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Bringing New Meaning to the Term "Adaptive Trial": Challenges of Conducting Clinical Research During the Coronavirus Disease 2019 Pandemic and Implications for Implementation Science

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Although implementation of evidence-based practices takes an average of 17 years, in the context of the global pandemic, coronavirus disease 2019 (COVID-19) interventions were adopted in a greatly compressed time frame. This rapid uptake creates major challenges for conducting COVID-19 clinical research studies, because quickly evolving standards make it difficult to adapt in real time. The rapid dissemination and implementation of COVID-19 interventions is the realization of goals long pursued by the implementation science community. However, the downside of the rapid implementation is that low-quality evidence with little to no scientific vetting may be quickly integrated into clinical care, resulting in lost opportunities to advance our scientific understanding about how to manage infected patients. In the future, novel adaptive designs embedded into electronic health records (Embedded Quantified, Integrated-into-Practice Trial [EQuIPT] designs) that allow for easier and better access to clinical trials may simultaneously improve care and advance healthcare innovations.

Keywords. adaptive clinical trials; COVID-19; diffusion of innovations; implementation science.

The delay from the time an intervention is demonstrated to improve clinical outcomes until it is implemented in routine care is typically 17 years [1]. In this background of slow change, pragmatic and adaptive clinical trial designs were developed to conduct treatment studies that would mimic real-world clinical practice and allow for study design changes [2, 3]. Adaptive trials come in all shapes and sizes; common adaptations include changing sample size, removing doses or medications that appear less effective, adaptive randomization schemes, targeting recruitment to specific groups, and changing stopping parameters [4]. Adaptive designs are attractive for clinical studies during the pandemic, because they allow for adjustments to be made as new knowledge is generated.

We are conducting one such pragmatic, adaptive clinical trial within the VISN-1 Clinical Trials Network (NCT04359901). The trial was initially designed as a 3-armed pragmatic trial, comparing interleukin (IL)-1 inhibition (anakinra) to IL-6 inhibition (tocilizumab) to standard of care alone. However, this design—which continues to be relevant—was quickly deemed infeasible as neither drug was available for purchase, and our institution's stock of medication could treat a total of 1 patient with anakinra and 6 patients with tocilizumab. Rapid dissemination and adoption of case-report level data had prompted widespread purchase of the drugs for treatment outside of a clinical trial setting, resulting in national shortages and supply chain barriers. We were able to purchase sarilumab, another IL-6 inhibitor, and so the study was adapted before it even began.

The ongoing trial is designed with a progressive play-the-winner approach, such that patients are increasingly likely to be randomized to the treatment arm that appears to be the most effective. The first 20 patients are randomized 1:1, with updates to the randomization probability weighting after prespecified checkpoints (every 10 patients). We chose this design to meet the need to gather high-quality evidence to guide future care, while recognizing that there were few proven treatment options and discomfort among clinicians and patients about not offering some therapy. We designed our trial with pragmatic features in mind: broad inclusion criteria, few exclusions, and an off-the-shelf medication (sarilumab) that was rapidly ruled to be exempt from a US Food and Drug Administration (FDA)

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Investigational New Drug (IND) application, because we were using it at its FDA-approved dose. We chose to administer the drug as a subcutaneous injection—in line with its labeling—for simplicity and with an eye toward early implementation and dissemination. Additional pragmatic features include use of open-label drug, embedding within the VA electronic health record (EHR), and expectation for standard of care to evolve. Based on prior experience and understanding about *Diffusion of Innovations* [5], we anticipated that this strategy would be flexible enough to accommodate the changing landscape of coronavirus disease 2019 (COVID-19) treatments.

However, despite our best intentions, several unanticipated challenges occurred, requiring more adaptation and pragmatism than is typical even for adaptive trials. A major challenge was that, in the desperation of the COVID-19 crisis, the processes of evidence review, followed by discussion and early adoption, then followed later by diffusion and dissemination, did not occur sequentially. Instead, unverified, unvetted, and unproven statements were disseminated on social media and in the popular press, prompting rapid action and adoption by frontline providers; based on these reports, key stakeholders integrated changes to institutional treatment guidelines rapidly, sometimes within hours. This was a major challenge for the conduct of our study; on April 27, Regeneron put out a press release stating that in its own study of sarilumab, the standard dose (200 mg) was no longer going to be studied, because an interim analysis indicated benefit primarily in intubated patients and only at a higher dose (400 mg) [6]. On the basis of this press release and another announcement about the efficacy of another IL-6R antibody, tocilizumab, at a high dose [7], we opted to increase our dose to 400 mg, although we maintained the subcutaneous administration.

