DSMB Charter

A Cluster-Randomized Trial of the Northwestern Embedded Emergency Department Physical Therapy (NEED-PT) Protocol for Acute Low Back Pain

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DATA AND SAFETY MONITORING BOARD (DSMB) CHARTER

A Cluster-Randomized Trial of the Northwestern Embedded Emergency Department Physical Therapy (NEED-PT) Protocol for Acute Low Back Pain

Principal Investigator: **Howard S. Kim, MD MS**
Biostatistician Co-Investigators: **Jody D. Ciolino, PhD; Jacob M. Schauer, PhD**
Clinician Co-Investigator: **Danielle M. McCarthy, MD MS**

I. INTRODUCTION

The purpose of this charter is to define the responsibilities of the DSMB and provide written guidance and documentation of the DSMB procedures. In essence, it serves as a plan of operations for the DSMB. The DSMB may refer to the International Conference on Harmonization (ICH) E6 and E9 documents in addition to the FDA Guidance on the Establishment and Operation of Clinical Trial Data Monitoring Committees for reference.

NEED-PT is a single center physician-randomized trial of an embedded emergency department (ED) physical therapy intervention for patients with acute low back pain. Individual physicians will be consented to undergo randomization to either the NEED-PT intervention (i.e., an embedded physical therapist on their primary treatment team) or usual care; patients will be individually consented and enrolled and allocated to the study group of their treating physician. The primary outcome is pain-related functioning as measured by PROMIS-Pain Interference scores over three months of follow-up; the main secondary outcome is patient-reported opioid use.

The trial is sponsored by the Agency for Healthcare Research and Quality (AHRQ) through grant award #R01HS027426; Principal Investigator: Howard S. Kim, MD MS. The investigator team and coordinating activities for the trial are located at the Northwestern University Data Analysis & Coordinating Center (NUDACC) in the Feinberg School of Medicine.

The Data and Safety Monitoring Board (DSMB) provides independent safety review and trial guidance during the course of the ongoing trial. This document outlines the formal operating procedures for the NEED-PT DSMB.

The DSMB will review safety data and primary outcome data summarizations both overall and by study arm at a minimum of every six months during the conduct of the trial. The DSMB will collectively determine whether the overall safety and feasibility of the trial remain acceptable given the information provided in the interim reports, during formal DSMB meetings, and in any communication regarding the trial in between meetings.

Specifically, the DSMB will review summary reports of all serious adverse events (SAEs), and they may review individual cases in detail if deemed appropriate or necessary to address potential safety concern(s). The investigators, sponsor representative(s), or combination may also request additional *ad hoc* DSMB review should a concern arise. The DSMB may recommend a new course of action for one or both study arms or may suggest other appropriate courses of action to address general study safety issues which may arise. If warranted, the DSMB may recommend at any time that the entire protocol be suspended temporarily or terminated permanently. These recommendations will be directed to the principal investigator (Dr. Howard Kim), who has the responsibility to accept, reject, or modify DSMB recommendations. Dr. Kim will ensure AHRQ and Northwestern University's

Institutional Review Board (IRB) receive the written DSMB recommendations and any written decisions to accept / reject / modify them.

II. ORGANIZATION OF THE DSMB

Composition of the DSMB

The DSMB membership includes **five voting members**:

1. Chair: Dr. Timothy Platts-Mills, MD, MSc
2. Dr. Rogelio Coronado, PT, MPT, PhD
3. Dr. Janel Fedler, PhD
4. Dr. Dave Lu, MD, MSCI, MBE
5. Dr. Diana Wilkie, PhD, RN

There will also be a designated DSMB Secretary to take minutes during portions of the meeting in which the study team investigators are not present (i.e., closed session); during all other portions of the meeting the study team will have a research coordinator available to take minutes.

Board members may not participate in the NEED-PT study as co-investigators, study physician participants, or study patient participants.

Conflicts of Interest

DSMB members must be free of any financial, intellectual, or other conflicts of interest. The Department of Health and Human Services Guidance on Financial Conflicts of Interest may be referenced for further information (https://www.hhs.gov/ohrp/regulations-and-policy/guidance/financial-conflict-of-interest/index.html). Prior to initiation of DSMB service, all members will affirm they either do not have or will declare any relevant conflicts of interest. At the start of each DSMB meeting, all members will disclose any updates or changes to conflicts of interest. If a change in conflict of interest arises at any point during a member's service on the NEED-PT DSMB, then the member should notify the principal investigator, who may consider finding a replacement for that member. Updates to the charter and membership will be made as needed.

