REporting PrEclinical Anesthesia sTudy (REPEAT)
Evaluating the Quality of Reporting in the Preclinical Anesthesiology Literature: Protocol

Start Date and Anticipated Completion Date

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Principal Investigator/Guarantor of Review

Manoj M Lalu, MD, PhD, FRCPC
manojlalu@gmail.com
1053 Carling Avenue, Mail Stop 249
Ottawa, ON K1Y 4E9

Review Team Members and their Organizational Affiliations

Manoj M Lalu[+]
- *Department of Anesthesiology, The Ottawa Hospital*
- *Regenerative Medicine Program, The Ottawa Hospital Research Institute*

Marc T Avey[+]
- *Clinical Epidemiology Program, The Ottawa Hospital Research Institute*
- *Faculty of Medicine, University of Ottawa*

Dean Fergusson[+]
- *Clinical Epidemiology Program, The Ottawa Hospital Research Institute*

Jiho Hong[+], Long H Nguyen[+], Carly C Barron[+], Mathew Bocock, Ryan McGinn, Yuan Yi Dong, Abhilasha Patel
- *Faculty of Medicine, University of Ottawa*

Sylvain Boet, Sarah Larrigan
- *Department of Anesthesiology & Department of Innovation in Medical Education, Clinical Epidemiology Program, The Ottawa Hospital Research Institute*
- *The Ottawa Hospital, University of Ottawa*

Stephane Bourque, Rohan Mittal
- *Departments of Anesthesia and Pharmacology, University of Alberta*

Ronald George, Kimberly Vella
- *Department of Anesthesia, Pain Management & Perioperative Medicine*

Ferrante S. Gragasin, Kristen Biefer
- *Department of Anesthesiology and Pain Medicine, University of Alberta*

David Mazer, Neil Goldenberg, Ben Steinberg
- *Department of Anesthesia, University of Toronto*

Philippe Richebe, Sarah Maximos
- *Department of Anesthesiology, University of Montreal*

Tarit K. Saha, Kai Chen
- *Department of Anesthesiology and Perioperative Medicine, Queen's University*

Sonja Sampson, Courtney Manuel
- *Department of Anesthesia, Memorial University*

Duncan J. Stewart
- *Regenerative Medicine Program, The Ottawa Hospital Research Institute*
- *Department of Cellular and Molecular Medicine, University of Ottawa*

Summer Syed, Prathiba Harsha
- *Department of Anesthesia, McMaster University*

On behalf of the Canadian Perioperative Anesthesia Clinical Trials Group (http://canadianpact.ca/)

+ = core group of investigators that have led conception and design of study

Protocol Development and Contributions
The Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) has been used as a general guideline in reporting this protocol. The core group of investigators (noted above) led the conception, design, and initial drafting of this protocol. All protocol authors had reviewed and edited it critically for important intellectual content.

Organizational Affiliation of Review

Ottawa Hospital Research Institute (www.ohri.ca)

Funding Sources/Sponsors

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Conflicts of Interest

None. Funders have no influence on the design, conduct, or reporting of this study.

Background and Rationale

Irreproducibility of experimental findings poses a significant problem to scientific advancements. Scientists become incapable of building on others' research as they are unable to adequately evaluate the reliability of previous findings. Currently, multiple sources contributing to the irreproducibility in biomedical research have been identified, these includepoor training of researchers, poor experimental designs, failure to report fundamental elements of the study, and professional misconduct [2,5,6]. In particular, inadequate reporting has shown to be an important factor that may be modified [3,6].

Similar to other domains of research, preclinical research involving animal models has been demonstrated to be vulnerable to inadequate reporting [1,2,4,6]. Methodology that addresses experimental design and internal validity (i.e. randomization, blinding, sample-size estimation and data handling) are underreported [2,5,7]. Reporting of these elements is particularly crucial, as it allows other investigators to assess the potential risk of bias and reliability of a study.

In response to the poor quality in preclinical reporting, several groups have provided guidance to address the need for improvements. For example, in 2010 the National Centre for Replacement, Refinement and Reduction of Animals in Research (NC3Rs) published the Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) guidelines to improve reporting and increase reliability of experimental findings [1,4]. Although over 600 journals have endorsed the ARRIVE guidelines, investigations have demonstrated that journals are not effectively enforcing the use of these reporting standards [1,9]. The poor implementation of these guidelines has not been explained, however a lack a familiarity with reporting guidelines as well as the large number of items described by ARRIVE may have presented a barrier to their uptake.

A more streamlined approach to reporting has been developed by the The National Institutes of Health (NIH). These guidelines outline a core set of seven reporting standards: 1) community based reporting standards, 2) replicates, 3) statistics, 4) randomization, 5) blinding, 6) sample-size estimation and 7) inclusion and exclusion criteria. Unlike the broad ARRIVE guidelines, the

NIH guidelines focus only on essential elements that are believed to contribute to rigorous study design, conduct and analysis.

