ProTECT™ III

Progesterone for the Treatment of Traumatic Brain Injury

Trial Publication Protocol

Supported by:
National Institute for Neurological Disorders and Stroke

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ProTECT III Trial Procedures for the Development of Publications

The ProTECT III publications process protocol supplements the Neurological Emergencies Treatment Trials Network (NETT) Standard Operating Procedure for NETT affiliated publications.

Overview

The primary goal of the publications protocol is to ensure rapid and accurate translation of study results to the scientific, medical, and global community and maximize the scholarly productivity of the trial. This procedure protocol outlines the steps for publishing data related to the ProTECT III trial, including concept generation and submission, writing and analysis responsibilities, and authorship. The publication process will be guided by the ProTECT III publications committee (listed below). Writing groups will be created to analyze the data and prepare the publications.

The primary results generated from the study are the initial priority for publication. Following publication of the primary paper, several secondary hypotheses have been pre-identified that will be explored for publication. Additional ideas for manuscripts are highly encouraged. The ProTECT III leadership considers it important to allow all interested investigators and ProTECT III participants the opportunity to publish from the ProTECT III data set. ProTECT III affiliated personnel will have priority for manuscript development during the first year after the final analysis, however non-NETT parties can participate. Data will be released to the public per the pre-specified Data Sharing Plan.

ProTECT III Publications Committee (PPC) Members

- **David W. Wright, MD - Emergency Medicine, Emory University (Chair)**
- Yuko Palesch, PhD – PI of the ProTECT Statistics and Data Management Center
- Sharon Yeatts, PhD – Lead Unblinded Statistician ProTECT Statistics and Data Management Center
- Vicki Hertzberg, PhD - Biostatistics, Emory University
- Geoff Manley, MD, PhD - University of California, San Francisco
- Robert Silbergleit, MD - NETT Clinical Coordinating Center
- Erin Bengelink – NETT ProTECT III Project Coordinator
- Kurt Denninghoff – Hub PI Representative (highest enrolling Hub)
- Art Pancioli, MD – Spoke PI Representative (highest enrolling spoke)
- Scott Janis, PhD – NINDS Scientific Program Officer

The PPC has the primary responsibility for overseeing submission of the ProTECT III primary and secondary analyses, as pre-specified in the ProTECT III Statistical Analysis Plan. The PPC will meet on an as needed basis in response to requests and inquiries regarding ProTECT III related publications. In addition, the PPC has the following responsibilities:

- Set publication priorities for the ProTECT III trial data
- Review and approve all ProTECT III publications (manuscripts, abstracts, posters, presentations) prior to the public release of data
- Facilitate writing groups and approve or assign a designated leader
- Ensure correct interpretation and representation of ProTECT III data

- Ensure appropriate authorship designation and provide final ruling on disputes
- Track manuscript development and encourage timely submissions
- Evaluate outside requests for data use (prior to availability of public use data set)
- Approve the use of ProTECT III data for grant submissions

General process for hypothesis / analysis submission and approval

- Submit idea / hypothesis via AdobeWEB form (https://adobeformscentral.com/?f=4psehX-yAYiDyjHf4Q%2A9yA#) (minimum 6 weeks prior to data need)
- Notify the Chair of the PPC of the submission via email, and alert to any time sensitive issues
    - PPC will then review the submission within 2 weeks
    - PPC will prioritize request and ensure no overlap with planned proposals
- Upon approval by the PPC, form Hypothesis Writing Group (HWG) with PPC's oversight
- Identify lead author/Chair of the writing group
- Submit detailed description of data items needed (per SDMC requirements)
    - If SDMC is providing statistical support, analysis will be coordinated with HWG
    - If SDMC is not providing statistical support, a ProTECT III Internal Trial Dataset (ITD) will be provided once available. This dataset is considered confidential and should only be used for the specific proposal at hand.
- Draft manuscript, create author list, and identify journal for submission (draft should be in format per journal specifications – word counts, etc)
- Present near-final draft to PPC
    - PPC reviews final manuscript
    - PPC submits to NINDS for review if required
- After final approvals, ensure proper authorship and appropriate acknowledgement (see below) and submit final version to journal
- If significant rewrites or new analyses are required by the Journal, resubmission to PPC may be required

The PPC will attempt to engage and include as many interested investigators as possible. Hub PIs, members of the CCC, and SDMC have initial publication rights. Ideas not pre-specified in the primary and secondary analysis plan will be evaluated on a first-come, first-served basis. Once the hypothesis/manuscript idea has been vetted and approved by the PPC, an HWG will be formed from the interested parties. The HWG will propose a Group leader, who will serve as the organizer, delegate and direct the manuscript writing process, oversee a timely draft submission, and ensure the highest quality manuscript possible. The final draft must be approved by the PPC before submission to a journal. The PPC retains the right (and ultimate authority) to appoint members to the writing group, assign a group leader, disapprove a manuscript, require edits to the manuscript, and/or reassign a Group leader (e.g poor progress, significant dissention, other).

