Preclinical Experimental Design and Reporting Workshop

Friday, October 26, 2018, 1:00-7:00 pm
Ivor Petrak Room
Fairmont Banff Springs Hotel, Banff, Alberta

Workshop co-developed by:

BioCanRx
Canada's Immunotherapy Network
Le réseau canadien d'immunothérapie

OTTAWA METHODS CENTRE

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None of the speakers were paid either directly or indirectly by Novartis.

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AGENDA

Time	Session Title	Speaker
12:45 – 1:00 pm	Registration open, buffet lunch served	
1:00 – 1:05 pm	Opening Remarks & Lunch	Manoj Lalu
1:05 – 1:15 pm	NIH Core – Standards	Joshua Montroy
1:15 – 1:40 pm	Speaking from Experience	Carolina Ilkow
1:40 – 1:55 pm	Validity of Experimental Design	Joshua Montroy
1:55 – 2:35 pm	NIH Core – Replicates	Carly Barron
2:35 – 2:45 pm	Break	
2:45 – 3:45 pm	NIH Core – Reporting Statistics & Intro Sample Size Estimation	Dean Fergusson
3:45 – 4:15 pm	NIH Core – Inclusion/Exclusion Criteria	Carly Barron
4:15 – 4:30 pm	Break	
4:30 – 5:15 pm	NIH Core – Randomization	Manoj Lalu
5:15 – 6:00 pm	Dinner	
6:00 – 6:45 pm	NIH Core – Blinding	Carolina Ilkow
6:45 – 6:50 pm	Closing Remarks & Resources	Manoj Lalu
6:50 – 7:00 pm	Workshop Evaluation – Help us improve	Joshua Montroy

BACKGROUND FOR WORKSHOP

Improving our Practices: Preclinical Experimental Design and Reporting:

Assessments of the reporting quality of preclinical research have consistently found that important elements of research design are often missing from published work. Multiple surveys of work across basic biomedical science have demonstrated that few studies report the use of design elements such as blinding and randomization (1-5). To assess if incomplete reporting is related to differences in design, systematic reviews of preclinical intervention studies have compared the effect sizes between studies that report, and do not report, key information such as randomization. For instance, a synthesis of 30 preclinical systematic reviews (>7000 comparisons using >120,000 animals) found that studies which did not report randomization had significantly higher effect sizes (6).

To address the incomplete reporting of research design, new reporting guidelines have been developed and are being implemented by funding agencies, universities, publishers and journals. The two most widely endorsed reporting guidelines for preclinical research are the Animals in Research: Reporting In Vivo Experiments (ARRIVE) guidelines (7) and the NIH Principles and Guidelines for Reporting Preclinical Research (8). The ARRIVE guidelines are similar to reporting guidelines for clinical studies (9), which cover every aspect of the paper from the title to the discussion. The NIH Guidelines are based on a set of core reporting items that are considered crucial for the design and evaluation of research. In addition, top-tier journals are now requiring authors to report on many of these items. These new reporting requirements, such as randomization and blinding, are intended to promote change in how experiments are designed and conducted by investigators.

Purpose:

In response to these reporting guidelines, we aim to address these new challenges by providing preclinical scientists with a one-day workshop on experimental design and reporting based on the new NIH Principles and Guidelines for Reporting Preclinical Research (and design) requirements.

Workshop Learning Objectives:

1. Preclinical scientists will have a working knowledge of basic experimental design and reporting for the NIH core items as well as working knowledge on how to implement these in the design of their experiments.
2. Investigators will be aware of resources available to them to assist with research design and reporting.

REFERENCES

1. Avey MT, Moher D, Sullivan KJ, Fergusson D, Griffin G, Grimshaw JM, et al. The Devil Is in the Details: Incomplete Reporting in Preclinical Animal Research. PLoS One. 2016;11(11):e0166733.
2. Hackam DG, Redelmeier DA. Translation of research evidence from animals to humans. JAMA. 2006;296(14):1731-2.
3. Leung V, Rousseau-Blass F, Beauchamp G, Pang DSJ. ARRIVE has not ARRIVEd: Support for the ARRIVE (Animal Research: Reporting of in vivo Experiments) guidelines does not improve the reporting quality of papers in animal welfare, analgesia or anesthesia. PLoS One. 2018;13(5):e0197882.
4. Mattina J, MacKinnon N, Henderson VC, Fergusson D, Kimmelman J. Design and Reporting of Targeted Anticancer Preclinical Studies: A Meta-Analysis of Animal Studies Investigating Sorafenib Antitumor Efficacy. Cancer Res. 2016;76(16):4627-36.
5. Wieschowski S, Chin WWL, Federico C, Sievers S, Kimmelman J, Strech D. Preclinical efficacy studies in investigator brochures: Do they enable risk-benefit assessment? PLoS Biol. 2018;16(4):e2004879.
6. Hirst JA, Howick J, Aronson JK, Roberts N, Perera R, Koshiaris C, et al. The need for randomization in animal trials: an overview of systematic reviews. PLoS One. 2014;9(6):e98856.
7. Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. PLoS Biol. 2010;8(6):e1000412.
8. National Institutes of Health. Principles and Guidelines for Reporting Preclinical Research 2015 [
9. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. PLoS Med. 2010;7(3):e1000251.