III. RESPONSIBILITIES AND FUNCTIONS OF THE DSMB

This DSMB will be coordinated by the NEED-PT study team. Each DSMB member will receive a $250 (US) honorarium for participation after each scheduled meeting. Meetings will last on average approximately two hours, and members will receive relevant materials approximately one week in advance of each meeting.

A. Initially, the DSMB is responsible for:
   1. Finalizing and signing this DSMB Charter with approval of the NEED-PT study team.
   2. Reviewing the NEED-PT study protocol, providing comment as appropriate, and approving the protocol prior to initiating enrollment.
   3. Defining, with input from the NEED-PT study team, safety and related parameters to be monitored, frequency of committee monitoring reviews and interim safety analyses, methods for review, statistical methodologies, quorum of Committee members, and establishing criteria for making recommendations to the NEED-PT study team.
   4. Documenting and approving the procedures defined above.

B. The DSMB will review study data and study safety events every six months. The designated DSMB secretary will take minutes during the closed sessions and report them to Drs. Kim and

Ciolino, who will disseminate meeting minutes and recommendations to AHRQ, IRB, and the NEED-PT study team as appropriate.

C. The DSMB will recommend one of the following actions to the investigators, in writing, following each interim data review:
   1. Continue the study according to the protocol and any related amendments.
   2. Modify the study protocol. Modifications may include, but are not limited to: changes in inclusion/exclusion criteria, frequency of visits or safety monitoring, alterations in study procedures, changes in duration of observation or follow-up.
   3. Suspend enrollment or discontinue the study.

D. After each meeting, the DSMB will issue their recommendations and minutes via a letter signed by the DSMB Chair within seven business days of receipt of the draft minutes from the NEED-PT study team. These recommendations will also be included in the final open minutes and distributed by email to the DSMB members and the NEED-PT study team.

E. In between scheduled DSMB meetings, if an SAE that meets relevant criteria (unexpected, SAEs that are determined to be possibly, likely, or definitely related to the study intervention) occurs (see DSMP), then the DSMB members will receive a narrative and relevant information surrounding that event (email is an acceptable mode of communication for these instances). The investigators will request the DSMB members review these SAEs and determine whether they merit a formal meeting, and the DSMB members may make any recommendations as in Part C above. A quorum vote via email may suffice as documentation for recommendations following these events unless the DSMB Chair or the investigators call(s) for a formal meeting.

IV. RESPONSIBILITIES AND FUNCTIONS OF THE NEED-PT STUDY TEAM

The statistical team, including Drs. Jody Ciolino and Jacob Schauer, in collaboration with the DSMB secretary, is responsible for the coordination of the DSMB activities and materials including the following items. While this is not a blinded study, every effort will be made to conceal allocations on data collection tools and outcome assessments, and data in general will not be summarized by study arm. Thus, we will ensure 'blinding' to the extent possible, especially for Dr. Kim and the co-investigators. With this in mind, the statistical team will be unblinded, and thus serve as the reporting statistician(s) to the DSMB. Drs. Ciolino and Schauer will oversee the preparation of the data to be reviewed by the DSMB and the following:

A. Recommendation of DSMB members and providing the initial DSMB Charter Draft to the members for their review.

B. Management of transfer of clinical safety data and relevant study data to the DSMB for review. Drs. Ciolino and Schauer (NUDACC-affiliated statisticians) will coordinate and oversee preparation of the interim reports containing summaries of the safety and outcome data pertinent to DSMB review as outlined in the Data and Safety Monitoring Plan (DSMP). Approximately one week prior to each DSMB meeting, the DSMB will receive two reports:
   1. An **open report** that will NOT contain any unblinded information or summarizations.
   2. A **closed report** that will contain interim summarizations grouped by 'masked' study arm (e.g., 'Arm A' and 'Arm B', while not disclosing in writing what 'A' and 'B' signify). A NUDACC representative will verbally disclose the meaning of these codes during the DSMB meeting closed session upon request from the DSMB.