Primary Hypothesis/Manuscript

The PPC and the ProTECT III Working Group (PWG) will serve as the writing group for the manuscript reporting the primary outcome and select supporting secondary analyses for the ProTECT III trial. The ProTECT III Statistical Analysis Plan specifies the analyses that will be conducted and presented in the primary paper. The ProTECT III PI will Chair the writing group and develop the initial draft. Final authorship will be guided by the International Committee of Medical Journal Editors' rules for authorship

and will include a list of key contributors and the statement referencing the supporting participants: "*on behalf of the NETT Investigators"*. The full list of ProTECT/NETT III investigators will be listed per the journal's specifications (appendix, supplement, etc.) with the intention of authorship acknowledgement and contribution. The primary paper should be completed within 6 months of the primary data analysis availability. The Primary data will be published regardless of the study results.

Secondary Manuscripts - Preplanned Hypotheses

In addition to the primary hypothesis, several secondary hypotheses were pre-identified for analysis and potential publication. The PPC will work with ProTECT III investigators and team members to garner levels of interest and form writing groups. HWGs will include individuals with expertise in the area of interest (e.g. imaging writing group), and other skills (e.g. statistics). The Group leader, most often the primary author, will organize the HWG, direct hypothesis development, and oversee the writing of the publication. Group leaders will also determine authorship per the authorship guidelines outlined in this document (Authorship) and ensure expeditious high quality manuscript submission.

Tertiary Manuscripts

Tertiary papers are post-hoc analyses that relate to the central hypotheses being tested, but not pre-specified in the SAP or the grant application. HWGs will be formed as described for the secondary manuscripts.

Quaternary and Newly Generated Hypotheses

Quaternary papers utilize the dataset for data that most often do not relate to the initial hypotheses of the study. The ProTECT III trial was a rigorously conducted Phase III clinical trial that includes a treasure trove of information and data from multiple sources (e.g. epidemiology, clinical assessments, clinical management, vital signs, laboratory data, guideline compliance and transgressions, confounding conditions, surgical interventions, adverse events information, and a multitude of outcome measures all linked to imaging and serum biomarker data). In addition, the fact the ProTECT III is one of the largest EFIC trials to have been conducted in TBI, there are many important questions that can be addressed. It is anticipated that numerous new hypotheses will be generated to advance the knowledge of TBI patients. The ProTECT III PI and or designees have the first rights to publish collective study data per the PPC approval. ProTECT III team members are highly encouraged to review the case report forms and consider important clinical questions that can be answered with the ProTECT data. The process for submitting and authorship will follow the standard guidelines in this document.

Ancillary Studies

Two ancillary studies have occurred alongside the ProTECT III primary trial. Peer ProTECT, a study of the perceptions of subjects enrolled under EFIC and BIO-ProTECT, a serum biomarker study. Publications related to Peer – ProTECT will follow the same protocol as outlined for other ProTECT III submissions. BIO-ProTECT has a separate Publications Committee that will guide the Primary BIO-ProTECT manuscript submission process. In general the guidelines outlined in this document will cover BIO-ProTECT with the addition of the BIO-ProTECT PI Chairing the publications committee review of BIO-ProTECT manuscripts and working collaboratively with the PPI for ProTECT III.

Methods papers and Study-independent Publication Procedures

Members of the NETT CCC, SDMC and Hub PIs may wish to publish methods papers that describe the ProTECT III operations, network's function, or papers that are otherwise wholly independent from the trials conducted. These paper proposals and final manuscripts will be submitted to the ProTECT III PPC and NETT General Publications Committee when appropriate. General Publications Committee includes the NETT CCC PI, the NETT CCC Publications Director, the NETT SDMC PI and co-PI and a NINDS Program Director. The NETT publications committee does not have authority over PPC. Papers published from this group will not address topics in the studies' specific aims, and will require authorship and review by the PPC if data from ProTECT III is used.

