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EVIDENCE FOR THE PEOPLE: FACILITATING COMMUNITY-BASED TRIALS

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Summary

Randomized clinical trials are essential for generating high-quality answers to pressing medical questions. Yet the vast majority of US patients have never been enrolled in a trial, the costs of conducting them continue to climb, and trials disproportionately enroll white and relatively healthy patients.* Community-based trials, which meet people "where they are," may help lower costs and generate more representative data. Federal institutions such as Food and Drug Administration (FDA), National Institutes of Health (NIH), and the Office for Human Research Protections (OHRP) have crucial roles to play in encouraging these by harmonizing with the Good Clinical Trials Collaborative's principles and simplifying consent forms.

> * While advanced cancer trials generally enroll patients that are very sick, other indications tend to enroll patients with less multimorbidity (eg, combinations of three or more common diseases) than one might expect.

Challenge and Opportunity

Clinical trials have a simple logic — randomization to either an experimental or control arm, and check what happens — but are complicated to carry out in practice. Over time, regulation and a desire by the biopharmaceutical industry to generate more data (such as through additional lab testing or measurements) have led to rising trial costs. Compared to standard medical care, carrying out a trial adds substantial administrative burden: training for investigators and sub-investigators; development of and approval of consent forms and protocols by institutional review boards (IRBs); and often a myriad of different software (a typical trial may have 20 different systems covering data collection, randomization, drug supply, pharmacovigilance, monitoring, and more); and failure to use data that is already being collected or reported for usual medical practice or reimbursement claims. In addition, trials face a substantial monitoring and auditing burden, estimated to account for 25-40% of trial costs. These inconveniences add up.

When trials span multiple sites, it becomes even more complicated, with multiple IRBs and hospital/clinic administrators becoming involved. This administrative burden has made conducting clinical trials difficult for healthcare settings without substantial expertise. Academic centers and hospitals like St. Jude's Children's Research Hospitals have experienced IRBs and administrators, can implement vague federal guidance without excessive caution, and attract the necessary research staff to conduct many high-quality trials; but the majority of patients are not served by such institutions.

Though the regulations and risk-aversion that led to this situation were well-intentioned, they can be substantially streamlined without harming participants. Health policy experts and senior regulators have recognized this for several years, with FDA Comm. Califf[1] and Principal Deputy Commissioner Woodcock[2] both writing publicly about them.

There are rigorous and cost-effective clinical trials that can serve as guideposts. RECOVERY[3] (Randomised Evaluation of COVID-19 Therapy) is a UK-based trial, begun in March 2020, that tested 18 different treatments for COVID-19 on 49,000 patients across 186 hospitals and found four effective therapies, at a cost of roughly $500 per patient. This is almost 80x cheaper than cost estimates of pivotal trials of new therapeutics[4], which are around $41k per patient. This was not the result of a cost advantage of repurposing old drugs: RECOVERY tested generic drugs (dexamethasone, hydroxychloroquine); repurposed drugs (tocilizumab, baricitinib); and novel unlicensed drugs (monoclonal antibodies). In addition, these were tested across "high-risk" populations that are normally difficult for trials to reach: pregnant women, neonates, the very elderly, and the immunosuppressed.

What are the lessons of the RECOVERY trial?

- Define the key study question(s) and focus on those things that are critical to answering the question reliably.
- Integrate the trial into the clinical care pathway: Minimize the additional burden for front-line clinical staff and for participants (anyone can design a trial that nobody can do; the trick is to design a trial that anyone can do).
- Take advantage of information that is already being collected as part of routine healthcare and where possible, make use of linkage to routine healthcare data (e.g. claims data, national death registry) to minimize loss-to-follow-up even when participants leave hospital or move to another medic.

RECOVERY was not exclusive to the UK National Health Service (NHS) — over 1,500 participants were enrolled in Asia and Africa, with Nepal contributing nearly 1,000 patients — proving it is not necessary to have a single-payer system like the NHS to make such trials successful.

Getting there in the American context requires regulators and funders to clear the way and lead by example.