   Each report will be password protected, and the DSMB members will be asked to destroy / delete each report within seven business days after each meeting. NUDACC will maintain all

interim reports in a secured location with restricted access to study team members only (and unblinded team members only for closed reports) on Northwestern University's protected servers.

C. *Ad hoc* data summaries may be prepared upon written request by the DSMB to address a specific safety concern (email is an acceptable method of communication). Ad hoc reports will be prepared by the NEED-PT study team. Drs. Ciolino and Schauer will oversee preparation of any unblinded ad hoc reports.

D. We do not anticipate that there will be serious adverse effects resulting from this non-invasive physical activity and behavioral intervention for low back pain. However, given the natural history of non-specific low back pain we expect to discover a baseline level of serious adverse events in both study arms (e.g., hospitalization, surgery) during the one-year of follow-up. We will plan to summarize and report adverse events and serious adverse events at each regularly scheduled DSMB meeting.

E. Serious Adverse Events determined to be possibly, likely, or definitely related to the study intervention will be reported to the DSMB within seven days of the NEED-PT study team becoming aware of these SAEs. Dr. Kim and Dr. Ciolino will oversee preparation of these interim SAE narratives and any additional data shared with the DSMB (e.g., laboratory data or clinical history as appropriate). Refer to Section III.E above and Section II of the DSMP for additional details.

F. Maintaining DSMB Charter, meeting minutes, and recommendation documentation in secure locations on Northwestern University's servers.

G. Maintaining the DSMB files and archives of electronic data sets and programs used to generate each summary report.

H. Making resources available in a timely fashion to the DSMB as required to carry out its designated functions including:
   1. Study documents (e.g., protocols, manuals of procedures, consent, protocol amendments).
   2. Study data.
   3. SAE reports.
   4. Additional medical records and supporting documentation as requested to address specific safety concerns.
   5. Other data/information as requested in writing by the DSMB.

CONDUCT OF DSMB MEETINGS

Scheduled Meetings

An initial meeting of the DSMB will be held before any participant enrollment in the study occurs in order for the members to finalize the DSMB charter, establish a meeting schedule, review the study protocol, and study/participant termination guidelines.

The DSMB will meet twice per year (every six months) once study enrollment begins. DSMB meetings will be conducted via teleconference. The actual frequency of convened DSMB meetings and conference calls may vary depending on participant recruitment, safety concerns, DSMB member schedules, and potentially other factors. Ad hoc meetings may occur if the study team, IRB, sponsor, or any other party related to the NEED-PT study conduct and safety deems it appropriate.

Voting
DSMB members vote on all recommendations to be submitted to the PI. To vote, a DSMB member must be present in person or over telephone/video conferencing at convened scheduled meetings. In rare circumstances, if a DSMB member cannot attend a meeting, then he/she may provide his/her vote after reviewing the DSMB interim report(s) and the draft meeting minutes following the meeting. In these instances, the meeting minutes and recommendations will be finalized after the absent member has provided his/her responses. The absent member must provide his/her absent vote and the meeting minutes must be finalized by the DSMB within seven business days of receipt of the draft minutes from the NEED-PT study team. All members present must reach a consensus at any meeting in order to pass a proposal, motion, or recommendation to the PI.

Quorum
A minimum of three DSMB members, including the DSMB chair, constitutes a quorum for the purposes of voting on recommendations to the NEED-PT Study Team.

Procedures for Communicating DSMB Recommendations to the NEED-PT Investigators
The DSMB chair will send voted and passed DSMB recommendations to the PIs in writing within seven working days of the meeting at which the recommendation was formulated and passed. The PI will have the responsibility to communicate final recommendations to the NEED-PT Study Team, IRB, and AHRQ, if required.

Minutes
Meeting minutes will be kept for each meeting of the DSMB, by a member of the NEED-PT study team for the open session and by the designated DSMB secretary for the closed session. The PI and DSMB chair will keep these meeting minutes on file for the duration of the study. If necessary, two separate versions of the minutes will be generated: 1) Open Minutes will be completely blinded to study arms; 2) Closed Minutes may contain partially unblinded information, and will be distributed to DSMB members and the unblinded statisticians (NUDACC).

