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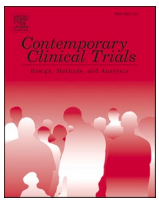

Preface to theme issue on pragmatic and virtual trials: Progress and challenges

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The clinical research enterprise holds the potential to generate the needed evidence to improve public health, yet it is vastly underperforming. Clinical research is being outpaced by advances in understanding of the biology of health and underlying pathophysiology of disease. Major advances integrating genomics, biotechnology, computational biology and large-scale population-based studies with deep molecular and imaging data increase the breadth and depth of our understanding of health and disease and generate multiple potential biological targets [1,2]. Likewise, health care systems are accumulating data in an unprecedented pace, which could lend insights into individual and population-based risk for poor health outcomes. However, our clinical research system is not keeping up with the rest of science.

We aspire to a learning health care system where data can be turned into knowledge regarding the best treatments or strategies of care to improve health for all [3,4]. Instead, we have a sluggish system that is inadequate for solving important healthcare problems, even in the face of declining life expectancy in the United States (US) [5]. While the COVID-19 pandemic has recently contributed to the decline, life expectancy has been declining for a decade due to drug overdoses, worsening cardiovascular disease, and other chronic health conditions [6]. Even the age-standardized rate of cardiovascular disease, which had been declining in high income countries, has been steadily rising [7]. These failings articulate an urgent need to implement cost-effective evidence generation systems, policies, and best practices. More evidence, generated through clinical trials, could help achieve substantial improvements in population health.

However, the barriers for conducting clinical trials in the US are many; they include high financial costs, long duration, administrative complexity, low recruitment and retention of participants, and a large disparity between what we learn from clinical research and translation of this knowledge to actual medical care. The differing cultures of different stakeholders including academic centers, industry, and government agencies create additional challenges. Over the last decade, many have enumerated the increasing costs of clinical trials with resultant renewed interests in simplifying the conduct of clinical trials or developing new methods for evidence generation [8,9]. Yet, despite these reports and national attention, the cost of trials is still too high due to the inefficiencies and complexities of trials [10,11]. Previous solutions recommended greater use of electronic health records (EHR), looser trial enrollment restrictions, simplified clinical trial protocols, reduced source data verification, wider use of mobile technologies, use of lower cost-facilities or at-home procedures, and improvements in the overall review processes. While progress has been made on some of these fronts, there remains much to do. The pandemic accelerated interests in the development of rapid cycle, innovative trials [12–14], which have served as proof-of-concept for improving the clinical trial ecosystem. However, it will take much effort to expand this progress beyond the pandemic environment and reduce barriers to enable fast, efficient, cost-effective clinical research to address the major public health problems that burden society.

In this thematic issue of *Contemporary Clinical Trials* on Pragmatic and Virtual Trials, we have brought together leaders who are rethinking clinical trials covering key aspects of the development, conduct, and oversight of clinical trials. The articles include practical approaches and real-world experience on how clinical trials can be done better while maintaining high-quality results with digital technology, direct-to-participant methods, and electronic health records. However, the decentralized approaches involved in many pragmatic and virtual trails have their own challenges, including retention of participants and fidelity to interventions [15,16]. There are also outstanding ethical issues and dilemmas that need to be considered, especially because greater access to data that includes details regarding personal health, economic status, and social determinants of health raises important privacy and ethical considerations that researchers should consider and that patients should understand. The balance of societal benefit versus individual protections on privacy or decisions is critically important, particularly in an era in which trust in science is at a critical juncture. The articles in this issue are designed to recognize the advances in evidence generation

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while sharing the challenges and gaps that still need to be addressed. Ultimately, the clinical research ecosystem must improve, not only to keep pace with the advances in basic or translational science, but to improve population health in meaningful ways such that life expectancy and quality of life can improve.

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