Charter, Data and Safety Monitoring Board for the Study in Outpatient Medicine using Nudges to improve Sleep: The SOMNUS Trial
September 12, 2024

1. Introduction

This Charter is for the Data and Safety Monitoring Board (DSMB) for the *Study in Outpatient Medicine using Nudges to improve Sleep: The SOMNUS Trial*. The Charter is intended to be a living document. The DSMB may wish to review this Charter at regular intervals to determine whether any changes should be considered.

2. Responsibilities of the DSMB

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, ensuring data quality, evaluating clinical equipoise, and for monitoring the overall conduct of the study. In order to do this effectively in a trial, the DSMB is expected to review the data in an unmasked fashion in closed session.

The DSMB is an independent group advisory to IRB(s) and the investigators, and is required to provide recommendations about starting, continuing, and stopping the study. DSMB members must be cleared of any potential Conflict of Interest (COI) before participating in any meeting.

In addition, the DSMB is asked to make recommendations, as appropriate about:

- Efficacy of the study intervention
- Benefit/risk ratio of procedures and participant burden
- Clinical equipoise (at onset and throughout the study)
- Ability of study design to answer the primary question
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Data and statistical analysis plan
- Initial protocol, informed consent form, and data reporting shell
- Amendments to the study protocol and consent forms, including whether any new data from other sources affect the equipoise of the study being monitored
- Impact of any changes in enrollment targets on the power of the study and whether ultimately the scientific questions can be adequately addressed
- Performance of individual centers and core labs
- Participant safety, including review of consent form
- Notification of and referral for abnormal findings
- Review of the primary endpoint paper, methods and result sections
- Participant safety and parent study burden of proposed ancillary studies, including whether the total burden of ancillary studies might compromise the parent study

3. Organization and Interactions

The following description illustrates the relationship between the DSMB and other entities in this study.

Communication with DSMB members will be primarily through the study Project Director and Data Analyst. It is expected that study investigators will communicate with DSMB members about the study only as needed to make decisions related to meetings and meeting materials.

4. DSMB Members

DSMB members and their expertise are listed in Appendix A and accompanied by bio-sketches. Each DSMB is assigned an Executive Secretary (ES) that is usually a member of the DSMB to take minutes and work with the Chair (or the ES can be the DSMB Chair if sufficient) to produce final recommendations and meeting report. Dr. Rui Wang will serve as the ES for the first 2 meetings, this role will rotate to another member for future meetings. The DSMB Chair is responsible for assuring the accuracy and timely transmission of the final recommendations and DSMB's report. *Ad hoc* members may be added to the DSMB to supplement expertise, as necessary for single or multiple meetings.

5. Scheduling, Timing, and Organization of Meetings

The purposes of the first meeting are to:

- Review this Charter;
- Provide an overview of study SOMNUS activities; and
- Review and accept the protocol, informed consent, and data reporting shell, or make recommendations for changes related to human subjects' safety and ethics.

Enrollment in a study cannot begin until the DSMB's recommendation for approval has been accepted by the NHLBI Program Office, and IRB approval has been obtained.

Meetings are held approximately twice a year, with additional meetings scheduled as needed. The NHLBI Program Office will be notified of scheduled meetings in advance should Program Officer and/or delegate wish to monitor the meeting.

- Review of interim data analyses will occur as needed
- Ad hoc meetings may be scheduled as needed

The agenda for DSMB meetings and calls may be drafted by the study Project Director. The study Project Director will finalize the agenda after consultation with the DSMB Chair. The agenda and meeting materials will be distributed by the Project Director, 1 week before each meeting. The NHLBI Program Office may receive this material at the same time as DSMB members.

When the agenda is sent out, and again at the beginning of each meeting, the ES or Chair will ask all DSMB members to state whether they have developed any new conflicts of interest since the last DSMB meeting. If a new conflict is reported, the Chair and study staff will determine if the conflict limits the ability of the DSMB member to participate in the discussion. Examples of conflict of interest include significant collaborations in publications or other activities during the past few years, employee reporting relationships, or financial or intellectual stake in the research to be monitored.

