Adaptive Platform Trial Scientific Meeting

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CanTreatCOVID

Canadian Adaptive Platform Trial of Treatments for COVID in Community Settings

Ethical Considerations in Adaptive Platform Trials

Ross E.G. Upshur, BA (Hons.), MA, MD, MSc, MCFP, FRCPC, FCAHS

Dalla Lana Chair in Clinical Public Health and Head, Division of Clinical Public Health, Dalla Lana School of Public Health

Senior Scientist, Lunenfeld Tanenbaum Research Institute and Staff Physician, Hennick Bridgepoint Hospital

Sinai Health

Professor, Department of Family and Community Medicine and DLSPH, University of Toronto

Outline

1. Obligations of Researchers
2. Basic Concepts in Research Ethics
3. Addressing Challenges of Adaptive Designs
4. Ethics and Adaptive Platform Trials as part of a Learning Health System Ecology

Why Ethics Matters to Research

- Health research rests upon an ethical foundation: to gain knowledge to improve human well being
- There is no right to be a researcher, it is a privilege
- Researchers are self regulating: there is no regulatory body to enforce standards as in the health professions
- Obligations to enrolled participants are as stringent as that between a physician and patient
- Ethics in research is more than just REB approval, but relates to the integrity of the entire structure of the research ecosystem

Wright et al. 2023

- Ethics considerations are inherent in the decisions made throughout every aspect of clinical research: when it is conceived, funded, planned, reviewed, implemented and disseminated. Research ethics committees provide independent review of some of these decisions. However, such safeguards do not, in themselves, make research practice ethical.

Scientists behaving badly

Brian C. Martinson, Melissa S. Anderson and Raymond de Vries *Nature* **435**, 737-738 (June 2005)

Table 1 | Percentage of scientists who say that they engaged in the behaviour listed within the previous three years ($n = 3,247$)

Top ten behaviours	All	Mid-career	Early-career
1. Falsifying or 'cooking' research data	0.3	0.2	0.5
2. Ignoring major aspects of human-subject requirements	0.3	0.3	0.4
3. Not properly disclosing involvement in firms whose products are based on one's own research	0.3	0.4	0.3
4. Relationships with students, research subjects or clients that may be interpreted as questionable	1.4	1.3	1.4
5. Using another's ideas without obtaining permission or giving due credit	1.4	1.7	1.0
6. Unauthorized use of confidential information in connection with one's own research	1.7	2.4	0.8 ***
7. Failing to present data that contradict one's own previous research	6.0	6.5	5.3
8. Circumventing certain minor aspects of human-subject requirements	7.6	9.0	6.0 **
9. Overlooking others' use of flawed data or questionable interpretation of data	12.5	12.2	12.8
10. Changing the design, methodology or results of a study in response to pressure from a funding source	15.5	20.6	9.5 ***
Other behaviours			
11. Publishing the same data or results in two or more publications	4.7	5.9	3.4 **
12. Inappropriately assigning authorship credit	10.0	12.3	7.4 ***
13. Withholding details of methodology or results in papers or proposals	10.8	12.4	8.9 **
14. Using inadequate or inappropriate research designs	13.5	14.6	12.2
15. Dropping observations or data points from analyses based on a gut feeling that they were inaccurate	15.3	14.3	16.5
16. Inadequate record keeping related to research projects	27.5	27.7	27.3

Note: significance of χ^2 tests of differences between mid- and early-career scientists are noted by ** ($P < 0.01$) and *** ($P < 0.001$).

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The Haunting of Medical Journals: How Ghostwriting Sold "HRT"

Adriane J. Fugh-Berman

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Citation: Fugh-Berman AJ (2010) The Haunting of Medical Journals: How Ghostwriting Sold "HRT". PLoS Med 7(9): e1000335. doi:10.1371/journal.pmed.1000335

Published: September 7, 2010

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Historical context

1. **World War 2 Medical War Crimes**
2. **The Tuskegee Syphilis Study**
3. **The Jewish Chronic Disease Hospital Study**
4. **The Willowbrook Study**
5. **The San Antonio Contraceptive Study**
6. **For More see: http://www.ahrp.org/history/chronology.php**

Evolution of Codes

- Nuremberg Code
- Declaration of Helsinki
- CIOMS
- Belmont Report
- National Guidelines
- TCPS

Canadian guidelines

Tri-Council Policy Statement

- **It mandates minimum and universal standards**
- ***Living document, reflecting evolving field of scholarship***

Ethics review

Research requiring review

REBs are responsible for ethics review of research involving humans as subjects of research

Research Ethics Boards (REBs)

The REB has the authority to approve, disapprove, propose modifications to, or terminate any proposed or ongoing research involving human subjects

Review process

REBs adopt a proportionate approach to ethics review, based on the principle that the more potentially invasive or harmful the research, the more care should be taken in its review.