1 https://jamanetwork.com/journals/jama/article-abstract/2819603

2 https://www.nejm.org/doi/full/10.1056/NEJMp2107331

3 https://www.recoverytrial.net/

4 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7295430/

Plan of Action

Recommendation One: The RECOVERY trial followed the principles articulated in the Good Clinical Trials Collaborative[5] (and which were adopted by WHO Best Practices for Clinical Trial). These guidelines were widely co-developed, are applicable to the broad range of interventions that may be studied (not just drugs and vaccines), and can be applied as new innovations and ways of doing trials emerge: they are not fixated on the operational details of today's world.

An important advantage of these guidelines is the attention paid to the oft-overlooked downside of administrative burden. Representative sections are reproduced below:

- *RCTs should not be wasteful of staff and participants' time, use of interventional or other medical supplies, energy, or environmental resources. Where there are strengths and safeguards in routine systems, these should not be duplicated or altered without careful justification.*
- *Rational monitoring focuses on the issues that will make a material difference to the participants in the trial and the reliability of the results (e.g. trial recruitment, adherence to allocated intervention, blinding, and completeness of follow-up). It informs corrective actions, supports staff, and enables improvements. It is important not to confuse more documentation for better quality. Example approaches that may be used include central review (including statistical analysis) of trial data and performance metrics to assess performance of staff and sites, in– person or virtual support and mentoring for trial staff (e.g. through observation of study visits, with participant consent), and visits to clinical trial sites and facilities.*
- *Regulatory, auditing or inspection requirements should be proportionate and sensitive to the scientific and ethical qualities and objectives of a RCT. They should recognize the opportunity-cost of, and avoid, setting irrelevant or disproportionate requirements that might discourage the conduct or participation in good RCTs that are designed to address important questions.*

US regulators and funders should adopt these principles. Specifically:

- FDA should harmonize its Good Clinical Practice (GCP) regulations with these principles.
- As a condition of funding, NIH should require studies to follow these principles.
- The Office of Human Research Protections (OHRP) should undertake a revision of the Common Rule (which governs the conduct of IRBs) to harmonize it with these principles.

Recommendation Two: Regulators and funders need to radically simplify consent. The aim of the consent process is to allow potential participants to make an informed decision about participating in a trial. In practice, institutions attempt to use consent forms to shield themselves from legal liability, resulting in longer[6], less readable documents. For example, a study[7] of the consent documents used in four COVID-19 Phase III RCTs found that they averaged 8,000 words in length, exceeded the recommended reading level, and obscured key information (and took more than half an hour to read). The UK has managed to improve its consent process through providing online guidance[8] to researchers and ethics committees. US regulators and funders could consider the following options:

- NIH, OHRP, and FDA should develop rules that set strict limits on word count and readability for consent forms, with the ultimate goal of producing comprehensible, short, and prioritized consent forms for potential participants. HHS has recommended readability levels (below sixth-grade reading level) already, but these recommendations do not appear to have regulatory power.
- To minimize the burden on federal regulators, they could consider adopting, in part or in whole, the UK's Health Research Authority's general principles[9].
- As a condition of funding, any federally funded studies, or studies submitted to the FDA, would be required to comply with the resulting regulations. Non-compliance with these regulations would be considered violations of participants' informed consent, since long and unreadable consent forms do not fulfill the intended purpose of human subject protection.

5 https://www.goodtrials.org/

6 https://www.jstor.org/stable/25703699

7 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8082317/#zoi210320r2

8 https://www.hra-decisiontools.org.uk/consent/index.html

9 https://www.hra-decisiontools.org.uk/consent/principles-general.html

Conclusion

Harmonizing US regulations with the principles of the Good Clinical Trial Collaborative and simplifying consent will reduce trial barriers and make trial populations more representative of average Americans. While high-level regulators have repeatedly signaled their interest in community-based trials, the actual regulations on trials have not appreciably eased. Taking concrete steps to do so is a common-sense approach to democratizing trials for all.

About the Author

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