The DSMB will review adverse event data, other safety data, quality and completeness of study data, and enrollment data at each meeting to ensure proper study conduct. It will also conduct an ongoing assessment of clinical equipoise in the study. Study personnel should provide any new literature particularly pertinent to the study, along with their recommendation as to whether it affects the study conduct or design. The DSMB will review the informed consent form when it reviews the protocol. The DSMB will review the consent periodically and/or as needed and consider whether the consent form requires revision in light of any new findings or amendments. In the case of clinical trials, at intervals, as noted above, the DSMB will also review formal interim analyses of the primary end point. Based on an overall assessment of risk and review of the data, the Board will make recommendations, including whether the study should continue and/or be modified.

In addition to regular meetings, it may be necessary to convene the DSMB urgently on an *ad hoc* basis to discuss new data or other information that raises questions about equipoise, safety, or anything else in the study.

The expertise of the attending members should be appropriate for the agenda of the meeting. It's expected that all DSMB members will attend every meeting, but this may not always be possible. Therefore, the DSMB may establish a quorum for voting. A quorum is 3 members (usually half the members plus 1). The Board Chair and in most instances the Biostatistician, must be present at all meetings. All standing Monitoring Board members are voting members. The Board may also decide in advance whether *ad hoc* members can vote.

6. Meeting Format

DSMB meetings will be organized into open, closed, and executive sessions.

- During **open sessions**, information will be presented to the DSMB by the study investigators, with time for discussion.

- During **closed sessions**, the DSMB, required staff from the study (generally a study statistician), and the NHLBI program staff at the Chair's discretion, will discuss confidential data from the study, including information on efficacy and safety by treatment arm. Select unblinded staff from the study may stay to explain the data reports. If DSMB does not receive unmasked data, the DSMB will discuss and decide during each meeting whether to remain masked to the treatment assignments. Unblinded study data analyst should be able to provide treatment assignments immediately should DSMB wish to be unmasked during a meeting. If the closed session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the closed session.

- The DSMB may hold an **executive session** in which only the DSMB members, and NHLBI program staff at the Chair's discretion, are present in order to discuss study issues independently.

Voting on recommendations will follow Robert's Rules of Order**.**

If the executive session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the executive session.

At the conclusion of the closed and executive sessions, the participants may be re-convened so that the DSMB chair may provide a summary of the preliminary recommendations and provide an opportunity for participants to clarify the recommendations. The meeting is then adjourned.

7. Expedited Safety Reporting

Safety events requiring expedited reporting (as defined in DSM Plan) will be sent to the full Board and NHLBI program office within 2 days of learning of the event. DSMB chair will respond to the study Project Director and NHLBI program office with recommendations within 3 days. Safety event definitions and reporting timelines are documented in the data and safety monitoring plan or protocol.

8. Reports to the DSMB

For each meeting, the study data analyst will prepare summary reports and tables to facilitate the oversight role of the DSMB. The DSMB will discuss at the first or subsequent meetings what data they wish to review and how it should be presented.

9. Reports of DSMB Deliberations

- Full Summary and Recommendations: The DSMB Chair, in conjunction with the ES (if there is one), is responsible for the accuracy and transmission of DSMB meeting summary to the entire Board within 14 calendar days of the meeting. The summary must be signed by the DSMB Chair and will include reports of the closed session and executive session if an executive session was held. Study data analyst may receive the full summary as decided by the DSMB chair on a meeting by meeting basis.

- Summary and Recommendations, edited so as not to expose the investigators to confidential or unblinded information and signed by the DSMB Chair, will be sent to the investigators within 14 calendar days after the meeting. These summary minutes and recommendations at minimum include a statement as to whether the study is approved to continue as planned, any requests for additional data, and response of the investigators to prior recommendations.

  Requests for additional data from the investigators or DCC/statistician should include an expected due date.

  DSMB recommendations must be submitted to appropriate IRB(s). If a multi-site study, it is the responsibility of each site to submit to their local IRB.

- Action plan: Summary and Recommendations (including approval of revisions to study documents like protocol, statistical analysis plan, or consent), and the study's follow-up plans will be submitted to the DSMB and NHLBI Program Office within 14 calendar days after the DSMB meeting.