FOCUS IS ON HUMAN SUBJECT PROTECTION

Fundamental principles

The moral imperative of respect for human dignity translates into other correlative ethical principles:

1. Respect for **free and informed consent**
2. Respect for **vulnerable persons**
3. Respect for **privacy and confidentiality**
4. Respect for **justice and inclusiveness**
5. Balancing **harms and benefits**

Emanuel's 7 Requirements

Table 2. Seven Requirements for Determining Whether a Research Trial Is Ethical*

Requirement	Explanation	Justifying Ethical Values	Expertise for Evaluation
Social or scientific value	Evaluation of a treatment, intervention, or theory that will improve health and well-being or increase knowledge	Scarce resources and nonexploitation	Scientific knowledge; citizen's understanding of social priorities
Scientific validity	Use of accepted scientific principles and methods, including statistical techniques, to produce reliable and valid data	Scarce resources and nonexploitation	Scientific and statistical knowledge; knowledge of condition and population to assess feasibility
Fair subject selection	Selection of subjects so that stigmatized and vulnerable individuals are not targeted for risky research and the rich and socially powerful not favored for potentially beneficial research	Justice	Scientific knowledge; ethical and legal knowledge
Favorable risk-benefit ratio	Minimization of risks; enhancement of potential benefits; risks to the subject are proportionate to the benefits to the subject and society	Nonmaleficence, beneficence, and nonexploitation	Scientific knowledge; citizen's understanding of social values
Independent review	Review of the design of the research trial, its proposed subject population, and risk-benefit ratio by individuals unaffiliated with the research	Public accountability; minimizing influence of potential conflicts of interest	Intellectual, financial, and otherwise independent researchers; scientific and ethical knowledge
Informed consent	Provision of information to subjects about purpose of the research, its procedures, potential risks, benefits, and alternatives, so that the individual understands this information and can make a voluntary decision whether to enroll and continue to participate	Respect for subject autonomy	Scientific knowledge; ethical and legal knowledge
Respect for potential and enrolled subjects	Respect for subjects by (1) permitting withdrawal from the research; (2) protecting privacy through confidentiality; (3) informing subjects of newly discovered risks or benefits; (4) informing subjects of results of clinical research; (5) maintaining welfare of subjects	Respect for subject autonomy and welfare	Scientific knowledge; ethical and legal knowledge; knowledge of particular subject population

