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Evidence and Ethical Dilemmas in Clinical Research: Assessing Stopping Rules for Clinical Trials

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Abstract

In this work, we address some ethical issues that emerge from stopping early a medical trial, in particular a randomized controlled trial (RCT). A clinical trial may be stopped after an interim data analysis for one of three reasons: Harm, Efficiency, or Futility. In particular, when committees make decisions about decide to adopt a policy to stop a trial defining (in some sense) the "early detection" of "harm" or "efficiency", the ethical dilemma that researchers face is how to weight the potential costs/benefits of stopping the trial early for the participants versus the challenge of gathering "scientifically valid" evidence for the benefit of the larger community. A complicating factor when arriving at a decision is that the standard of evidence needed to make sense of "early detection" is incompatible with the standard of absolute evidence (geared to establish scientific validity/invalidity). Since a commonly held theoretical standpoint from which a "best practice" can be defined⬜⬜namely, evidence-based medicine (EBM)⬜⬜only recognizes one standard of evidence, "absolute evidence", there is no commonly held theoretical framework that Data Monitoring Committees (DMC) could use to adequately addresses the ethical concerns that arise when they consider if they should stop a trial early. In short, although RCTs are frequently stopped in part as a response to the data collected during an interim analysis and in light of some ethical norms, there is no consensus on whether the type of evidence gathered during this analysis is adequate to make an evidence-based decision (Bassler [2011]). As such, the ethical norms applied during the cost/benefits analysis can be unsuitably vague since the concept of evidence and the methods used to determined "early detection" of harm or efficiency is "not well-established or fully understood" (Chow [2008]). A decision framework that can be applied to guide the ethical decisions of DMCs requires a concept of *evidence* that can move between the standards invoked both in "early detection" and contexts that can establish "scientific validity", so the costs and benefits to society and the participants can be addressed. It is only from this point of view that it becomes possible to

address adequately the complex ethical issues that arise distinctly when an experiment is stopped for potential harm or for potential benefit.

In this work, we address these ethical issues. First, we develop a framework in which these ethical issues *can* emerge by articulating a gradualist conception of evidence according to which data collected in the initial stages of an RCT offer *partial* evidence (although not full evidence) for or against the hypothesis under test. As a result, as opposed to what happens with absolutist conceptions of evidence, researchers do face an ethical dilemma when the partial evidence they gather in the initial stages of a trial seems to support strongly their hypothesis (or its negation). This new theoretical stance is more consistent with the decisions reached by actual DMC (Bassler [2010]; Goodman [2007]) than the decisions that we would expect to find if we only considered the absolutist conception of evidence.

We then apply the resulting framework to a variety of RCTs, examining several factors that make the resulting ethical dilemmas more (or less) pressing, namely: (1) the severity of the results obtained in the initial stages of the trial (the degree of expected bias associated with the statistical method used); (2) the size of the trial (the number of people involved in the experimental and in the control groups); (3) the nature of the medical condition involved (the current prognosis for the condition); (4) the availability (if any) and evidence for of alternative treatments, and (5) the potential benefit of the information gathered from a completed trial to the general community. Depending on these factors, different stopping principles will be appropriate, and more or less pressing ethical dilemmas will emerge in each case. We conclude the project by showing how the proposed framework can be put to work by investigating several RCTs that were stopped early in the past. In particular, we indicate which kind of assessment the framework provides of these trials (the nature of the ethical dilemmas that emerged in each case, and the overall assessment of the decision to stop the trial early). This will offer a test of the proposed framework. We will then consider current RCTs in which an early stop is being entertained, and we will discuss how *they* are assessed in light of the proposed framework. This will indicate the strength of the framework to offer some prospective guidance for assessing stopping rules for clinical trials.

 In terms of *deliverables*, we propose to write two papers on the ethical issues that emerge from stopping rules in clinical research: (a) The first paper will develop the gradualist conception of evidence, and show how this concept can be used to explain the ethical dilemmas in clinical research at the intersection of ethics and epistemology; (b) The second paper will show how the gradualist conception can be applied to significant RCTs that were stopped early in the past, and the sort of assessment the conception offers of the resulting ethical dilemmas. This paper will also apply the gradualist conception to current RCTs in which an early stop is being considered, and will indicate the prospects of the gradualist conception to guide the assessment of current ethical dilemmas in clinical research. The papers will be submitted for 2 publication in major refereed journals (such as *Philosophy of Science*, *British Journal for Philosophy of Science*, or *Studies in History and Philosophy of Biological and Biomedical Sciences*).