- If the DSMB does not identify any safety or other protocol-related concerns, the Summary Report will state that:
    - A review of outcome data, adverse events, and information relating to study performance (e.g., data timeliness, completeness, and quality) across all centers took place on a given date
    - No safety concerns were identified
    - A review of recent literature relevant to the research took place,
    - The study remains in clinical equipoise and
    - The DSMB recommended that the study continue without modification of the protocol or informed consent

10. Statistical Monitoring Guidelines

The DSMB will review the adequacy of the statistical monitoring plan. The final plan, whether part of a research protocol or separate document, will be maintained as an appendix to this Charter. The DSMB should discuss the statistical monitoring procedures that will be followed to guide recommendations about termination or continuation of the trial. These procedures could include guidelines for early termination for benefit, futility, and/or safety reasons.

The statistical monitoring procedures should ensure the development of clinical trial stopping rules for reasons of safety-related events or futility, which are clearly defined in advance as part of initial study review.

DSMB Charter Approval

The Charter was approved at the **July 25, 2024** meeting of the DSMB, as reflected in the minutes.

Appendix:

Appendix A. DSMB members

Appendix B. Data and Safety Monitoring Plan

Appendix C. Statistical Analysis Plan

Appendix A. SOMNUS DSMB members

[CHAIR] Jeffrey Kullgren, MD, MS, MPH, Research Scientist, VA Center for Clinical Management Research, PO Box 130170, 152, Ann Arbor, MI 48113. Phone: (734) 845-3613, jkullgre@med.umich.edu. **Expertise in behavioral economics and clinical decision-making**

Dr. Kullgren practices both outpatient and inpatient general internal medicine at the VA Ann Arbor Healthcare System. Dr. Kullgren holds undergraduate and medical degrees from Michigan State University and a Master of Public Health degree from the University of Michigan. Dr. Kullgren's research aims to develop innovative approaches to help patients and clinicians make decisions that will improve the value of health care. In this work, he uses survey and qualitative methods to identify opportunities for interventions to improve decision-making and targets these opportunities with novel interventions that translate behavioral science insights.

[EXECUTIVE SECRETARY] Rui Wang, PhD, Landmark Center, 401 Park Drive, Suite 401 East, Boston, MA, 02215, rwang@hsph.harvard.edu. **Expertise in Biostatistics and Sleep Medicine**

Dr. Wang is the Lagakos and Zelen endowed Chair and Professor of Population Medicine at the Harvard Pilgrim Health Care Institute and Harvard Medical School. She is the Director of the Division of Biostatistics. Additionally, she is an Associate Professor in the Department of Biostatistics at Harvard T.H. Chan School of Public Health. Dr. Wang received her PhD Degree from Harvard University. Dr. Wang's research interests include the design, monitoring, and analysis of parallel and stepped-wedge cluster randomized trials, where a group of subjects, as opposed to individuals, are randomized to each of the treatment arms in the trial. The particular questions she is addressing include the investigation of how the complex correlation structure within clusters affects the sample size and power of the trial, and how to analyze data from such trials efficiently, taking into account the correlation structure and the issue of missing data.

Constance Fung, MD, MSHS, Professor of Medicine, David Geffen School of Medicine at UCLA, Phone: (818)891-7711 x36075, cfung@mednet.ucla.edu**. Expertise in sleep medicine and geriatrics**

Dr. Fung is an Associate Clinical Professor at UCLA. She is a sleep medicine physician with training in geriatrics. Dr. Fung is a Beeson Scholar and former American Sleep Medicine Foundation Physician Scientist Training Awardee, VA Advanced Geriatrics Fellow, and John A. Hartford Center of Excellence Scholar. She studies behavioral interventions to improve sleep in older adults.

Adam Sacarny, **PhD,** Assistant Professor of Health Policy and Management, Columbia University Mailman School of Public Health, 722 West 168 Street, 4th Floor, New York, NY 10032, ajs2102@columbia.edu. **Expertise in behavioral economics and randomized trials**

Dr. Sacarny is Assistant Professor, Health Policy and Management at Columbia University. Dr. Sacarny's research explores the relationship between health care payment policy, provider and patient decision-making, and clinical quality. Much of this work involves using randomized controlled trials to test interventions in the health care delivery system. His research on health care providers has studied the effects of behavioral interventions on overprescribing, the adoption of hospital documentation and coding practices, and the relationship between hospital clinical outcomes and market share.

