Initiative for Multicenter Pragmatic Anesthesiology Clinical Trials (IMPACT): *Letter of Intent & Full Application Instructions*

The Multicenter Perioperative Outcomes Group (MPOG), Association of University Anesthesiologists (AUA), and Department of Anesthesiology at the University of Michigan are delighted to announce a three-year, $950,000 funding opportunity to support a multicenter pragmatic clinical trial in perioperative anesthesiology. The trial should be designed to answer a compelling clinical question with a clear gap in the current literature. The proposed work should address a question around *which clinical equipoise exists and can be ethically addressed without individual patient consent*.

The award will be made to a single clinical coordinating center (CCC) that is an MPOG active member. The MPOG Data Coordinating Center (DCC) at the University of Michigan will act as the DCC for the trial. In addition to the direct financial support from IMPACT ($700,000) for the CCC and performance sites, MPOG will provide support in-kind as the DCC for the trial with the necessary technical, research process, clinical informatics, and statistical support (an additional $250,000 in personnel costs). Health systems not participating in MPOG are welcome to serve as performance sites but must demonstrate the ability to submit monthly trial-specific data to the DCC in an agreed upon format consistent with the proposed data specification received from MPOG sites.

The award will be made in a phased manner with a Year 1 Feasibility Phase ($100,000) and milestone-based progression to Years 2-3 Full Scale Phase ($300,000 per year). MPOG Data Coordinating Center in-kind support will include MPOG data extraction, clinical phenotype development and validation, statistical analysis design and execution, DSMB support, and enrollment site operational metrics and reporting. Year 1 Feasibility Phase milestones will define progression to the Year 2-3 Full Scale Phase, as adjudicated by the MPOG Executive Board, and include (but are not limited to):

Infrastructure Development Milestones: i) Development of Full Scale protocol; ii) obtaining relevant CCC IRB approval with waiver of consent; iii) confirmation of performance site engagement; iv) finalizing trial data elements; and v) establishing a Full Scale Data and Safety Monitoring Plan.

Pilot Trial Execution Milestones: i) Successful patient accrual with waiver of individual patient consent at one pilot site ; ii) successful randomization via proposed mechanism (e.g. cluster crossover, clinician-level, hospital-level, etc.); iii) adequate adherence to the intervention(s) as defined by *a priori* power analysis; iv) adequate outcome ascertainment as defined by *a priori* power analysis.

Key Dates:

Aug 14, 2023	Request For Proposals released
Aug 18, 2023	Optional informational webinar and Q&A (will be recorded)
Sep 22, 2023	Mandatory 2-page Letter of Intent (LOI) submitted by 8pm ET
Sep 27, 2023	LOI scoring opens
Oct 6, 2023	LOI scoring closes 8pm ET
Oct 16, 2023	MPOG Executive Board Invites approximately 5-8 LOIs for solicitation of full proposal
Dec 15, 2023	Final full proposals submitted to MPOG Coordinating Center by 8pm EST
Feb 2, 2024	Up to three finalists contacted, summary statements released, additional info requested
Feb 23, 2024	Additional information response window closes at 8pm ET

Mar 8, 2024	MPOG Executive Board endorses winning proposal
July 1, 2024	Year 1 Feasibility Phase Start
May 1, 2025	MPOG Executive Board reaches decision on suitability for progression to Full-Scale Phase
July 1, 2025	Year 2 Full Scale Phase Start *(if approved)*
June 30, 2027	Year 3 Full Scale Phase End *(if approved)*

Letter of Intent Submission Process

Interested applicants should provide a 2-page Letter of Intent (LOI), sent to mpog-research@med.umich.edu, from which applications will be selected to provide full proposals. The Principal Investigator(s) must have primary faculty appointments (i.e. not affiliated or adjunct appointments) at an *active* MPOG center. The determination of *active* status will be made at the time of LOI and full proposal review. Each center may submit more than one LOI (and potentially more than one full proposal, if selected). A LOI is required to submit a full proposal, and should include:

- Project title / Principal Investigator(s)
- Research Question & Background
- Study Population & Research Settings
- Comparators & Outcomes
- Study Design
- Rationale for waiver of individual informed consent
- Sample Size, Power, and Analytical Plan
- Key Personnel
- Prior Relevant Experience of the Study Team
- Summary of Necessary Data Elements from MPOG dataset
- Distribution of Total Anticipated Budget to CCC versus Performance Sites
- Objective milestones by which the success of an initial Year 1 Feasibility Phase should be assessed
- Literature cited (not included in the 2-page limit)

The Letter of Intent should:

- Demonstrate a clear and compelling rationale for addressing the proposed clinical question via a pragmatic randomized trial design
- Propose a project which can be accomplished using (i) patient-level waiver of informed consent; (ii) data already collected as part of participation in MPOG; and (iii) additional data (if any) feasible to be collected within the constraints of the IMPACT budget and MPOG Bylaws.
- (Only if needed): include plans for involvement of non-MPOG sites, if those sites were able to provide a limited amount of automatically extracted data to the DCC consistent with a data file specification matching the trial-specific MPOG data extract
- Demonstrate willingness to model this approach and collaborate for future projects seeking federal funds via an established pragmatic clinical trials network in Anesthesiology.

