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Perspective

Improving Clinical Trial Enrollment — In the Covid-19 Era and Beyond

Crystal M. North, M.D., M.P.H., Michael L. Dougan, M.D., Ph.D., and Chana A. Sacks, M.D., M.P.H.

More than 3 million people in the United States are known to have been infected with SARS-CoV-2.[1] If every study registered on clinicaltrials.gov as of mid-June meets its target enrollment, less than 4% of those diagnosed with Covid-19 will have been enrolled in a randomized, controlled trial. In the face of a new disease in dire need of proven treatments, every patient not offered enrollment in a well-designed, well-conducted study represents a missed opportunity to advance scientific knowledge, develop therapeutic strategies, and ultimately improve care for everyone who will come next.

Evaluating the many unknowns inherent in a novel infection emerging on this scale requires a broad national (and international) trial infrastructure. Without it, clinical gestalt and idiosyncratic practice variation become the foundation for so-called standards of care. In Covid-19, this approach has led to the widespread, off-trial, off-label use of medications — from hydroxychloroquine to statins to tocilizumab, among many others — that may have a plausible scientific rationale but have no demonstrated benefit in this disease.[2,3] Instead of answering questions systematically by enrolling the smallest number of participants required to power definitive trials, such practice patterns expose thousands of patients to the potential risks of untested interventions with no reliable way of drawing conclusions about efficacy and safety.

The formidable barriers to designing, implementing, and completing clinical trials, especially in the midst of a pandemic, are clear. Well-conducted studies require resources — dollars, trained investigators, research staff, and oversight teams — at the same time that hospitals throughout the country have redeployed every available asset to increase clinical capacity for patient care. Developing trial protocols, recruiting collaborators, securing funding, obtaining regulatory approval, and launching a randomized trial usually takes a year or more. In this pandemic, the critical volume of patients compressed that time frame, in some cases to a matter of weeks. With hundreds of proposed interventions, medical centers faced choices about how to prioritize potential trials.

To meet these challenges, our hospital, Massachusetts General Hospital, established a centralized scientific review committee, in addition to the ethical oversight of the institutional review board, to determine the portfolio of Covid-19–related trials that would be launched and to continuously

evaluate newly proposed studies. This committee based decisions on scientific priority (How important and answerable is this research question?), the number of participating sites (Will this be a multisite trial that would be able to continue enrolling if case numbers fell here?), and logistic considerations (How much scarce personal protective equipment will be required to complete the study?). Such a process ensures that selected trials are diverse in approach, targeted at multiple viral and host pathways, and structured to maximize the chance that the research question will be definitively answered.

Centralizing key elements shared among trials is an important mechanism for overcoming resource constraints and preventing prioritization of the best-funded trial over those with the greatest potential impact. For example, rather than requiring each study team to provide personnel to draw blood for laboratory tests, administer study drugs, and organize data entry, a core group coordinated these procedures across trials. Especially in the context of a disease that is disproportionately affecting vulnerable communities, centrally committing resources to have the ability to obtain informed consent in every needed language is critical to ensuring access and inclusion for patients with limited English proficiency.

Having eight or more trials seeking to enroll patients on a given day crystallizes the logistic challenges of simultaneously conducting studies that broadly target the same patient population. Without a coordinated central effort, the default would be to have study teams each create their own independent processes for identifying and approaching patients. Such a system would advantage teams with the largest staffs that could identify and recruit patients at all hours of the day or night, and it could create confusion and chaos for patients, families, and care teams.