Appendix B. Data and Safety Monitoring Plan

Grant Title: *The **S**tudy in **O**utpatient **M**edicine using **N**udges to improve **S**leep: The **SOMNUS** Trial*

Grant PI: Jason Doctor, PhD

Brief Description of Intervention:

Intervention	Description
Education Control	Guideline education.
Justifications	Guideline education. Justify orders discordant with guidelines. Justifications entered in the medical record.
Defaults	Guideline education. Pre-populated default doses.
Justifications & Defaults	Guideline education. Justify orders discordant with guidelines. Justifications entered in the medical record. Pre-populated default doses.

Stage of Behavioral Intervention Development: Stage III

NIH Phase III Clinical Trial? Yes

Multiple Site Trial? No

Specific Aims

1. We will conduct an 18-month cluster randomized trial in 60 primary care clinics in the Midwestern United States. We will modify electronic health records and compare defaults and accountable justification nudges against education control.

Brief Description of Project Design

The SOMNUS Trial is a cluster-randomized controlled trial randomized at the clinic level to avoid intra-clinic contamination of the intervention. We will modify electronic health records and compare: 1) defaults, 2) social accountability nudges, 3) defaults combined with social accountability, and 4) education control. All clinicians have access to a cognitive behavioral therapy for insomnia referral containing CBT-I resources for patients. The intervention period will be 18-months in length for all participants, with a 12-month follow-up period to measure the persistence of effects after the interventions end.

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1.0 PARTICIPANT SAFETY

1.1 POTENTIAL RISKS AND BENEFITS FOR PARTICIPANTS

Potential Risks:

This is a minimal risk study. All IRB approvals will be in place before any human subjects research begins. Sites will be using SMART IRB reliance to cede to USC's IRB as the IRB of record. We will include written details in our study protocol about prompt reporting of any adverse events or unanticipated problems to this IRB. USC IRB will have a record of this data safety plan within our project file.

1.1.1 There is a small risk of loss of confidentiality with the collection of data from the intervention sites. Every effort will be made to avoid this risk. The minimum necessary data are being extracted to address our study objectives.

1.1.2 Individuals involved in this study will be subject to minimal risk through their participation. The study collects information about clinicians' clinical decision making. While we work to keep this information confidential, there is a risk of loss of confidentiality.

1.1.3 Participants can withdraw from the study at any time. If a participant decides to withdraw during the study period, we will only analyze data from their patient encounters up to the point of their written withdrawal. We will turn off study clinical decision support as soon as possible for a clinician that requests to withdraw.

1.1.4 We do not anticipate the need to remove participants from the research study without their approval.

Potential Benefits:

1.1.5 There may be no direct benefits to participants in this study. The knowledge gained from this study however, will help clinicians and others in the healthcare industry better understand why clinicians make certain treatment choices. This has the potential to benefit patient care including the care of the patients seeing the clinicians in the study if the piloted interventions lead their clinicians to make safer prescribing decisions.

1.2 ADVERSE EVENT/SERIOUS ADVERSE EVENT/UNANTICIPATED PROBLEM COLLECTION AND REPORTING

1.2.1 AE/SAE Definitions

Adverse Event (AE):
Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

Serious Adverse Event (SAE):
Any adverse event that:

- Results in death

- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

Unanticipated Problem (UP):
Defined by DHHS 45 CFR part 46 as any incident, experience, or outcome that **meets all the following criteria:**

- unexpected, in terms of nature, severity, or frequency, given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the study population;
- related or possibly related to participation in the research (in this guidance document, 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 participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Adverse Events versus Unanticipated Problems

• The vast majority of adverse events occurring in human subjects are not unanticipated problems.
• A small proportion of adverse events are unanticipated problems.
• Unanticipated problems include other incidents, experiences, and outcomes that are not adverse events.

