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Biostatistics
Unit



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Randomization WG Learning Session

Ethics of Adaptive Designs

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- Part I: Introduction
- Part II: Overview of Cambridge workshop on Ethics of ADs
- Part III: Recap of the resulting position paper

Outline

1. Introduction

2. Overview of Cambridge workshop on Ethics of ADs

2. Recap of the resulting Position Paper

What is a Response-adaptive Design?

A Response-adaptive (RA) design is an experimental design where the allocation of experimental units to the different (treatment) options to dynamically change based on available *data* with the goal to optimise the experiment (*in some way*).

- Response-adaptive Randomisation (RAR) is an RA in which:
 - (1) is implemented through **randomisation** and;
 - (2) and where the resulting allocation probabilities to **change** (or adapt) **based on the evidence/data** collected at interim points.
- RAR is perhaps the oldest form of an adaptive design of experiments. Proposed by [Thompson1933] for *saving individuals otherwise sacrificed to an inferior treatment*

probability of treatment by the two methods of $f_{(P)}$ and $1 - f_{(P)}$, respectively. **If such a discipline were adopted, even though it were not the best possible, it seems apparent that a considerable saving of individuals otherwise sacrificed to the inferior treatment might be effected. This would be important in cases where either the rate of accumulation of data is slow or the individuals treated are valuable, or both.**

RAR debate

If you are planning a randomized comparative clinical trial and someone proposes that you use [response] adaptive randomization, Just Say No. *[Thall2020]*

... optimal response-adaptive randomization designs allow implementation of complex optimal allocations in multiple-objective clinical trials and provide valid tools to inference at the end of the trial. In many instances they prove superior over traditional balanced randomization designs in terms of both statistical efficiency and **ethical** criteria. *[Rosenberger et al.2012]*

Response adaptive randomization (RAR) is a noble attempt to increase the likelihood that patients receive better performing treatments, but it causes numerous problems that more than offset any potential benefits. We discourage the use of RAR in clinical trials. *[Proschan and Evans2020]* [See *[Villar et al.2021]* for a short response]

The Ethics Debate in RAR

Presenting the ideas of RAR triggers polarized perspectives:

Proponents' View

“RAR is more ethical because it allows more patients in the trial to be assigned to superior treatments as the trial progresses...”

“RAR is a middle ground that allows to continue randomizing when evidence of a treatment being inferior is appearing”

Critics' View

“If RAR is ethical, then not using RAR is unethical...”

“RAR is not ethical; by attempting to minimize exposure to suboptimal arms, you risk exposing more patients to them by chance due to early noise.”

- **Fundamental Questions:** The debate forces us to re-examine *when* and *why* we randomize in clinical research.

Summary. We believe that the ethics of RAR needs more attention from ethicists, including collaborations between ethicists and statisticians to address the caveats and complexities of this broad family of methods. Positions based purely on statistical or ethical arguments in isolation are likely to be inadequate and arguments that involve ethical metrics should ideally be jointly discussed with multiple stakeholders. It is important to bear in mind that compromises between statistical and ethical objectives have very different implications under different settings. For example, the trade-offs between these two objectives may look very different in a two-arm trial setting compared to a multi-arm trial.

Robertson et al. (2023)

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Motivation

- Claims in the statistical/methodological literature that adaptive designs are “more ethical” or have “ethical advantages”
- But what do we mean by “ethical”? We need to ask the ethicists!
- Need for collaborations between ethicists and statisticians
- Recognition that arguments that involve ethical metrics should be jointly discussed with multiple stakeholders
- Why ADs and not RAR? A Difference of Degree, Not of Kind:

RAR is often the “lightning rod” for skepticism toward all adaptive designs; it is not an outlier, but the ultimate expression of the adaptive philosophy—paying for the “sins” of the family simply because it makes our ethical and statistical trade-offs impossible to ignore.

Workshop overview

- Full-day hybrid workshop held in April 2025 at the University of Cambridge focused on ethical and methodological issues surrounding adaptive clinical trial designs
- Brought together statisticians, ethicists, industry representatives, policymakers, regulators, health technology assessment (HTA) representatives, patient and public involvement (PPI) contributors
- Discussion of the evolving landscape of adaptive clinical trial designs and their ethical implications
- Over 100 participants with 12 invited speakers

Workshop structure

- Statistical methods for adaptive designs
- Ethical aspects for adaptive designs
- International and Industry Perspectives
- Regulatory perspectives + Patient focus

Note: most talks were recorded and are available at <https://www.cmu.edu/ethics-ai/events/adaptive-trials-2025.html>

Group photo



Note: a few speakers are missing from the photo!

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- Trials are Crucial Decision-Making Tools: They generate evidence that influences patient health, health system efficiency, resource use, and innovation.
- Trials as Social & Ethical Undertakings: Their design must simultaneously meet complex scientific, statistical, and ethical requirements.
- The interactions surfaced two ethical tensions:
 1. Divergent Perspectives: on what is an Adaptive Design (and what is not) and on the relative value of different design options.
 2. Design Uncertainty is Underappreciated: Design uncertainty (in key assumptions like effect sizes) is often underestimated by many stakeholders, impairing scientific and ethical merit.

Divergent Perspectives in Trial Design

These complicate communication and evaluation of trial designs.

- Definition of “Adaptive Trial”: pre-planned versus ad hoc adaptations; specific types (e.g., response-adaptive randomization) included while excluding others (e.g., group sequential designs); Adaptive designs and Bayesian methods.
- Normative Attitudes: “adaptive” as a purely descriptive term, or as with stigma from past controversies (like the ECMO study) or positive aura due to demonstrated virtues (especially during the COVID-19 pandemic).
- Perceptions of Status: often incorrectly labeled as “novel,” reinforcing the status of fixed designs as the “gold standard,”
- Ethical Associations: ADs often linked to “individual ethics”
Fixed designs are often linked to “collective ethics”.