WORKSHOP DESIGN & EXECUTION TEAM

Dean A. Fergusson, MHA, PhD

Dr. Fergusson is a Senior Scientist and Director of the Clinical Epidemiology Program (CEP) at the Ottawa Hospital Research Institute and a Full Professor in the Department of Medicine with cross-appointments to the School of Epidemiology & Public Health and the Department of Surgery at the University of Ottawa. He is renowned internationally for his scholarship and leadership in two major areas: 1) transfusion medicine and transfusion alternatives and 2) innovative methodological research into the design and analysis of clinical trials. Dr. Fergusson has been intimately involved in the conception and development of the MSC clinical research program at The Ottawa Hospital. He is also responsible for pioneering the clinical trial accelerator concept for novel biotherapeutics that includes the establishment of a multi-disciplinary research approach and infrastructure to accelerate the translation of cell therapies from the pre-clinical to clinical evaluation space.

Manoj Mathew Lalu, MD, PhD, FRCPC

Dr. Manoj Lalu is an Associate Scientist at the Ottawa Hospital Research Institute CEP and Regenerative Medicine Programs, an Anesthesiologist at the Ottawa Hospital, and an Assistant Professor at the University of Ottawa Department of Anesthesiology and Pain Medicine. His current research is largely preclinical and translational, focusing on cell therapies for critical illness and cancer. He leads the Blueprint Translational Research Group with Dean Fergusson, which is focussed on methods to improve the speed and success of bench-to-bedside translation. An important aspect of this is helping implement ways to reduce the risk of bias in preclinical work.

Carolina Ilkow, PhD

Dr. Ilkow is originally from Buenos Aires, Argentina where she obtained her Bachelor's degree in Science. She then decided to move to Edmonton, Canada, to continue her graduate studies at the University of Alberta, where she obtained her PhD in cell biology, after which she joined Dr. John Bell's lab as a post-doctoral fellow. Carolina's work in the Bell lab aimed at developing novel and tailored virotherapies to fight Pancreatic cancer. Her discoveries in this field led Carolina to win a prestigious Researcher in Training Award and to publish impactful papers. In July 2016, Carolina was recruited as a Scientist at the Ottawa Hospital Research Institute, and an Assistant Professor in the department of biochemistry, microbiology and Immunology at the University of Ottawa. Her research is focused on understanding how the tumour microenvironment modulates the effects of virus-based immunotherapies.

Carly Barron, MD, MSc

Dr. Carly Barron is Resident Physician in the Department of Medicine at McMaster University. She has a background in preclinical research having studied the implications of GLUT proteins and metabolism in cancer. Her current research focuses on improving translation of preclinical studies and reducing harm associated with oncology therapies.

Joshua Montroy, MSc

Joshua Montroy is a Research Associate with the Blueprint Translational Research Group at the Ottawa Hospital Research Institute. His background is in clinical epidemiology, where he completed a Masters degree specializing in transfusion research. His current research is focused around improving the bench-to-bedside translation of biotherapeutics using a novel, multidisciplinary approach.

RESOURCES

1. Standards

• ARRIVE Guidelines
  - https://www.nc3rs.org.uk/arrive-guidelines

• National Institutes of Health Principles and Guidance
  - https://www.nih.gov/research-training/rigor-reproducibility/principles-guidelines-reporting-preclinical-research
  - A call for transparent reporting to optimize the predictive value of preclinical research (https://www.nature.com/articles/nature11556).

• Biosharing.org (search for standards relevant to your work)
  - https://biosharing.org/standards/?selected_facets=isMIBBI:true

• Journal-specific checklist examples
  - *Nature* (https://www.nature.com/authors/policies/ReportingSummary-flat.pdf)
  - *Cell (https://www.cell.com/pb-assets/journals/research/cell/methods/Methods%20Guide.pdf)*

• Resource Identification Initiative
  - *https://scicrunch.org/resources*

• Minimal Information About a Proteomics Experiment (MIAPE)
  - *http://www.psidev.info/miape*
  - *https://www.nature.com/articles/nbt1329*

2. Validities

• Internal/External/Construct validity described for preclinical research
  - Threats to validity in the design and conduct of preclinical efficacy studies: A systematic review of guidelines for animal experiments (http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001489)
  - Critical Appraisal of studies using laboratory animal models (https://academic.oup.com/ilarjournal/article/55/3/405/644697)
  - Refinement of experimental design and conduct in laboratory animal research (https://academic.oup.com/ilarjournal/article/55/3/383/644342)
  - Establishing the internal and external validity of experimental studies (https://www.ncbi.nlm.nih.gov/pubmed/11760921)
  - Practical aspects of experimental design in animal research (https://academic.oup.com/ilarjournal/article/43/4/202/981687