Because this is a study of electronic health record (EHR) clinical decision support (CDS) aimed at promoting evidence-based, non-experimental practices, we do not anticipate that these interventions will increase adverse events for patients. There are no anticipated adverse events for clinicians. We will monitor for specific unanticipated problems during the study period that might be related to the study intervention. This study involves the following nudges:
*An **accountable justification*** is a social accountability nudge, delivered as an electronic health record prompt that asks a clinician seeking to prescribe a Z-drug to explain, in a brief free-text response, the reason for this treatment decision. The prompt is visible in the patient's medical record under "high-risk prescribing," and if no justification is entered, the phrase "no justification given" appears in the patient record. Poor justifications that appear in the electronic health records may engender reputational concerns,(Lerner and Tetlock 1999; Baumeister and Hutton 1987; Jerdee and Rosen 1974; Milinski, Semmann, and Krambeck 2002) thereby motivating behavior change to preserve one's clinical reputation when there is no valid justification. Studies by ourselves(Meeker et al. 2016) and others have shown that justifications are effective.(O'Connor et al. 2014; Mola et al. 2010; Karlovich et al. 2021; Hammami et al. 2020; Staples et al. 2020; Mehta et al. 2019; Sardar et al. 2018; Zenziper Straichman et al. 2017)
Defaults are the outcome that results when the clinician does not take action. For example, if a medication order is pre-populated with 10 pills, a clinician who completes the order without a change to the number of pills has accepted the default. Defaults have enjoyed wide-spread success in helping improve decisions in many areas, including organ donation,(Johnson and Goldstein 2003) retirement savings,(Choi, Laibson, and Madrian 2004) and judicious prescribing of opioids.(Delgado et al. 2018)

Intervention	Description
Education Control	Guideline education.
Justifications	Guideline education. Justify orders discordant with guidelines. Justifications entered in the medical record.
Defaults	Guideline education. Pre-populated default doses.
Justifications & Defaults	Guideline education. Justify orders discordant with guidelines. Justifications entered in the medical record. Pre-populated default doses.

While we don't believe there is a relevant, specific safety measure for sleep prescribing safety CDS, we will investigate all clinician reported adverse events or unanticipated problems for all study CDS.

1.2.2 Classification of Severity and Study Relatedness

Severity

- **Mild:** Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- **Moderate**: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning
- **Severe**: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating

Expectedness

- **Unexpected** - nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure, or investigator brochure.
- **Expected** - event is known to be associated with the intervention or condition under study.

Relatedness

- **Definitely Related**: The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.
- **Possibly Related**: An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the

suspected intervention, but that could readily have been produced by a number of other factors.

- **Not Related**: The adverse event is clearly not related to the investigational agent/procedure - i.e., another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

1.2.3 AE/SAE reporting

Safety measure for discontinuing or reducing sleep medications: hospitalization or ED visit for withdrawal. Event is the occurrence of a hospitalization or ED visit for withdrawal, detected through a query of the intervention site data. The denominator for this measure is all patients for whom a study clinical decision support nudge targeting a sleep medication was triggered.

We will monitor **new drug prescriptions for benzodiazepines** and compare rates between treatment and control; because the intervention is randomized we can infer cause from comparing differences for all safety measures. We will monitor the use of these drugs at all visits and among persons who had received a prior prescription for a Z-drug.

For a subset of patients who enroll to use our study CBT-I text message-based sleep tool, we will include the Stanford Sleepiness Scale as part of the daily sleep diary which measures their degree of sleepiness. We will monitor and report findings to the DSMB.