Adaptive and Fixed Designs: Definitions

To improve communication and evaluation, clinical research requires sound, statistically, and ethically relevant definitions:

- **Fixed Design:** A study where all design elements are determined at the start and remain unchanged throughout.
- **Adaptive Design:** Any pre-planned, data-driven alteration to a trial aspect, coupled with a corresponding prespecified design-based analysis. [ICHE20]

Examples include: Changing participant allocation (randomization ratio), sample size, or study population.

- These definitions have many virtues (e.g. explicitly exclude unplanned, ad hoc alterations) but in our arguments they make it easier to compare how “design” uncertainty affects the relative merits of both.

Fixed vs. Adaptive Trial Designs

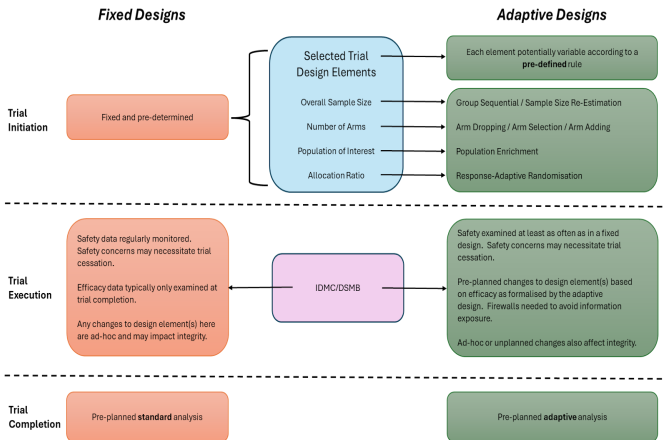


Figure: Fixed vs. Adaptive Designs: Key differences in design elements (top), IDMC/DSMB function (middle), and final analysis (bottom).

The Ethical Requirement for Considering Adaptive Designs

Core assertion: the best trial design is identified by first foregrounding ethical values and then assessing whether fixed or adaptive elements best promote these values under realistic, practical circumstances.

Clinical trials must meet a combination of three ethical requirements:

1. **Social Value (Core Mission):** Generating the necessary evidence to improve the safety, effectiveness, efficiency, and equity of patient care and health systems.
2. **Minimizing Participant Harm:**
Reducing or eliminating avoidable harms to participants.
3. **Responsible Resource Stewardship:** efficiently using scarce resources, including the time and effort of participants and clinical personnel, as well as financial costs.

Arguments to support the paper's claim

- Adaptive designs can sometimes reduce the risks to meeting this ethical criteria caused by under-estimating the level of residual uncertainty. Next Slide!
- Adaptive Designs can sometimes facilitate fidelity to ethical requirements in Practice.
- Adaptive Designs can promote coordination across multiple efforts
- Prioritizing ethics counters bias, fads, and rigid adherence to old practices.
- Very important caveat: An AD needs to be feasible and implemented with a high quality execution (integrity preserving due to information leakages).

Fixed vs. Adaptive Trial Designs

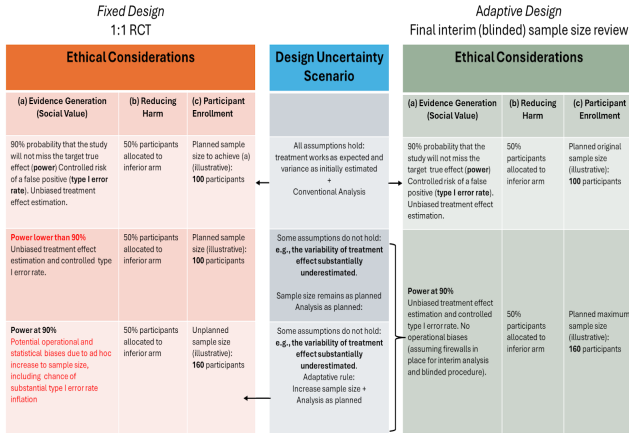


Figure: Conceptual comparison of FD vs. SSR under design uncertainty. Impact on social value, participant harm, and resource stewardship.

What we found useful to assess merits of different statistical designs for a given context is:

1. **Foregrounding Ethics:** Proactively centering trial designs comparisons on those three ethical objectives.
2. **Actively considering Design Uncertainty:** Explicitly evaluating the impact of design uncertainty on the ability of both fixed and adaptive elements to meet these goals.
Enable a more explicit, rigorous evaluation of adaptive designs.
3. **Path to Adoption:** Facilitate the adoption of adaptive methodologies (where feasible) when they may demonstrably promote ethical objectives through operational safeguards.

The Ethical Roadmap to randomisation

- **Scientific Integrity**

- ▶ Randomization is the "bridge" to valid inference.
- ▶ Choosing a procedure that risks selection bias or type I error inflation is an ethical negative, as it devalues the evidence.
- ▶ **High Predictability Risk?** Prioritize procedures with maximum randomness.
- ▶ **Time-Varying Effects?** Prioritize tight balance/stratification to ensure fairness across the recruitment window.

- **Operational Ethics & Resource Management**

- ▶ Balance methodological "purity" with practical implementability.
- ▶ Resource-heavy designs must be justified by a clear increase in the reliability of the evidence.









- **Conclusion:** Randomization is a strategic choice that dictates the quality of evidence produced. By using the 'Roadmap' to align procedure choice with statistical goals, we ensure the trial generates robust, unassailable evidence of high social value.

The end!

Thank you for your attention!

Any questions?

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