Abstracts, Posters and Oral Presentations

Publications and presentations of all types that use ProTECT III data require prior approval, and in general will follow the same process as for manuscripts. Conversion of abstracts, posters and oral presentations into full manuscripts is highly encouraged and in most cases mandatory. After acceptance to the presentation forum (scientific meeting, assembly, other), a draft manuscript should be submitted to the PPC prior to the actual meeting presentation.

Acknowledgements

Acknowledgements at a minimum should include the following statement: *Research reported in this publication was supported by the National Institute Of Neurological Disorders And Stroke of the National Institutes of Health under Award Numbers NS062778, 5U10NS059032, U01NS056975, the General Clinical Research Center at Emory University, and the Grady Memorial Hospital. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or other supporting entities*. Other acknowledgements will depend on the specific manuscript.

Authorship

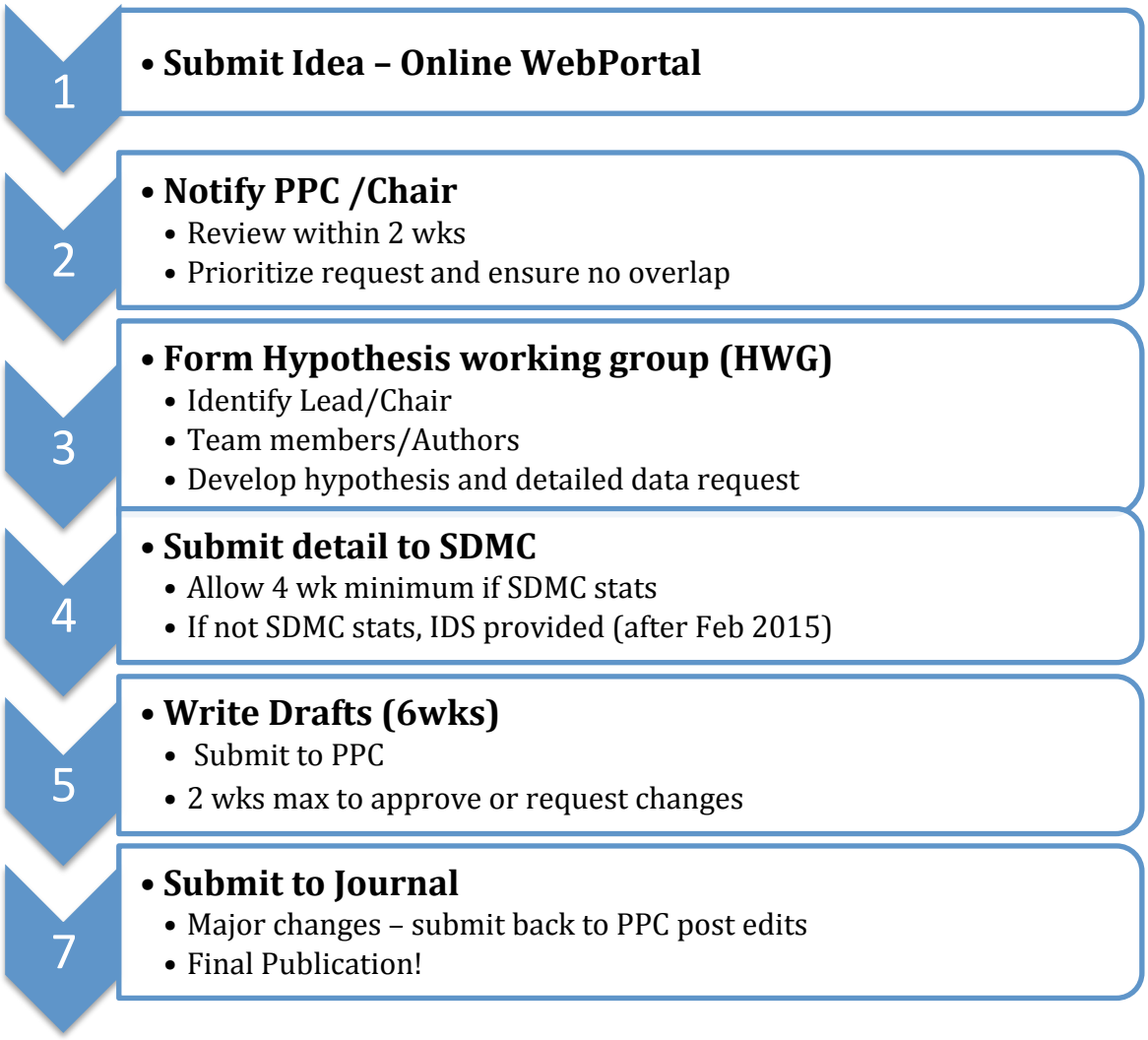
Authorship on ProTECT III related publications will be guided by the International Committee of Medical Journal Editors (ICMJE) recommendations. The ICMJE recommends that authorship be based on the following 4 criteria (quoted from the ICMJE website):