Clinician reported adverse events/unanticipated problems. At any time, participating clinicians can report an adverse event or unanticipated problem potentially related to study participation. We do not expect there to be adverse events directly influenced by the clinical guidance being delivered in this study. All study interventions encourage clinicians to follow well-established national guideline recommendations and known best practices. While the expectedness of adverse events is very low, we will investigate each and every numerator case identified in all safety measures described above. For cases identified by the safety monitoring measures, we will perform manual physician chart review of Epic EHR documentation to examine the clinical circumstances and to make a judgment (1) the **expectedness** of the event [unexpected, expected], (2) the likelihood that the safety event was study **related** [not related/possibly related/definitely related] and (3) judge the event's **severity** [abnormal clinical finding without symptoms/symptoms requiring clinical intervention/short term disability or hospitalization/death AND separately define the severity as mild, moderate, or severe]. These will be conducted only by authorized study personnel who are physicians. Study personnel will interview patient's treating clinicians when needed to obtain additional information. Each case identified will have a case report form with these variables and will be signed and dated by study staff completing the form. These forms will be stored in site PIs locked office and presented to Dr. Doctor via telephone in a de-identified fashion. Each adverse event will be given an identification number. If study personnel believe that a patient that experienced an adverse event would benefit from seeing or communicating with their clinician who previously received study clinical decision support, the relevant Site PI will (within 2 business days) reach out to this clinician advising them to contact the patient as soon as possible.

All study personnel will be trained in HIPAA-compliant procedures. Data will be kept on a password protected drive on a secure network, to which study personnel will have restricted access.

All outcome data will be obtained from clinical site EHRs. Only authorized research team members will have access to identified data. Analytic files will be stripped of all identifiers

(both patient and clinician). This limited data set will be shared with USC via secure file transfer process.

Within one business day we will report any clinician-reported adverse events, safety analysis, or unanticipated problems to the USC IRB. Our report will include appropriate identifying information for the study, a detailed description of the adverse event, and a description of any changes to the protocol or other corrective actions that have been taken or are proposed. If an adverse event occurs, we will review relevant clinical decision support and ensure others are not at a greater risk of harm than was previously known or recognized. We will notify our NHLBI Program Officer of any serious adverse events.

Clinician participants are only receiving EHR based clinical decision support. Deaths are not expected in this minimal risk study. Patients are not aware that we are reviewing their clinical data as part of this study. All study decision supports encourage guideline recommended care. Patient deaths related to this study are not expected. However, should we identify a patient death in safety measures described above we will report the death to the NHLBI Program Officer, Dr. Doctor, relevant clinical Site PIs, and the USC IRB within 24 hours of our knowledge of the death.

The seriousness of the adverse event will be documented on the case report form. We will categorize all of the following as serious adverse events: patient death, life-threatening event, hospitalization-initial or prolonged, disability/incapacity, and events that required intervention to prevent permanent impairment. The clinician reviewing the event will determine the seriousness of the event. If it is an event other than those listed above that the reviewing clinician feels is an 'other' serious event, it will be discussed with another clinical study team member to reach consensus. All details will be documented on case report form.

If a study related serious adverse event (SAE) that was unanticipated (not listed above) occurs, the PI and study medical monitor (Jeffrey Linder) will review and adjudicate the event. If deemed appropriate, it will be reported to the DSMB and NHLBI Program Officer and relevant clinical Site PIs within 48 hours of study's knowledge of the event. As noted above, assessment of expectedness, relatedness, and severity will be performed by clinical Site PI in consultation with Dr. Doctor.

The summary of all SAEs (both anticipated and unanticipated) and safety measures will be reported and shared with the NHLBI Program Officer and the USC IRB quarterly (onceDSMB has reviewed and provided their assessment), unless otherwise requested. In addition, the summary for reporting all adverse events (including a report of all numerator cases to all safety measures identified in this report) will be shared with the NHLBI Program Officer quarterly, unless more frequent reports are requested by the NHLBI.

Unanticipated Problems that are unexpected, related or possibly related to this research (including anywhere there is a reasonable possibility that the incident or outcome may have been caused or associated with the study) and that suggests that the research places clinicians or patients at greater risk of harm than was previously known or recognized will be thoroughly and promptly investigated. The Unanticipated Problem will be investigated, formally written down with a corrective plan and measures to prevent reoccurrence. This report will be shared with the NHLBI Program Officer within 48 hours of study's knowledge of the problem.

1.3 PROTECTION AGAINST STUDY RISKS

1.3.1. This cluster-randomized clinical decision support study will be conducted with a waiver of clinician consent, which has already been approved by the USC IRB. However, we will

communicate to participating clinicians several ways. We will send eligible clinicians an email notifying them about the study procedures and how to contact study personnel. We will collect electronic informed consent from clinicians who participate in either the clinician survey and the educational module. The consent form has been reviewed and approved by the USC IRB. We will communicate with site clinical leaders directly to explain the nature of the study and how to contact study personnel. Third, we will offer practices the opportunity to have study staff introduce the study at clinician meetings and answer questions.

