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Considerations for Stopping a Clinical Trial Early

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High quality clinical trials are key to progress in medicine. Clinical trials provide evidence to facilitate patient treatment recommendations by healthcare providers who would otherwise depend solely on experience that could be biased and misleading. Given the importance of clinical trial results, it is critical to ensure that trials yield interpretable results while preserving the safety of study subjects. A recent national multicenter clinical trial for the management of hypertension[1] that began in 2009 was stopped early in 2015 because of benefit and raised awareness of the ethical and safety issues of stopping clinical trials early for benefit. The early-stopping rule has the potential to minimize harm and to maximize benefit for the patients enrolled in a randomized trial. Stopping a clinical trial early because of evidence of benefit has been widely debated in the literature.[2-6]

The Systolic Blood Pressure Intervention Trial (SPRINT) was a randomized, multicenter clinical trial to determine whether maintaining blood pressure levels lower than current recommendations further reduces the risk of cardiovascular disease, chronic kidney disease, dementia, and age-associated cognitive decline. SPRINT enrolled 9,361 participants age 50 years or older with systolic blood pressure (SBP) $\geq$130 mmHg. Participants were randomized to an SBP goal of $<$120 mmHg (intensive treatment group) or $<$140 mmHg (standard treatment group).[1] In August 2015, the National Heart, Lung, and Blood Institute accepted the recommendation of the Data Monitoring Committee (DMC) to stop the trial early because of the lower rate of cardiovascular outcomes and total mortality in the intensive arm of the trial.

Multiple other clinical trials have been stopped early for benefit, including the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA)[7] and the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF).[8] Statistical stopping rules for clinical trials and the statistical science on which they are based have an extensive literature.[9,10] These stopping rules are typically implemented by the DMC of the trial.

Ethically, clinical trials must sometimes be stopped early when the results show no justification for exposing human subjects to additional potential risk by continuing the trial. The 3 ethics scenarios are based on safety, benefit, and futility concerns.

1. **Safety**: The risks to human subjects unexpectedly outweigh the benefits because of unexpected severe adverse events. When the institutional review board (IRB) approves a trial, it has determined that it meets US Food and Drug Administration (FDA) criteria for IRB approval at 21 CFR 56.111. Section (a)(2) states: ''Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.''[11] This determination changes when a study unexpectedly causes serious illness or death in human subjects. The study may then be suspended by the FDA, the sponsor, and/or the IRB until the risk-benefit ratio is reevaluated. An example is drug manufacturer Bial's phase 1 clinical trial in healthy volunteers.[12]
2. **Benefit:** The study hypothesis is unexpectedly proven early within predesignated criteria. Continuing to expose subjects in the inferior arm to additional potential risks or keeping them from benefitting from the therapies in the superior arm is hard to justify ethically. An example is the SPRINT study discussed above.
3. **Futility**: The study hypothesis is unexpectedly shown to be unprovable within the constraints of the trial based on a statistical analysis of early study data, usually done at a planned interim analysis. In such cases, there is no benefit to balance against subjecting subjects to potential risks. An example is the cessation of the Verastem VX-6063 phase 2 clinical trial.[13]

Apart from the ethical issues involved in discontinuing a trial early, a number of pros and cons must be considered. An important advantage to discontinuing a trial early for benefit lies in the ability to translate study findings into the clinical arena more rapidly and thereby benefit patients. Additionally, the longer a trial lasts, the greater the risk for retention issues with patients dropping out of the study and for disrupting the study's statistical ability to answer the scientific question. Finally, clinical trials are expensive enterprises. The ability to end a trial early may result in significant cost savings, an important consideration in an era when research funds are quite scarce.

Disadvantages also exist with early discontinuation of a trial. When the DMC finds a significant difference favoring one arm over the other based on a primary endpoint, the trial could be discontinued prior to answering the questions about secondary endpoints. However, although a trial may end early with discontinuation of the intervention, ongoing collection of secondary endpoints can still be done. In SPRINT, an important secondary endpoint was the effect of the intensive vs standard-of-care SBP targets on prevention

of cognitive decline in the elderly. Although the SPRINT intervention was discontinued, the study teams are continuing to collect data on cognitive function from the individuals who agreed to continue to be part of the trial to answer this secondary endpoint. If enough subjects continue to stay engaged for the additional testing and data collection, it is possible that even though the study ended early, data for analysis of this secondary endpoint will be adequate. Additionally, early discontinuation of a trial may overestimate treatment effects at the earlier time point and decrease the ability to detect long-term advantages and disadvantages of the intervention, particularly if the intervention is intended to be a lifelong therapy. Finally, early discontinuation of a trial may decrease the precision of results with fewer data points.

The decision to stop a clinical trial early for benefit is grounded in ethical principles. However, there must be a careful balance between ensuring the integrity of the trial and the accuracy of the study results vs preventing harm in patients randomized to an inferior treatment and the rapid dissemination of the evidence of treatment benefit to the broader medical community.[14] Although DMCs are responsible for implementing predefined rules for stopping a trial early, the responsibility to ensure that the stopping rules are in line with the goals of the study lies "with clinical investigators and statisticians involved in trial design—to protect patients against undue toxicity, to offer patients superior treatment once benefit is proven, and to ensure that the study will yield interpretable data for future generations of patients. Early stopping rules that do not capture each of these important elements may serve to undermine the clinical trial effort."[15]

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