Proposals with one or more of the following characteristics will be scored favorably:

- Pragmatic nature (see PRECIS-2 tool for more details: https://www.precis-2.org/)
- Effective uses of existing MPOG data

- Involves collaboration across MPOG centers
- Focuses on pressing health problem relevant to perioperative care
- Addresses known clinical practice variation or healthcare inequities.
- Demonstrates strength in the qualifications, experience, and prior collaboration of the investigator(s)

Non-responsive proposals include:

- Pilot trials (i.e., the IMPACT pragmatic trial is intended to be the causal inference informative trial)
- Career development proposals (i.e. IMPACT pragmatic trial is intended for established investigators)
- Clinical trials requiring individual, patient-level consent
- The need for data not available in a typical MPOG active site's contribution and not feasible to be collected within the constraints of the IMPACT budget and MPOG Bylaws.

All LOIs will be confidentially scored by the PCRC principal investigators of each active MPOG center. The PCRC principal investigators will use an NIH scoring system and refer to the call for proposals for programmatic goals. Meritorious LOIs will be invited for full proposal submissions. A summary of scores and any comments will be provided to all applicants.

Final Full Proposal Submission Process (invited only)

The MPOG Executive Board will review *non-binding* LOI scores and comments and finalize the Full Proposal invitation list. Applicants will submit their proposals via the MPOG platform, sent to mpog-research@med.umich.edu. Proposals will be limited to eight pages not including literature cited, budget, biosketches, and data specification.

Components of the full proposal include:

- **Application Form**
- **Proposal**
  1) **Specific Aims (1 page)**. Description of the project with statement of aims and objectives, as well as methods to be employed. Outline the intellectual merit of and broader impacts from the proposed study.
  2) **Research Plan (8 pages**, excluding specific aims page and literature cited). Narrative must include:
     a. Background and Significance
     b. Innovation & Pragmatic Alignment (with PRECIS-2 diagram: https://www.precis-2.org/)
     c. Preliminary Data
     d. Approach
        i. Study design & patient inclusion/exclusion criteria
        ii. Expectations for IRB review, justification of waiver of patient-level consent, evidence supporting likelihood of obtaining IRB approval of waiver
        iii. MPOG center-level eligibility for participation
        iv. Primary and secondary outcomes
        v. Summary of key data elements to be collected within the existing MPOG research infrastructure
        vi. Proposed statistical analyses, including statistical testing, power calculations, methods for handling missing and invalid data, secondary and sensitivity analyses.

e. Use of MPOG Resources: Needs from each participating site and MPOG Data Coordinating Center
f. Project Timeline (listing specific milestones for study completion)
g. Anticipated Obstacles / Threats and Alternative Strategies

3) **Literature cited**
4) **Data specification**
   a. Itemized list of existing MPOG phenotypes required for definition of comparators, outcomes, or descriptive variables. A data specification template is available at https://mpog.org/files/research/MPOG%20Query%20Spec%20Template.xlsx
   b. Derived data elements necessary for any new trial-specific phenotypes (to be also included in the data specification template).
   c. Data elements not included in MPOG extract (e.g., cluster randomization allocation)
5) **Itemized budget and justification** (please use template)
   a. Justification: include an explanation of the basis for cost estimates
   b. Funds may be used to support normal research expenditures. If salary support is requested, provide detail (for whom, nature and percentage of appointment, period of time, amount requested).
   c. Indirect costs are capped at 10% and included in the total funding allocation of $700,000
   d. (If applicable): Cost-share information (source and amount)
6) **Biographical sketch of each investigator**. Use NIH style, five pages maximum per investigator
7) **Letters of support** from the PI's Department Head of Practice / Chairperson (required), proposed performance site Department Head of Practice / Chairpersons (suggested), and other relevant stakeholders (*optional*).

Selection Criteria

Proposals will be reviewed by Subject Matter Expert (SME) reviewers. Consistent with NIH guidelines, application review criteria are:

- **Significance**
  - What is the potential for the proposed activity to:
    - Advance knowledge and understanding within perioperative care (*intellectual merit*)?
    - Benefit society or advance desired societal outcomes (*broader impacts*)?
  - What will be the effect of the study on the concepts, methods, technologies, treatments, services, or preventive interventions that drive perioperative care?

- **Approach**
  - Are the study milestones likely to be reached during the funding period?
    - Infrastructure Development Milestones:
      1) Development of Full Scale protocol;
      2) Obtaining relevant CCC IRB approval with waiver of consent;
      3) Confirmation of performance site engagement;
      4) Finalizing trial data elements; and
      5) Establishing a Full Scale Data and Safety Monitoring Plan.
    - Pilot Trial Execution Milestones:

1) Successful patient accrual with waiver of individual patient consent at one pilot site;
2) Successful randomization via proposed mechanism (e.g. cluster crossover, clinician-level, hospital-level, etc.);
3) Adequate adherence to the intervention(s) as defined by *a priori* power analysis;
4) Adequate outcome ascertainment as defined by *a priori* power analysis.