• Biological sex bias in preclinical biomedical research
  - Research: Bias in the reporting of sex and age in biomedical research on mouse models (https://elifesciences.org/articles/13615)
  - Sex bias exists in basic science and translational surgical research (https://www.sciencedirect.com/science/article/pii/S0039606014004255)

• Exploratory vs. Confirmatory Research:
  - Distinguishing between exploratory and confirmatory preclinical research will improve translation (http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1001863)

• Study Quality
  - Systematic Reviews and Meta-Analysis Facility (SyRF). Why assess study quality? (http://syrf.org.uk/systematic-review/step-6-study-quality/)

- Instruments for assessing risk of bias and other methodological criteria of published animal studies: A systematic review (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3764080/)

• SYRCLE's Risk of Bias Tool
  - http://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-14-43
• CAMARADES Study Quality Checklist
  - http://stroke.ahajournals.org/content/35/5/1203.full.pdf+html
• Risk of Bias tools assessment for preclinical toxicology studies
  - http://ehp.niehs.nih.gov/1206389/

3. Replicates

• Replicability vs. Reproducibility
  - Enhancing research reproducibility: recommendations from the Federation of American Societies for Experimental Biology ((https://www.faseb.org/Portals/2/PDFs/opa/2016/FASEB_Enhancing%20Research%20Reproducibility.pdf)
  - A statistical definition for reproducibility and replicability (http://biorxiv.org/content/early/2016/07/29/066803)
  - What does research reproducibility mean? (http://stm.sciencemag.org/content/8/341/341ps12.short)
• Biological vs Technical Replicates
  - Replication (http://www.nature.com/nmeth/journal/v11/n9/pdf/nmeth.3091.pdf)

4. Inclusion/Exclusion Criteria

• Attrition in animals studies
  - Where have all the rodents gone? The effects of attrition in experimental research on cancer and stroke (http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1002331)

5. Sample Size Calculations & Statistics

• How not to consult with a statistician
  - https://www.youtube.com/watch?v=PbODigCZqL8
• Planning statistical analyses
  - Statistics for biologists (https://www.nature.com/collections/qghhqm)
  - Guidelines for the design and statistical analysis of experiments using laboratory animals (http://ilarjournal.oxfordjournals.org/content/43/4/244.full.pdf+html)
  - Effect size, confidence interval ad statistical significance: a practical guide for biologists (https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1469-185X.2007.00027.x)
• Software:
  - G*Power (Free & Designed for Specifically for Sample Size Calculations)
  - (http://www.gpower.hhu.de/en.html)
  - PASS ($, Power and Sample Size calculator) (https://www.ncss.com/software/pass/)
  - R (Free) https://www.r-project.org/
  - STATA ($) http://www.stata.com/
  - • Websites: Two Sample Tests (http://www.sample-size.net/)
  - Free online sample size calculator (https://www.stat.ubc.ca/~rollin/stats/ssize/)

• Good starting place for thinking about POWER
http://www.ma.utexas.edu/users/mks/statmistakes/PowerMistakes.html

6. Randomization

- Why randomization matter in preclinical studies: https://www.youtube.com/watch?v=_I12EZbkYek
  - Evidence for the efficacy of NXY-059 in experimental focal cerebral ischaemia is confounded by study quality (https://www.ahajournals.org/doi/abs/10.1161/strokeaha.108.515957)The need for randomization in animal trials: An overview of systematic reviews (http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0098856)

• Sequence Generation

- https://www.semanticscholar.org/paper/Generation-of-allocation-sequences-in-randomised-Schulz-Grimes/314e37518963a476c5b856e6bf97ff7599652b3b
  - Allocation Concealment
- https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(02)07750-4/fulltext (free article, just need to sign in)

• Tools:

- http://randomization.com/
- Excel has built in rand function – Customizable (i.e. can use to generate sequence for randomization to surgery and then to treatment)

7. Blinding

• Why blinding matters

- https://www.youtube.com/watch?v=mVKuCbjFfIY
- Emergency medicine animal research: Does use of randomization and blinding affect the results? (https://onlinelibrary.wiley.com/doi/full/10.1111/j.1553-2712.2003.tb00056.x)
  - Clinical definitions of type of blinding
- Blinding: Who, what, when, where, how? (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2947122/)
- European Patients Academy Resource (https://www.eupati.eu/clinical-development-and-trials/concept-blinding-clinical-trials/)
- Blinding: A detailed guide for students (https://www.students4bestevidence.net/blinding-comprehensive-guide-students/)

This and other resources will be available through a website to go live for BioCanRx in early 2019. Resources compiled by the Blueprint Translational Research Group, Ottawa Hospital Research Institute.