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Group authorship is encouraged. In general, all members of the HWG that significantly contribute to the content of the manuscript should be included. ProTECT III publications will include the phrase "…for the ProTECT III Trial Investigators" at the end of the author list. All ProTECT III Trial Investigators (Hub and spoke) and coordinators will be named in the publication in a format that meets the journal of

submission's guidelines. Additionally the ProTECT III PI (usually listed as the last in the formal list), Central Coordinating Center PI, SDMC PI and manuscript statistician will also be included as authors and be required to participate as authors based on the guidelines for authorship. Order of authors between the first author and last author will be the responsibility of the lead author and consensus of the HWG. Group leaders should attempt to resolve any authorship issues or disputes early in the writing process. The PPC/ProTECT III PI will have final word on authorship in settings where resolution cannot be reached within the HWG.

Approval Process and Expected Timelines



Typical Timelines:
Submit Idea to Web portal and notify PPC ---> Review by PPC (2 wks) ---> OK'd – set up HWG, provide detail data/hypotheses request to SDMC (variable time) ---> SDMC to provide data, database, or analysis depending on agreement (4 wks minimum) ---> Manuscript draft by HWG (6 wks) ---> Submit semifinal draft to PPC (2 wks) ---> Edit or ok to submit to Journal (2 wks) ---> Journal review (variable) ---> Edit – resubmit to PPC if major (2 wks) ---> Final Submit to Journal.

The purpose of the approval process is to help track and *prioritize* publications, prevent overlap of ideas

development, and ensure the highest quality and timely publications. In addition, significant resources are often required to prepare and provide the variety of datasets needed for hypothesis testing and analysis.

At least 4 weeks are required to obtain data from SDMC, with more time allowed for specific analyses. Respect of the SDMC's time and role in this process is important and will be monitored on an ongoing basis. Additionally, the ProTECT III was funded by the NINDS-NIH U-grant mechanism which provides the NINDS a role in decisions related to the ProTECT III trial. The PPC will submit the near-final manuscript to NIH NINDS for review and comments. If major changes are required from the journal (or NIH), the PPC many need to review the revised manuscript (submission of the comments from the journal to the PPC along with the edits will expedite this process. Requests for urgent reviews/analyses will go to the PPC and accommodated if possible, but cannot be guaranteed.

Confidentiality and Data Release

No ProTECT III data should be released to the public or non-ProTECT III entities unless prior approval is obtained from the PPC or ProTECT III Executive committee. All data and correspondence regarding publications are considered confidential until approval for release. All data associated with ProTECT III, whether locally or centrally stored should be de-identified prior to release, sharing, or publication. Investigators are not allowed to present data gathered from their Hub or clinical sites before the primary analyses are published. ProTECT III results should not be discussed with the media without authorization from the ProTECT III PI.

Only the trial PI and their designees, Hub PIs, and members of the NETT CCC and SDMC have collective data rights until one year after the publication of the primary data. Individual Institution's shall retain ownership of all data that they generate. Institutions shall grant to NETT/ProTECT III non-exclusive license to use data for educational and research purposes. The PPC will retain oversight of the collective data and decision-making authority with respect to the collective data prior to public release. Finally, one year following the publication of the primary results, the public use data set will be submitted to the Federal Interagency Traumatic Brain Injury Research (FITBIR) database for storage and public use. Clinical data, imaging data, and biomarker data will be linked in FITBIR through a pseudo Global Uniform Identification number (Pseudo-GUID). Request for and review of data will be managed through the NINDS FITBIR database per NINDS guidelines.

Individual Hub Investigator Publication Rights

Hub Investigators who wish to publish their own institution's data will be able to proceed with such publication, provided that the Hub PI has first sought approval for multi-site publication in accordance with the procedures set out under the study-specific publication procedure. Individual Hub investigator publication can be delayed for one year after the primary results have been published.

Adherence to Policy

Participation in NETT requires adherence to the publication policy described in this SOP, even though Hub PI's retain ownership of the data collected at their sites. Authors who publish articles that are not compliant with this policy must contact the journal and retract the publication.

Journal Submission

Within 2 month of receiving the Publications Committee comments and approval, the revised (if necessary) manuscript will be circulated by the HWG Chair to the other members of the HWG for final sign-off. The HWG members have no more than 3 weeks to review the final manuscript.