Meeting Format
With the exception of the initial meeting to review the Charter and study documents, meetings will follow the same general format:

1. **Open session**: During the initial open portion of a meeting, the investigators and DSMB members will first affirm they do not have any conflicts of interest and disclose any relevant updates to their conflicts of interest. Then, the investigators will briefly review the study data and progress as outlined in the open DSMB report, and the investigators will be available for questions from DSMB members.
2. **Closed session**: During the closed session of the meeting, the DSMB members and unblinded statisticians will be present. The unblinded statisticians will review unblinded data by study arm and respond to any questions from the DSMB members regarding blinded data.
3. **Executive session**: If desired, then the DSMB members may then request the statisticians leave the meeting as they discuss any concerns, vote, and finalize recommendations. The DSMB members will keep minutes as necessary during these sessions since there will not be a study team member present.
4. **Debrief session**: If desired, then the DSMB chair may then ask a NEED-PT study team representative(s) to return to the meeting for a final, open portion in which the DSMB chair will summarize the recommendations they plan to submit to the PI.

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The secretary and unblinded statisticians (in the event of closed meeting minutes that contain unblinded information) will finalize the meeting minutes and send to the DSMB members within seven business days of the meeting. The DSMB members will have seven business days to review and provide comment on these minutes once they receive the initial draft. If, at the end of these seven days, the committee members have not provided comment, then the minutes will be considered final.

REPORTS

DSMB reports containing enrollment data, patient safety data, primary outcome data, and adverse event summaries will be reviewed at the DSMB meetings. As mentioned previously, two versions of the DSMB report will be generated:

1. An **open report** that will NOT contain any unblinded information or summarizations.
2. A **closed report** that will contain interim summarizations grouped by 'masked' study arm (e.g., 'Arm A' and 'Arm B', while not disclosing in writing what 'A' and 'B' signify). Dr. Ciolino will verbally disclose the meaning of these codes during the DSMB meeting closed session upon request from the DSMB.

Contents of these reports will be guided by the Data and Safety Monitoring Plan (DSMP) with input from the DSMB members, and they may evolve as the study progresses and DSMB member needs change.

NEED-PT Study Team Response to DSMB Findings and Recommendations

Dr. Kim will review and respond to the DSMB recommendations. If the DSMB recommends continuation of the study without modification, then no formal response will be required. However, if the recommendations request action, such as modification of the protocol or study termination, then the DSMB will request that the PI provide a formal written response indicating whether the recommendations will be followed, and the plan for carrying out the recommendations or addressing the issues over a specific timeframe.

Confidentiality

All committee members will treat DSMB reports, meeting discussions, and minutes as confidential. DSMB members' signature on this charter will serve as this confidentiality agreement. Master copies of the DSMB reports and recommendations will be kept in limited access folders on Northwestern University's secure servers. Hard copies may be stored in locked file cabinets at Northwestern; however, DSMB members must shred / destroy / delete any DSMB meeting materials within seven business days. The members may retain minutes and recommendations for their records; however, the DSMB chair may be the only DSMB member to retain closed minutes in a secure location.

AMENDMENTS TO THE DSMB CHARTER

This DSMB Charter can be amended as needed during the course of this study. Information to be included as amendments will be any updates to the DSMB member roster, meeting formats / frequency, or any specific DSMB duties. All amendments will be documented via version control and dated, and they will be recorded in the minutes of the relevant DSMB meeting. Each revision will be reviewed and agreed upon by the NEED-PT Study Team and the DSMB Members. All versions of the charter will be stored in the trial master file and in secure locations at Northwestern University, along with meeting minutes and open / closed reports.

Attachments

Attachment 1: DSMB Members, Investigators, key personnel
Attachment 2: Data and Safety Monitoring Plan (DSMP)

DSMB Charter Signature Page

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My signature indicates my agreement with the above named version of the NEED-PT DSMB Charter. I agree to keep all reports, meeting discussions, and minutes as confidential. I confirm that:
☐ I have no conflicts of interest.
☐ I have the following potential conflict(s) of interest:

Signed,

Signature, date

Printed name

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ATTACHMENT 1: CONTACT INFORMATION

DSMB Chair

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DSMB Members

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