Ki Learning Session:
Highly Efficient Clinical Trials (HECT)

Designing Highly Efficient Clinical Trials at High Speed To Save Lives, at Reduced Costs

Problem

Randomized clinical trials (RCTs) are the gold standard for establishing the safety and efficacy of health interventions. However, they can be expensive and time-consuming—and the results can be hard to generalize.

In global health, investigators face an additional challenge: there tends to be important uncertainty about the disease and the setting being investigated and the likely implementation of interventions. As a result, it is often difficult to optimize RCT designs in the planning stage before patients are enrolled to the trial. Most trials in the global health arena have been poorly planned or insufficiently conducted to make strong inferences. Often, during the course of a trial, information may come to light that suggests that the trial could be less expensive, shorter, or otherwise different and better than originally planned. However, since most RCTs hold their designs fixed, investigators are stuck spending more and waiting longer for results that will be less helpful than they could be.

Better planning of clinical trials is imperative to achieve answers quickly that can save lives and avoid wasted resources. Planning should occur prior to trial initiation, yet can change with emerging evidence. This requires a strategic shift in planning, implementation, and interpretation of trials. There is a need for education of trialists, funders, and users of trial findings to better understand new approaches to clinical trials. Our proposal represents a radical departure from traditional RCTs in global health.

Solution

A solution to this is combining approaches used within the pharmaceutical fields, harnessing newer computational approaches, and involving end users in the design of trials. We refer to this as "Highly Efficient Clinical Trials."

HECT designs build in a process of (1) simulating different trial design options as a priority. These may include design options (eg. number of arms), intervention options (eg. dosing, comparators), populations, and outcomes; (2) Readiness to change by planning for potential adaptations within the trial according to emerging evidence from the internal data or from external sources; (3) Making thoughtful interim analyses; (4) evaluating the costs, human potential and saved resources when using the HECT approach, and (5) planning for the future.

Specific Approaches

1. Simulating scenarios relevant to the trial

Simulations are key to appropriate planning of trials. Computational simulations posit potential scenarios to choose the trial design, and internal factors. These include the overall optimal design (eg. two-arm vs multiple arm, cluster vs. individual, multi-arm vs factorial). It additionally may consider the dose or package of interventions worth considering, the duration of trial, outcomes to consider, specific populations, and cost per action.

2. Readiness to change

Readiness to change reflects modifying the trial design during the course of the trial based on emerging data. This added flexibility increases the likelihood of achieving a useful result while ensuring that such a result is achieved as quickly and cheaply as possible. This will frequently mean applying the paradigm of

adaptive clinical trial thinking, although does not mandate the use of adaptive trials. The adaptive thinking and focus reduces the number of patients exposed to risk, either by reducing the size of trials or by stopping failed trials early.

In the vast majority of cases, modifications to trial design are based on pre-determined statistical rules, to avoid the possibility of investigator bias or other arbitrary factors influencing the outcome of the RCT. Examples include:

- **SAMPLE SIZE RE-ESTIMATION:** It is common to see, in hindsight, that investigators either under- or overestimated sample sizes required for their RCT. Using sample size re-estimation, investigators can correct these errors midway through the trial. In under-enrolled trials, the sample size target may be increased to ensure that the trial is adequately powered. In over-enrolled trials, it is possible to reduce the size, thereby saving money and exposing fewer patients to risk.

- **SEAMLESS DESIGNS:** Typically, trials are done in phases, with a delay between phases. Trials with seamless designs, on the other hand, can save time by allowing for immediate continuation from one phase to the next. For example, a seamless phase II/III trial of 9-valent HPV vaccine tested three dosages in phase II (low, medium, and high) to select the dosage to be tested in a phase III trial against the standard-of-care 4-valent HPV vaccine. The seamless design substantially shortened the amount of time to complete a conclusive phase III trial, as there was no delay between phase II and phase III.

- **RESPONSE ADAPTIVE RANDOMISATION:** At the beginning of a trial, there is genuine uncertainty about the benefits of the intervention being tested, clinical equipoise that provides ethical justification behind randomizing patients into placebo or other control groups. Over the course of the trial, however, this uncertainty decreases with accumulating data. Based on interim comparative effect estimates and their respective degree of statistical certainty, it is possible to adapt the allocation ratio and assign more patients to the favorable arms of the trial. Responsive adaptive randomization applied with sensible and robust statistical techniques can help maintain the integrity of the trial while ensuring that more patients are allocated to intervention arms that provide benefits.