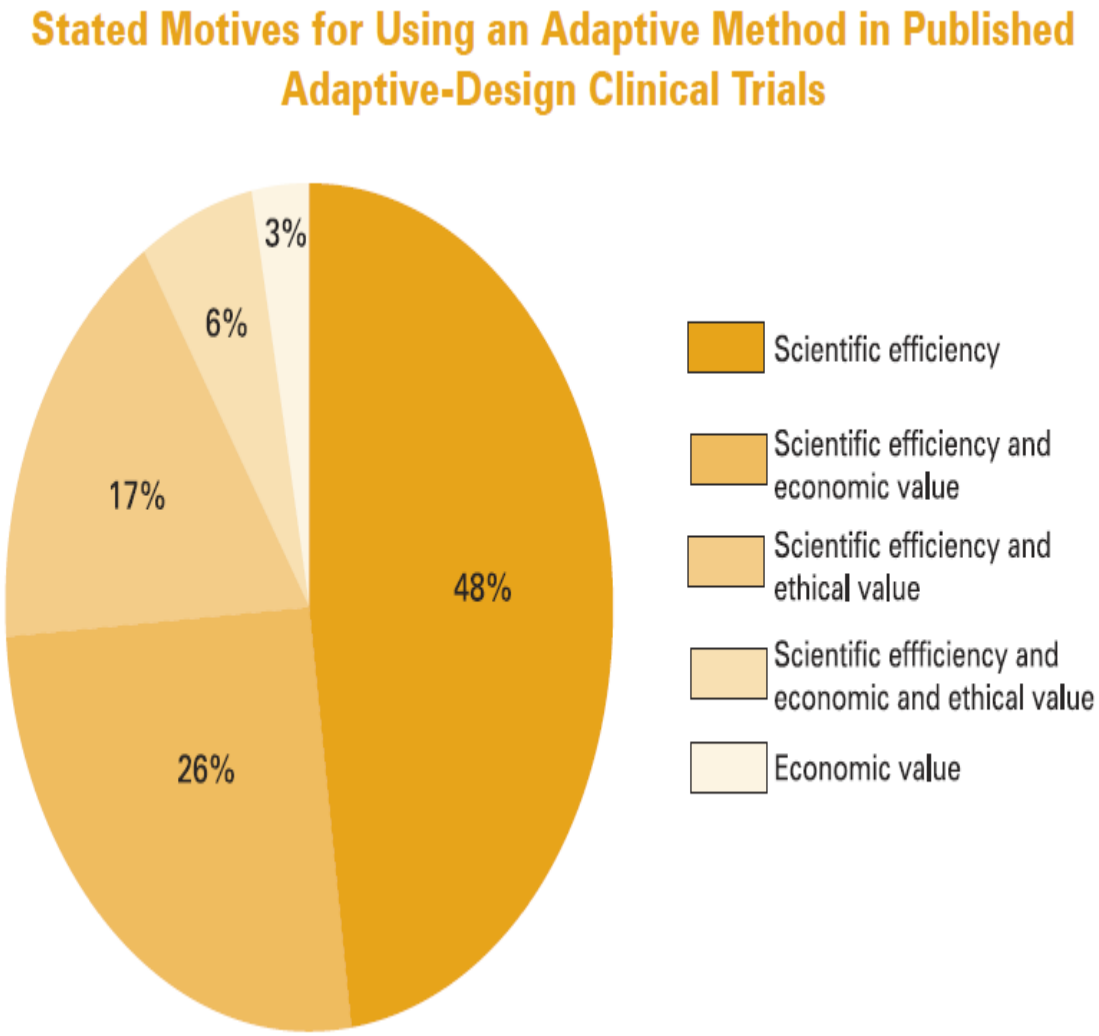
*Ethical requirements are listed in chronological order from conception of research to its formulation and implementation.

Challenges and Opportunities in Adaptive Platform Trials

Adaptive Platform Trials

- All the usual considerations of ethical review noted above pertain to APT'S
- APT's are considered novel designs even though they have been used for some time
- Many REB's have limited to no experience in their review
- This emphasizes the importance of a mutually respectful relationship between PI and REB
- Literature and guidance is sparse
- The SARS-CoV-2/COVID-19 pandemic increased our understanding of the strengths of APT's as well as some of the ethical challenges

Bothwell and Kesselheim Hastings Center Report 2017



Bothwell and Kesselheim Hastings Center Report 2017

- Thus, adaptive-trial IRB protocols and consent forms should be designed with extra care to clearly and effectively convey the trial design and allocation scheme to which patients could be assigned.
- Trial personnel taking patient consent should be granted extra time to explain the complexities of adaptive designs.

Ethical Considerations in APT's

- Debate about whether ATP's more ethical than fixed RCT design
- Fixed design rooted in collective ethics/ATP design rooted in individual ethics
- Concerns about informed consent

Adaptive clinical trials in public health emergency contexts: ethics considerations Singh, Wellcome Open 2023

- Ethical Issues relate to response adaptive randomization and frequent interim analysis
- RAR permits randomization proportions to be varied during the course of the trial. Such reallocation between arms increases the fraction of participants who receive the most effective treatment. Such adaptations can decrease the required sample size by allocating participants to arms most likely to be efficacious.
- More efficient, lower sample size, less exposure to potentially ineffective therapy

Adaptive clinical trials in public health emergency contexts: ethics considerations Singh, Wellcome Open 2023

- Critics of APT's question whether "increasing the proportion of subjects randomized to the more successful arm of the trial based on interim results is unethical in respect to equipoise, informed consent, justice, and potential investigator bias."