The quality of reporting in the preclinical anesthesiology literature has yet to be evaluated. The anesthesiology preclinical literature is diverse and researchers across a variety of biomedical domains contribute to it (e.g. neuroscience, cardiovascular, infectious disease, critical care, etc.). Thus, unlike previous reporting studies that have been limited in scope (e.g. evaluating only studies that used animal models of multiple sclerosis [1]), an evaluation of reporting in the preclinical anesthesiology literature would offer a unique perspective across a number of different disease and physiological domains. Moreover, an evaluation of completeness of reporting against all the core items identified by the NIH has yet to be performed.

Implications

As a group of preclinical, clinical, and translational scientists in perioperative medicine, we have a particular interest in transparent reporting of preclinical studies in our literature. These published preclinical studies are used by members of our group to: a) establish new preclinical studies, b) provide a biological basis for clinical therapies, and also c) provide an ethical basis to proceed to first-in-human studies. Establishing the magnitude and scope of potential issues in current reporting will be a first step in towards improving the rigor of reporting in our field.

Review Question

How completely do preclinical anesthesiology studies adhere to core reporting standards for rigorous study design?

Information Sources

An information specialist will be consulted and all articles published in Anesthesiology, Anesthesia & Analgesia, Anaesthesia, and the British Journal of Anaesthesia in years 2009, 2010, 2014, and 2015 will be identified.

The first widely accepted community based reporting guidelines (i.e. ARRIVE guidelines) were published late 2010; thus, the articles published in the years around (2009 and 2010) and after (years 2014 and 2015) their publication will be included for comparison. These journals were selected as they are the general anesthesiology journals with the highest impact factor within Journal Citation Reports' section for Anesthesiology. Of note, Anesthesiology and Anesthesia & Analgesia have not endorsed any reporting guidelines, whereas the British Journal of Anaesthesia and Anaesthesia have formally endorsed the ARRIVE guidelines.

Types of Studies to be Included

Inclusion Criteria

- *In vivo* preclinical studies
- No limitations of intervention, comparisons, or outcomes, or design
- Original research (full paper, excluding letters to the editor, review, commentary, etc.)

Exclusion Criteria

- *In vitro* or *ex vivo* studies
- Clinical studies

Outcomes

Primary Outcome: Completeness of reporting as assessed by the core set of reporting standards suggested by the NIH.

Study Selection

The process of study selection and data extraction will incorporate two independent reviewers. Citations will be uploaded to Distiller SR® (Evidence Partners, Ottawa Canada), a cloud based program designed for screening and data extraction. First, each study will be assessed by its title via accelerated screening method in which one reviewer is required to include a study and two reviewers are required to exclude a study. Two reviewers will then independently screen each study by its abstract. Studies that are deemed eligible will be retrieved to review their full articles for final screening.

Data Extraction

Data will be extracted independently in duplicate from the studies that meet eligibility criteria. Extraction forms have been generated in Distiller SR®. Given the large number of studies to be included, a model of disseminated group data extraction has been created to complete this study in a timely manner. Extractors from the Ottawa Hospital Research Institute will perform initial extraction and external extractors will perform duplicate extraction.

All extractors will be provided the protocol as well as a training resource containing an explanation of the elements to be extracted. All extractors will undergo training by extracting data from 8 studies; a kappa of 0.8 (compared to core investigator answers) will be required to be eligible to participate in full extraction.

The level of agreement between two reviewers will be measured by Cohen's kappa. Discrepancies in duplicate extraction will be resolved by the core group of investigators (listed above).

Description of Reporting and Strategy for Data Synthesis

We will evaluate the completeness of reporting of the selected studies using the seven core set of reporting standards (NIH guidelines). We have operationalized the NIH guidelines to include 12 sub-sections that would be evaluated as "yes" or "no" decisions in order to declare whether the sub-sections were reported in the studies. See example extraction sheets (Appendix).

The level of reporting will be scored based on the operationalized checklist. Data will be pooled and expressed as proportions and percentages. We will present completeness of reporting based on the seven core set of reporting standards using radar charts. We will compare the number of reported items (giving equal weight to each item) published before or after publication of community based reporting guidelines. We will test the data for normality and perform an analysis (either parametric or non-parametric) with two between-subjects factors, Endorsement (two levels) and Journal (four levels); and one within-subjects factor, Before versus After publication of community based guidelines (two levels).

Transparency and Data Sharing

Our protocol will be posted on the Open Science Framework (OSF) prior to initiating data extraction. Following acceptance of the study for publication, the full extracted data set will be made publicly available through the OSF.

Authorship

The ICJME requirements for authorship will be followed. Listed authors will be involved in 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. In addition, they agree 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.

Authors will be listed in alphabetical order, with the principal guarantor of the work listed as last and corresponding author. The core group that has led the conception and design of the study will be acknowledged in the authorship. This study has been endorsed by the Canadian Perioperative Anesthesia Clinical Trials Group (http://canadianpact.ca/) and will be submitted on behalf of the group.

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