1.3.2. Provisions to Protect the Privacy Interests of Participants:

1.3.2 .1. The following study team members will have access to de-identified data produced from this study. The only individuals who will see identified data are Persell, Linder, Lee.

Team Member	Institution	Expertise
Jason Doctor, PhD	USC	Behavior change, changing clinician behavior
Daniella Meeker, PhD	Yale	Informatics, data science, performance measurement
Emily Stewart	USC	Programmer Analyst
Jeffrey Linder, MD, MPH	NU	Primary care, informatics, antibiotics use, decision support, health system interventions
Stephen Persell, MD, MPH	NU	Primary care, internal medicine, clinical informatics, quality improvement, performance measurement, clinical trials
Ji Young Lee	NU	Enterprise data warehouse (EDW) analyst

1.3.3. Confidentiality and Data Management:

1.3.3.1 Data will come from the Northwestern Medicine EHR, our clinical trial site. Only designated members of the research team will have access to this data. Only data from eligible subjects will be analyzed. Descriptive analyses including frequency, counts and percentages will be used to summarize the sample. Any investigator receiving data from the clinical sites for this project must be on the Authorized Personnel listed in the IRB documentation. In the event that the investigator does download data containing PHI (names, dates, SSN, MRNs), the investigator must download and store the data to an encrypted device. The data must be stored as described in the IRB documentation for this project. Emailing of data containing PHI is not permitted and will not be done.

2.0 INTERIM ANALYSIS

We will assess study measures and safety measures by query of clinical site data at 6 months, 12 months and 18 months (intervention end). Chart review will be conducted as needed by Jeffrey Linder (Clinical Site PI and medical monitor). There is no additional interim analysis planned for this study as it is minimal risk. We do not plan an interim analysis of study effectiveness.

3.0 DATA AND SAFETY MONITORING

For this trial, a DSMB will be assembled and responsible for monitoring and reviewing any adverse events or unanticipated problems. Study team will be responsible for providing reports of adverse events to the IRB and the NHLBI Program Officer. The DSMB will convene before the study begins, and again at the preferred cadence of the DSMB. The procedures for the DSMB will be included in the DSMB charter.

3.1 FREQUENCY OF DATA AND SAFETY MONITORING

Reports of our safety measures will be delivered to our Data and Safety Monitoring Board at their preferred cadence, but likely at 6, 12 and 18 month intervals.

3.2 CONTENT OF DATA AND SAFETY MONITORING REPORT

The content of the data and safety monitoring report will include:

- Protocol synopsis
  - Project organizational chart and personnel
  - Brief statement of purpose of trial
  - Projected timetable and schedule
- Trial Summary
  - Study status
  - Previous meeting summary
  - Summary of protocol changes
- Participant status per site: Tables and figures
- Safety assessment for all participants where applicable

3.3 DSMB MEMBERSHIP AND AFFILIATION

See Appendix A.

3.4 CONFLICT OF INTEREST FOR DSMB

The DSMB members will have no direct involvement with the study or conflict of interest with the investigators or institutions conducting the study. Accordingly, each has signed a Conflict of Interest Statement.

3.5 PROTECTION OF CONFIDENTIALITY

Data will be recorded with SSL-protected websites to a data warehouse and transferred over a secure network protocol. Data will be kept in encrypted files on a secure research computing cloud at USC Schaeffer Center facilities. Study investigators will have access to a list of study ID codes that will be traceable back to actual subject contact identifiers for clinicians. These codes will be kept in locked offices at USC Schaeffer Center facilities. USC and Northwestern University have a fully executed Data Use Agreement in place.

Data will be presented in a blinded manner during the open sessions of the DSMB. At DSMB meetings, data and discussion are confidential. Participant identities will not be known to the DSMB members.

3.6 DSMB RESPONSIBILITIES

DSMB member responsibilities will be detailed in the Data and Safety Monitoring Board Charter prior to the first meeting.