified electronically within EPIC using an algorithm developed by the study team. This algorithm reviews patient records for diabetes codes in the Problem List. Patients 75 and over with one of the included codes are eligible. The algorithm then identifies their life expectancy category using comorbidity codes and assigns them to one of the three Choosing Wisely categories described in Section 4.2. Patients meeting eligibility will be automatically included, and all data collection will take place passively via the NYULH EHR system, EPIC. An EPIC reporting analyst will extract the relevant parameters from EPIC into a report. No study-specific case report forms will be used; rather, information from the patient's problem list, prescription history, and

demographics will be used to compute compliance with CW guidelines. Patients from the selected practice sites will undergo their usual interactions with their providers and no study-specific activities will take place.

5.4.1 Use of DataCore/Epic Information for Recruitment Purposes

Eligible patients will be identified electronically within EPIC using an algorithm developed by the study team.

5.5 Duration of Study Participation

Participants will be followed for 18 months.

5.6 Total Number of Participants and Sites

This is a single site study involving approximately 70 NYULH outpatient clinics serving a total of approximately 5000 participants.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Not applicable as the subjects are recruited at the clinic level.

5.7.2 Handling of Participant Withdrawals or Termination

Not applicable.

5.7.3 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 Drs. Troxel and Mann, the NIH/NIA, 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
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

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

6 Study Schedule

Participants will be included in this study by virtue of meeting eligibility criteria and having a patient encounter during the study period (i.e. the trial) of eighteen months from the date of randomization. There are no study-specific visits. Any patient meeting criteria who has one or more patient encounters during the 18-month study period will be included. Therefore, no study-specific visits are relevant for this study, so there is no schedule of visits.

6.1 Screening

Not applicable.

6.2 Enrollment/Baseline

Not applicable.

6.3 Intermediate Visits

Not applicable.

6.4 Final Study Visit

Not applicable.

6.5 Withdrawal Visit

Not applicable.

6.6 Unscheduled Visit

Not applicable.

7 Study Procedures/Evaluations

There are no study-specific procedures that patients will undergo. They will receive care as usual by their outpatient providers. In order to evaluate Choosing Wisely compliance status, the BE-EHR algorithm will capture information on demographics, diagnoses in the patient's problem list, prescription history, and relevant lab results (i.e. allergies and blood glucose (HbA1c)). The study team members will not collect this information directly; data will be collected in NYULH's EHR system, EPIC, and an EPIC Reporting analyst will extract the relevant parameters from the EHR into a report. The study team members only receive the ultimate determination from the algorithm that the patient is either CW-compliant or CW-noncompliant.

7.1 Procedures/Evaluations

Practice sites will be randomized using variable block sizes of 4 and 6 to ensure balance, with an even randomization ratio that will result in half of the sites randomized to the BE-EHR module activation (BE-EHR) and half randomized to usual care (UC). Randomization will be stratified by practice size (<= 100 patients vs > 100 patients over 75 with diabetes) to ensure balance. See Section 4.3 for greater detail.

Eligible patients from the chosen practice sites will be identified electronically within EPIC using an algorithm developed by the study team. This algorithm reviews patient records for diabetes codes in the Problem List. Patients 75 and over with one of the included codes are eligible. The algorithm is outlined below as well as a description of each component of the interventional module:

1. Evaluation of Choosing Wisely compliance using a built-in algorithm. The life expectancy algorithm was built into the BE-EHR module to drive timing and content of module firings that incorporate both patient life expectancy (high, medium, low) and target glycemic index per the CW guideline. These categories are defined as follows:

    1) healthy older adults with long life expectancy (>10 years): HbA1c target range of 7-7.5%
    2) those with moderate comorbidity and a moderate life expectancy (3-10 years): HbA1c target range of 7.5-8%
    3) those with multiple comorbidities and shorter life expectancy (≤3 years): HbA1c target range of 8-9%

2. Firings of various module components using internal EPIC reporting. Each of the six components is triggered when a participant who has lower than recommended glycemic control is encountered in the system.

    1) Tailored Advisory: The Tailored Advisory nudge activates in Epic for any patient who is not CW compliant. For each patient seen, clinicians can respond by clicking the "Agree with

recommendation. Action taken" button, or by selecting the "Clinically inappropriate. Please explain" option, with space for free text comments. A response is not required.

2) Refill Protocol: The Refill Protocol nudge activates in Epic any time a medication refill for either Metformin or a non-Metformin diabetes medication is generated for a patient over 75
3) Preference List: The Preference List nudge is a system level nudge at the pilot sites. Metformin is listed at the top of the page as the choice for "First-line Type 2 Diabetes," without restricting orders for non-Metformin medications.
4) Lab Result: The Lab Result nudge activates in Epic whenever there is a new A1c lab result for a non-CW compliant patient; the alert remains active in Epic for seven days following the result.
5) Peer Comparison: The Peer Comparison nudge is sent via a secured Microsoft Outlook account once per month. The subject line of the email is "Message from the desk of Dr. [Insert Practice Director Name]" and the email content includes three graphics: a CW compliance rate for the individual provider, a CW compliance rate for the clinician's practice site, and a CW compliance rate across all NYU Langone practices. Depending on whether the clinician's CW compliance rate was above or below the rate of their respective practice, the provider receives either a "negative" or "positive" version of the email
6) Campaign: The campaign toolkit for dissemination includes three gameshow-themed animations (Price is Right, Jeopardy, and Who Wants to Be a Millionaire), as well as a flashcard deck that quizzes physicians on CW best practices. The Price is Right campaign includes three unique variations and the Jeopardy campaign includes four unique variations.