- **ADAPTING TO EXTERNAL CHANGES:** For adaptive clinical trials, it is critical to pre-specify potential adaptations and their decision rules before starting the trial. However, it may occasionally be necessary to make post-protocol adaptations to the trial design due to external changes that occur. For example, in the case of recently published RCT in Kenya that investigated the effectiveness of text messages in supporting HIV patients undergoing treatment, there were considerable changes to Kenya's national HIV program including shift towards the test-and-treat-all policy that occurred during the trial. The retention rate (primary outcome) observed in the control group became considerably higher than expected (79%). Trial protocols, whether for conventional or adaptive trials, do not generally permit post-protocol adaptations; however, failing to adapt to such external changes also may result in failing to reflect real clinical practice. Post-protocol adaptations may well fall under the umbrella of global health adaptive trials.

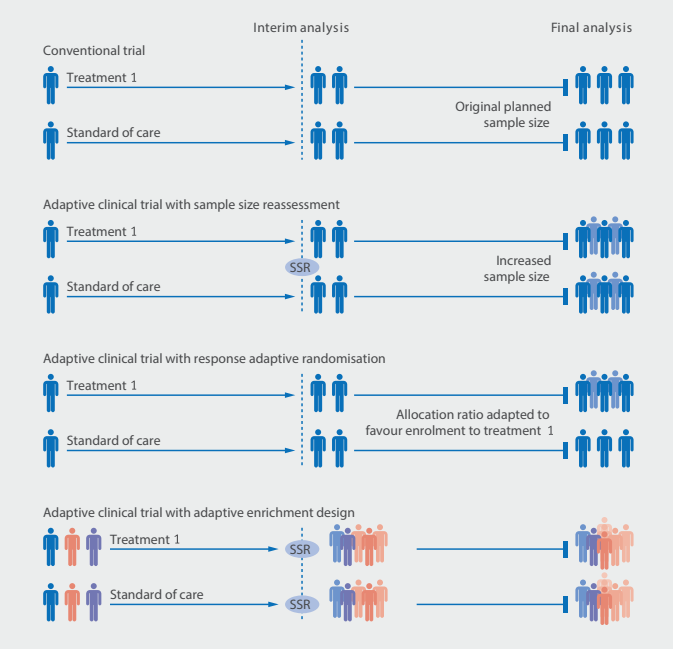

FIGURE 1. *Conventional and adaptive designs*

- **PLATFORM CLINICAL TRIALS:** In these dynamic multi-arm RCTs, individual treatments can be dropped and new treatments added during the trial. To test same number of treatments with conventional trial designs, it may be necessary to run several head-to-head trials separately, where a platform trial can test and compare all interventions, to each other and to placebo or standard of care. As a result, platform trial design can result in more highly efficient clinical trials while limiting the number of patients put at risk.

3. Making thoughtful interim analyses

Interim analysis refers to examining the data within a trial as it accumulates. An interim analysis may also occur due to external factors, such as awareness of intervention harms. However, usually this will occur utilizing statistical monitoring of the events occurring within the trial as listed above. While guidance exists for interpreting statistical findings from a trial, applying the findings in the context of the trial and foundation priorities is necessary to achieving rapid decisions.

4. Evaluating the costs, human potential and saved resources

Economic considerations are important for a trial to be initially funded and for any effective intervention to be rolled out. Economic considerations may include the costs associated with the direct running of a trial, such as the per-participant enrollment costs or intervention costs and whether sample size change or adaptations influence costs, through to whether an intervention can be meaningfully rolled out in the trial location or target settings. In particular, budget impact models relevant to both the trial conduct and the implementation scenarios are important.

5. Planning for the future

PERPETUAL CLINICAL TRIALS: By design and implementation, platform trials lend themselves well to long-term multi-intervention and multi-disease evaluations. This can create a framework where multiple questions can be perpetually addressed over time with a single trial, rather than conducting multiple clinical trials. Non-disruptive human resource utilization is critical in perpetual clinical trials. Instead of having to recruit experienced staff every time a new trial is initiated, perpetual clinical trials can help to maintain experienced staff while providing an opportunity to train junior staff; this can therefore facilitate an opportunity in building local capacity for clinical research in resource-limited settings. Perpetual clinical trials can also allow for long-term involvement of the community and discourse with its members on the planning of future clinical trials, so that further trust can be built over time from communities from which the patients are being recruited on an ongoing basis.

Next Steps

For global health research, there is enormous potential for HECT designs to improve clinical trial evaluations and enhance patient protection. The gains in efficiency may translate to a larger number of deaths and disability averted. HECT designs are more complex than conventional designs, but we believe the potential benefits outweigh the extra efforts that are required.

Resources

- Thorlund K, Haggstrom J, Park JJ, Mills EJ. Key design considerations for adaptive clinical trials: a primer for clinicians. BMJ 2018; 360: k698.
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- Saville BR, Berry SM. Efficiencies of platform clinical trials: A vision of the future. Clin Trials 2016; 13(3): 358-66.
- Bhatt DL, Mehta C. Adaptive Designs for Clinical Trials. N Engl J Med 2016; 375(1): 65-74.