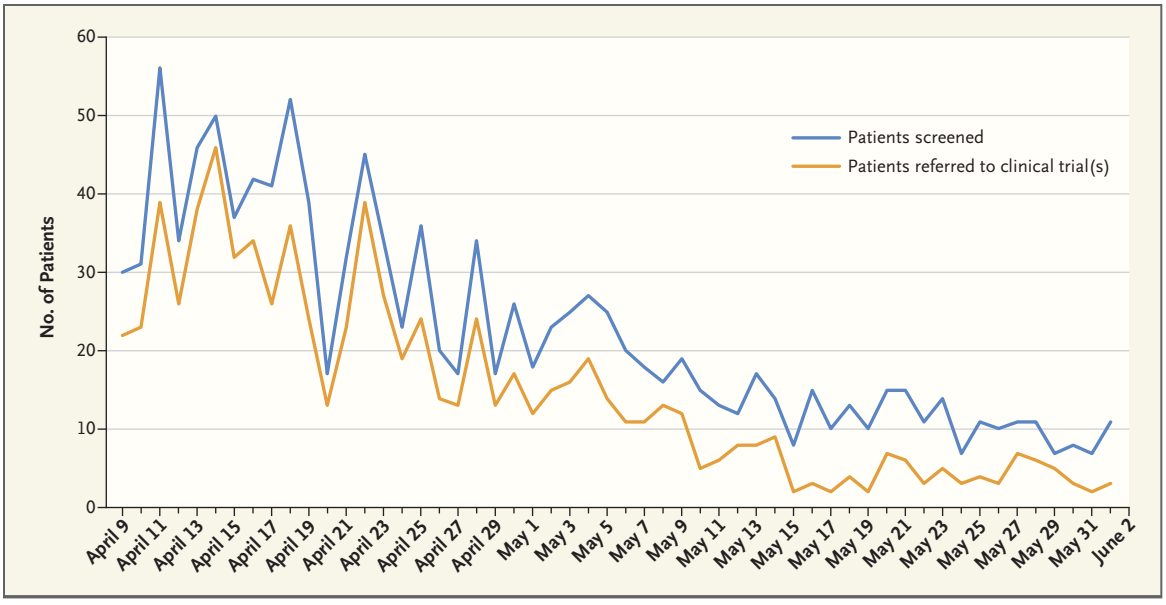
Alternatively, inpatient care teams could have the primary responsibility for referring their patients to specific trials. However, in addition to adding another task to busy clinicians' workflow, this approach could lead to referrals based on arbitrary factors such as which trial a particular clinician happened to have heard about — and it would risk missing eligible participants altogether. A rotating schedule could give each trial priority on a specific day of the week, but given the variation in daily admissions (Sunday mornings, we noticed, often had the fewest new admissions), this approach could introduce unpredictable, systematic bias into the selection process.

We therefore developed a process for centrally identifying and screening, according to each trial's inclusion and exclusion criteria, every patient newly admitted to the hospital or newly diagnosed with Covid-19, and for organizing the way they would be approached for enrollment. We also regularly rescreened all previously admitted patients to identify anyone who might newly meet eligibility criteria as their clinical syndrome evolved. Our process is similar to those implemented by other hospital systems[4] and was developed with the goal of offering access to clinical trials equitably to as many patients as possible.

As we continue to improve this approach, involving patients and families as central stakeholders is critical. Many questions require further work and rigorous evaluation: In a rapidly changing landscape with multiple potential trials, what is the right amount of information to provide to study participants that enhances rather than obfuscates informed consent? Does the physical separation forced by Covid-19 that prevents family members from being at the bedside affect patients' understanding of the risks and benefits of proposed interventions during the consent process? How does the intense media scrutiny of potential treatments for Covid-19 affect patients' interest in clinical trials? Improving our understanding of these — and many other — questions will be important as we work to further develop the infrastructure to support clinical trials.

So far, we have screened more than 1300 patients for 11 trials (the graph shows the number of patients screened and referred to clinical trials each day between April 9 and June 1, when our cases peaked and then declined). In total since the beginning of the pandemic, more than 350 patients have been enrolled, the majority of them after establishment of this centralized screening system. A rapidly evolving trial landscape has to build on new data as they emerge. For example, after it was announced that the remdesivir trial had met its primary end point,[5] all currently enrolling studies either had to allow patients to receive remdesivir or could approach patients only after they were evaluated for remdesivir as part of standard care under the emergency use authorization.

Local case numbers have come down, yet Covid-19 continues to surge around the country. How these trends will evolve remains to be seen, but some ebb and flow seems likely over the summer and



Number of Patients Screened at Massachusetts General Hospital for Covid-19 Clinical Trials, April 9 to June 1, 2020.

into the fall. As we move through this pandemic, three future directions are critical. First, we must maximize trial access and enrollment to answer the many open questions regarding the best possible care for patients with Covid-19. Second, we must improve national platforms to promote collaboration in clinical trials. A trial infrastructure fixed in a single location is inadequate for targeting a virus that is moving through geographic hot spots. Third, we should adapt this research infrastructure to answer questions beyond Covid-19. Every day in clinical practice, we apply so-called standards of care that are based not on good data but on expert opinion that is ripe for a challenge in the form of a randomized trial. A commitment to approaching such questions rigorously by sustaining a broad inpatient clinical trial network will improve the care we can provide to all patients — in the Covid era and beyond.

Identifying details have been changed to protect the patient's privacy.

Disclosure forms provided by the authors are available at NEJM.org.

From the Division of Pulmonary and Critical Care and the Medical Practice Evaluation Center (C.M.N.), the Division of Gastroenterology (M.L.D.), and the Division of General Internal Medicine and the Mongan Institute (C.A.S.), Department of Medicine, Massachusetts General Hospital; and Harvard Medical School (C.M.N., M.L.D., C.A.S.) — both in Boston.

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