The manuscript will immediately be submitted to a journal. A copy of the journal cover letter and final draft of the manuscript must be sent to the Publications Committee in addition to all co-authors.

To ensure compliance with NIH Public Access Policy (revised 4/7/08), the HWG Chair should take the following steps with regard to choosing a journal:

1. Ensure that any copyright release or transfer does not prevent the submission of the manuscript to NIH National Library of Medicine's PubMed Central (PMC). Should the chosen journal be unwilling to negotiate or comply with the copyright question, another journal must be selected for publication of the manuscript.
2. Ascertain if the target journal is on the NIH list of journals that automatically submit published manuscripts to the PMC. See http://publicaccess.nih.gov/submit_process_journals.htm for a list of these journals. If the journal is on the NIH list, the Study Chair and/or HWG Chair are not required to submit final manuscripts to NIHMS nor approve the final manuscript after submission. Given the requirements of the NIH Public Access Policy, the HWG Chair is strongly encouraged to use a journal on the PMC list, if at all possible. If the journal is not on the PMC list, additional responsibilities are placed on the HWG Chair (see below for details).
3. If the journal is not on the PMC list, determine if the journal has a publications position on compliance with the NIH Public Access Policy (i.e., If the journal staff does not submit the final manuscript to PMC on behalf of the authors within 12 months of publication, does the journal allow the author the right to submit the peer-reviewed manuscript to PMC within 12 months of publication). If the position of the journal is opposed to the NIH Public Access Policy, the Study Chair will assist the HWG Chair in negotiating with appropriate staff of the target journal for permission to retain the right to comply with the policy. If the chosen journal is unwilling to negotiate or comply with the NIH Public Access Policy another journal **must** be selected for publication of the manuscript.
4. If the journal does not automatically submit the published manuscript to the PMC, the HWG Chair also must determine if the journal has specific Public Access stipulation language that must be included in the manuscript to indicate the "publisher position". Any journal-specified language regarding Public Access that the HWG Chair or other members are aware of should be added to the penultimate draft PRIOR to review by the PPC. Should the HWG Chair, or other members, become aware of "publisher position" language subsequent to review by the PPC, that language must be forwarded to the PPC for review as soon as the HWG Chair, or other members, become aware of it.

To summarize, the HWG Chair is responsible for:

- Communicating with journal personnel prior to submission of the manuscript to determine the publications position on compliance with the NIH Public Access Policy
- Determining if the journal will submit to PMC on behalf of the authors within 12 months of publication
- Determining if the journal has specific Public Access stipulation language it requires to be

included in the manuscript to indicate the "publisher position".

- Assisting the Publications Committee staff in negotiating permission to retain the right to comply with the policy, should the publisher have a contravening policy.

The HWG Chair must keep the PPC and the co-authors informed as to the manuscript's progress through the journal review process. Following the final acceptance by the journal, the HWG Chair is responsible for providing the Chair of the PPC with the manuscript and all graphics and supplemental materials associated with the manuscript. Upon publication of the manuscript, the HWG Chair must provide either a reprint or copies of the final publication, and all graphics and supplemental materials associated with the manuscript, to the PPC.

If there are substantive changes made in the manuscript during the journal review process (major findings or conclusions, alterations of the sample, exclusion/inclusion of major covariates), the revised manuscript should be submitted to the PPC for re-review prior to resubmission to the journal. The revised manuscript must be resubmitted within 3 months of receiving the journal reviews of the original submission.

Manuscript Public Access Policy and Process

The ProTECT Trial Publication Policies are compliant with the voluntary NIH Public Access Policy mandated by the Consolidated Appropriations Act of 2008 (Division G, Title II, Section 218 of PL 110-161). The law stipulates that:

The Director of NIH shall require that all investigators funded by the NIH submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts **upon acceptance for publication**. The Director strongly encourages submission as soon as possible, but no later than 12 months after the official date of publication. The law further provides that the NIH public access policy shall be implemented in a manner consistent with copyright law.

Procedures and assignment of responsibilities in the ProTECT Trial Publication Policy document specifically address the NIH Public Access Policy requirements in the following manner:

- All peer-reviewed articles arising from ProTECT Trial data that are accepted for publication after April 7, 2008 should be submitted electronically by the HWG Chair or the publisher directly to PMC. (See Section 5.1.3 – Journal Submission).

- The HWG Chair is responsible for ensuring that any publishing or copyright agreements concerning submitted articles fully comply with the NIH Public Access Policy (See Section 5.1.3 – Journal Submission)