Challenges of Informed Consent

- Timing of consent:
- Should prospective trial participants be informed, as part of the informed consent process and in the interests of beneficence and transparency, that they may stand a better chance of being assigned to a more efficacious intervention if they enrol later in the trial, rather than at trial initiation.

Clinical Trial Governance Singh, Wellcome Open, 2023

- …clinical trial governance refers to the agreements, rules, regulations, processes, policies, standards of good practice, and actions adopted by trial sponsors, investigators, and trial decision-making structures to yield robust evidence on the safety and efficacy of the interventions being tested, enhance the ethical and scientific quality of a trial, and safeguard the welfare and interests of study participants.

Complex Governance

Potential governance instruments:
Letters of Agreements, Memorandums of Understandings, Contracts, Charters / Terms of Reference, Standard Operating Procedures (SOPs)

Governance instruments:
Laws, regulations, policies, [including local parameters for data access, data sharing, data export, and privacy].

ICH guidelines on quality, safety, and efficacy.

Research ethics guidance, including on good participatory practice, trial unblinding, and post-trial access.

Clinical Trial Governance Singh, Wellcome Open, 2023

- Important to convene an Ethics Working Group for the PAT
- An EWG can help inform decision-making relating to the design and implementation of the trial by guiding the resolution of any emerging ethical issues, in real-time. By being embedded in the trial as a core support structure, the EWG can serve as an ‘anchor’ on ethics issues and serve as a valuable resource to other trial structures, including the PI and Sponsor(s).

Opportunities

Ethical priorities for international collaborative adaptive platform trials for public health emergencies

Wright et al.

BMJ Global Health 2023

- Research ethics committees have struggled at times with the complexity and novel ethical questions raised by adaptive design methodologies.
- This raises specific questions of capacity strengthening, separate from existing well-recognised resourcing and capacity issues for ethical review systems in many parts of the world.
- Committee members need access to high-quality training resources to gain confidence in dealing with adaptive methodologies and the complexities of master protocols that will be implemented across multiple sites.
- Equally, researchers need to take responsibility for explaining their trial proposals clearly. More widely, the particular complexities of reviewing adaptive platform trials point to a longer-term need to develop more flexible and dynamic models of review, including the role of trial monitoring.

Opportunities

- We need a “healthy” and thriving research ecosystem
- Learning Health System approach offers an opportunity to see innovative ways to build empirical base for varied ethical challenges
- Fund studies on consent experience and participant understanding of APT’s
- Encourage mutual learning between researchers and REB’s
- I think this can be done while preserving REB independence

Ethical priorities for international collaborative adaptive platform trials for public health emergencies

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Box 1

Priority research questions to help inform equitable, person-centred research practice

- What can be learnt from the COVID-19 adaptive platform studies that would help strengthen the integration of ethics in an ongoing manner into project management processes?
- How can researchers, public health officials, communities and other key stakeholders in LMICs be meaningfully involved in planning and rolling out adaptive platform trials to ensure equitable partnerships?
- What were the barriers and enablers for good participatory practice (GPP) in the major COVID-19 adaptive platform studies, and how might this inform revised guidance on what GPP looks like in the context of platform adaptive trials?
- How can researchers be supported and encouraged to document and report on the experience and outcomes of community engagement, so that practice can be strengthened?
- What information is appropriate to communicate to participants on adaptive features of trials to support informed consent, and how can such information be shared effectively, including during an infectious disease outbreak?
- What were the challenges and experiences of research ethics committees and data safety and monitoring boards in reviewing protocols and data for adaptive platform studies during COVID-19, and how could committees be better supported in future?
- What evidence is there of benefit to less well-resourced countries from involvement in adaptive platform trials, including changed medical practice, improved health outcomes or strengthened research capacity?

LMICs: low-income and middle-income countries.

CFP CANADIAN FAMILY PHYSICIAN

Ask not what your REB can do for you; ask what you can do for your REB

Ross E.G. Upshur, MD MSc CCFP FRCPC

+ Author Affiliations

Correspondence: **Dr Ross E.G. Upshur,** Sunnybrook Health Sciences Centre, 2075 Bayview Ave, E3–49, Toronto, ON M4N 3M5; telephone 416 480-4753; fax 416 480–4536; e-mail ross.upshur@sunnybrook.ca

Research ethics boards (REBs) are perhaps the most unloved component of the