7.2 Laboratory Procedures/Evaluations

Not applicable.

7.3 Study Specific Biospecimens

7.3.1 Specimen Collection Procedures

Not applicable.

7.3.2 Specimen Preparation, Handling, and Storage

Not applicable.

7.3.3 Specimen Shipment

Not applicable.

7.4 Questionnaire Administration

Not applicable.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e., not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- <u>Related or possibly related to participation in the research</u> (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.

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

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Serious adverse events and unanticipated problems must be reported if they are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others.

For Narrative Reports of Safety Events

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.3.1 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.

9 Study Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see Section 11: Study Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

10 Statistical Considerations

10.1 Study Hypotheses

Patient in clinics receiving the BE-EHR module will have higher rates of CW compliance.

10.2 Sample Size Determination

Our preliminary data indicate that approximately 30-40% of eligible patients have care that is CW-compliant. We wish to be able to detect an increase in the rate of CW-compliant care of ten percentage points or more. We conservatively estimate an ICC (intra-class correlation coefficient, a measure of the degree of additional correlation among providers within the same practice) of 0.05; with an average of four providers per practice site at 70 sites, this leads to a design effect of 1.15. The sample of 280 providers becomes an effective sample size of 244, providing approximately 87% power to detect a difference of ten percentage points between the study arms.

10.3 Statistical Methods

We will begin all analyses with descriptive summary statistics and graphical displays of all variables. Primary analyses will utilize Poisson mixed-effects models for the provider-level CW compliance rate, with treatment group as the primary fixed effect of interest and practice as a random effect to accommodate clustering of providers within practices. We will assess whether negative binomial regression is warranted because of overdispersion. We will also explore non-parametric methods such as quantile regression and other rank-based approaches. Although randomization should obviate the need for any additional adjustment, we will explore whether adjustment for provider-level characteristics, such as demographics, panel size, or insurance mix, is necessary.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the study.

The EPIC electronic health record is the primary data collection instrument for the study. Study-specific case report forms will not be used.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

12 Ethics/Protection of Human Subjects

12.1 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.

12.2 Institutional Review Board

The protocol for study i19-01464, request for waiver of informed consent, and request for waiver of HIPAA authorization will be submitted to the IRB for review and approval. Approval of the protocol, the waiver of consent, and the waiver of HIPAA authorization 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.

12.3 Informed Consent Process

We will obtain a waiver of informed consent and a waiver of HIPAA authorization for patients seen in the participating clinics to acknowledge their participation at a clinic level. The risks to subjects are exactly equivalent to the risks experienced in the standard setting of patient care. The new module to be activated in EPIC relates only to guidance for physician decision-making regarding diabetes 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.

12.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Not applicable.

12.3.2 Consent Procedures and Documentation

Not applicable.

12.3.3 Research Use of Stored Human Samples, Specimens, or Data

No human samples or specimens will be collected.

- Intended Use: Data collected under this protocol may be used to study the effectiveness of the module.
- Tracking: Data will be tracked using Epic reports generated by study team members.
    - Disposition at the completion of the study. Data will be retained in de-identified electronic form on secure, password-protected digital storage media at the NYU central site, under the supervision of Drs. Troxel and Mann, for use by other researchers including those outside of the study.

12.4 Future Use of Stored Human Samples, Specimens, or Data

No specimens will be collected.

Data collected for this study will be analyzed and stored at NYU Langone Health. After the study is completed, the de-identified, archived data will be transmitted to and stored at the NYU central site, under the supervision of Drs. Troxel and Mann, for use by other researchers including those outside of the study.

When the study is completed, access to study data will be provided through the study database.

13 Data Handling and Record Keeping

13.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the study staff at NYULH under the supervision of Dr. Troxel. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

13.2 Study Records Retention

Study documents and data 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.

13.3 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 five working days of identification of the protocol deviation. All deviations must be addressed in study source documents and reported to the designated Safety Officer. 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.

13.4 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.

14 Study Finances

14.1 Funding Source

This study is financed through a grant from the National Institutes of Health – National Institute on Aging.

14.2 Costs to the Participant

There are no costs to participants in this study.

14.3 Participant Reimbursements or Payments

There are no participant reimbursements or payments.

15 Study Administration

15.1 Study Leadership

Dr. Troxel takes full responsibility for the study. The Safety Officer will govern the conduct of the study. The study PI will meet with the Safety Officer via teleconference at least annually.

16 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 NIA 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.

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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18 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.