- Is a waiver of informed consent feasible (i.e., meets all 4 elements under the Common Rule – see below), likely to be approved by performance site IRBs, and an optimal human subject research approach? **Common Rule Elements:**
    1) Subjects are exposed to *no more than* minimal risk;
    2) Waiver/alteration of consent does *not* adversely affect subject rights & welfare;
    3) Research would *not* be feasible without the waiver/alteration;
    4) Subjects will be provided additional information after participation, when appropriate
- Are the performance sites capable of implementing the clinical trial protocol, *within the constraints of the budget* provided?
- Are the data elements available in the existing MPOG data flows?
- Are the conceptual and clinical frameworks, design, methods, and analyses adequately developed, well-integrated, well-reasoned, feasible, and appropriate to the aims of the project?
- Does the applicant acknowledge potential problem areas and consider alternative approaches?
- Does the plan include a means to assess success?
- Are the requested data elements of sufficient quality to provide reliable evidence?

- **Innovation**
    - Does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in perioperative clinical care; or develop/employ novel concepts, approaches, methodologies, tools, or technologies within perioperative care?
    - To what extent do the proposed activities suggest and explore creative, original, or potentially transformative concepts, *while still retaining a pragmatic trial design*?

- **Investigators**
    - Are the investigators appropriately trained and well-suited to carry out the proposed study?
    - Is the work proposed appropriate to the experience level of the Principal Investigator(s) and other researchers?
    - Does the investigative team bring a track record of complementary and integrated expertise to the project?

- **Environment**
    - Does the scientific environment in which the work will be done contribute to the probability of success?
    - Does the proposed study benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements?
    - Is there evidence of institutional support?

- Are all key stakeholders capable of championing research efforts engaged?

- **Pragmatic Alignment**
  - Is the proposed study aligned with the IMPACT's goals and focus areas?
  - Does it incorporate a pragmatic approach (PRECIS-2 diagram) and engage researchers/experts from appropriate fields related to perioperative clinical care?
  - Is a pragmatic trial the logical next step in the investigation of the problem?

Formatting notes for LOIs and Full Proposals

Required forms, including budget templates, will be provided on the MPOG website. Where no forms are provided, please submit request information in text, single-spaced, 11 point Arial font, >15 characters per linear inch type density, 0.5" margins as consistent with NIH formatting specifications. Page limits apply to all tables, graphs, figures, charts, etc. Font sizes in figures, graphs, diagrams, and charts must be legible when the page is viewed at 100%.

Review Process

1) **LOI Review:** There are two phases of LOI review:
   a. All LOIs will be confidentially scored by each active MPOG member organization. Each organization will identify a single voting staff, assumed to be the MPOG research champion unless notified otherwise. A single overall impact score will be provided, based upon NIH methodology, with a range from 1 (no weaknesses) to 9 (significant weaknesses that cannot be addressed). Using these scores as a non-binding guide, the MPOG executive board will invite meritorious applications responsive to the Call for Proposals to provide a full proposal submission.
   b. The MPOG DCC will facilitate the use of MPOG Data Direct by successful LOI applicants to enable accurate preliminary data assumptions for Full Proposal development.
2) **Invited Full Proposal Review**: There are three distinct phases of full proposal review:
   a. **Phase 1**: All valid research proposals will be confidentially scored by an external review panel of Subject Matter Experts. Scoring will be based upon NIH criteria, with a range from 1 (no weaknesses) to 9 (significant weaknesses that cannot be addressed) across each criterion. An overall impact score with overall prose comments will be provided by each review panel members. In addition, the review panel leader will identify any areas requiring additional information (See below).
   b. **Phase 2**: The review panel and MPOG Executive Board will select up to three proposals for additional information. Additional information may be necessary to clarify methodological concerns, confirm enrollment site plans, refine power analysis assumptions, or address human subjects protection concerns. The external review panel and MPOG executive board will be provided the written responses to any additional information requests.
   c. **Phase 3:** The MPOG executive board will review the priority scores of up to three proposal and the additional information responses (if any). The final determination of the winning proposal will be made by the Executive Board, based upon the priority scores and prose comments. Selection of a proposal may be deferred if no sufficiently meritorious and feasible proposals are received.

Additional Information

A webinar for interested applicants will be held on **Aug 18, 2023 from 1-2pm EST** to address questions which may arise about the application process, programmatic goals, or feasible approaches. The webinar can be accessed at the link below:

https://umich.zoom.us/j/93794649436

A recording and FAQ page will be posted at the MPOG website (mpog.org/IMPACT-2023) one week after the webinar. Other questions may be directed to the **MPOG Research Facilitation Team** at mpog-research@med.umich.edu.