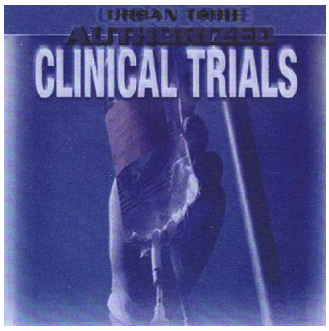
ICU
MANAGEMENT & PRACTICE

Adaptive Clinical Trials - the Ethical View



Adaptive clinical trials (ACTs) represent an innovative approach to trial design and conduct, where the primary goal of adaptations is to improve scientific value and statistical efficiency. In addition to having distinguishing scientific features, ACTs also may involve ethical considerations that differ from more traditional randomised controlled trials (RCTs).

A recent study, published in *BMC Medical Ethics*, aimed to elucidate the opinions of clinical trial experts regarding their beliefs about ethical aspects of ACTs. The clinical trial experts recognised potential ethical benefits of ACTs, including a higher probability of receiving an effective intervention for participants, optimising resource utilisation, and accelerating treatment discovery. At the same time, they posed potential challenges of adaptive trials, including the lack of equipoise that develops as the trial goes on and the inherent injustice that later enrolling subjects will get better treatments than earlier enrolling subjects.

"Collectively, the clinical trial experts participating in this study identified many of the ethically advantageous and potentially challenging aspects of ACTs that are already well known to specialists in this type of trial design," the authors write in the BMC journal report. "However, at an individual level, perspectives on the ethical advantages and disadvantages of ACTs varied considerably."

The findings suggest further discussion about the ethics of ACTs is needed to facilitate ACT planning, design and conduct, and ultimately better allow planners to weigh ethical implications of competing trial designs, the authors conclude.

Methodology

Researchers used a convergent, mixed-methods design employing a 22-item ACTs beliefs survey with visual analogue scales (VAS) and open-ended questions and mini-focus groups. They developed a coding scheme to conduct thematic searches of textual data, depicted responses to visual analogue scales on box-plot diagrams, and integrated findings thematically.

Fifty-three clinical trial experts from four constituent groups participated: academic biostatisticians (5); consultant biostatisticians (6); academic clinicians (22); and other stakeholders including patient advocacy, National Institutes of Health, and U.S. Food and Drug Administration representatives (20). Participants were asked to consider ethical advantages and potential ethical disadvantages of ACT designs from the perspective of patients, researchers and society. Data were collected with self-administered surveys, either by paper or on the Web, by using VAS and free-text responses.

Results and Discussion

This is the first known empirical study of clinical trial experts' views on ethical issues in ACTs. The constituent groups agreed that ACTs, including response-adaptive randomisation and dropping futile arms, would have ethical advantages for patients. For example, the groups agreed that "killing bad drugs" sooner — that is, leveraging the strengths of ACTs to evaluate drugs that do not have potential and ending such trials early — provides ethical advantages.

The participant groups agreed that adaptations need to be prespecified, and that having a clear understanding of what is being changed or "adapted" is prerequisite for conducting a valid, and hence ethical, ACT.

However, they identified potential risks and hence potential ethical disadvantages of ACTs. For example, if information about the results of interim analyses were leaked or inferred by clinicians involved in recruiting potential participants, bias could be introduced if the clinician then chose to enrol or not enrol patients on the basis of the information being leaked.

While there were some similar patterns of agreement and disagreement, there was substantive intra-group and inter-group variation. Given that all stakeholders — clinicians, biostatisticians, and others — must work together, understanding the anchor points and values of these groups relative to the potential ethical advantages and disadvantages of ACTS is important for the collaborative efforts needed to make these trials a reality.

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