Within 4 days, from April 27, 2020 to May 1, 2020, our study team put the trial on hold, amended the protocol,

and notified the Institutional Review Board (IRB) (all on April 27, 2020), reviewed suggested changes with our Data Monitoring Committee (DMC) (April 28, 2020), received approval from the DMC on May 1, 2020, and submitted the protocol to our IRB and to the FDA with a request for ongoing IND exemption on the same day. Our study was then on hold for a critical 27 days pending FDA determination, until we received notification of an exemption on May 29, 2020. Despite the initial rush to release findings, during the 66 days since the press releases were dispersed on social media, no peer-reviewed study has been published. Yet, this seemingly small change caused our study to temporarily close at a critical time in our state's pandemic: during the 32-day pause, the peak of the pandemic in Massachusetts fortunately passed. Before the adaptation, we were enrolling an average of 1 patient per day. Since the adaptation, we have enrolled zero.

Beyond dosing changes, we repeatedly adapted complicated and cumbersome informed consent processes to changing regulatory guidance, which led to repeated changes to the informed consent form and HIPAA (Health Insurance Portability and Accountability Act of 1996) authorization process. As data emerged about other systemic complications of COVID-19, including heart failure, clotting, and acute kidney injury, our secondary endpoints were expanded. We welcomed and solicited interest by regional VA facilities and rapidly adapted from a single center to a multicenter trial; although this greatly enhanced the potential for recruitment and minimized the bias associated with single-center studies, it complicated the operations and informatics of the embedded trial.

The theory of diffusion of innovations suggests that new practices are adopted and spread through the healthcare system in a predictable manner: first, the innovators, or risk takers, and then the first followers try the innovation [5]. Then, early adopters, generally opinion leaders in the field, begin to promote the concepts.

Their role in adopting change is critical, because of their position as leaders and stakeholders who can bring others on board. These groups are followed by the early majority, and then the late majority, who are skeptical of change but in time can be persuaded to join in the innovation. The "laggards," conservative and risk averse, are unlikely to ever buy into the innovation. Historically, this process of progressing through stages—from the innovators to the late majority—has taken an average of 2 decades. With COVID-19 as an accelerant, the process can take hours, for better and for worse.

So where do we go from here? Despite many attractive features of adaptive designs, barriers to enrolling patients—and ultimately progress—remain. Cumbersome recruitment, identification, and consenting processes are major barriers. Clinical trials, even in the setting of a pandemic disease without proven treatments, are enrolling primarily at large, academic medical centers with existing research infrastructure. This has 2 major consequences: first, access is limited to a small segment of the population; second, recent research demonstrates that even having a clinical trial open increases prescribing outside of the research setting [8]. Although unproven, we hypothesize that this phenomenon may be particularly strong for providers in institutions without evidence-based options for their patients and no access to a clinical trial.

To speed innovation and improve access, novel clinical trial designs that more closely link clinical care and clinical research are desperately needed. For approved medications with proven safety records and potential but unknown benefit, we propose Embedded Quantified, Integrated-into-Practice Trial (EQuIPT) designs. The EQuIPT design is an extension of the Learning Health System model [9], and an advancement in the concept of the pragmatic, adaptive clinical trial. For appropriate research questions, screening and identification would be integrated into the EHR. Such "embedding" would greatly reduce the research infrastructure

required onsite, reduce costs, and expand the number of sites eligible to participate. Adaptive randomization schemes would be used to maximize benefit to the largest number of patients. Innovative designs such as EQuIPT would have been appropriate for many of the interventions widely disseminated and implemented in an un-interpretable manner during the pandemic, such as hydroxychloroquine.

The pandemic presents challenges but also promises for improved translation of evidence-based interventions into bedside care. The rapid dissemination and implementation of findings generated during COVID-19 is the Holy Grail that the implementation science community has sought. In contrast, low-quality evidence with little to no scientific vetting has been rapidly integrated into clinical care, resulting in lost opportunity to collect data to guide rational decisions, and it is also raising concerns about harm, costs, and unintended consequences. The rapid implementation of COVID-19 treatment is the exception that proves the rule: although diffusion of innovations typically happens slowly and often incompletely, underlying evidence and risk aversion protect patients, providers, and ultimately the integrity of knowledge

acquisition to guide future decision making. The challenges of identifying effective therapies for COVID-19 underscore the upsides of this usually slow process, but it also demonstrates that rapid improvements to bedside clinical care are possible. It is possible that by using the lessons of the pandemic and leveraging technological advancements, the medical research community can identify a critical middle ground: EQuIPT designs.

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References

1. Green LW, Ottoson JM, García C, Hiatt RA. Diffusion theory and knowledge dissemination, utilization, and integration in public health. Annu Rev Public Health **2009**; 30:151–74.
2. Roland M, Torgerson DJ. What are pragmatic trials? BMJ **1998**; 316:285.
3. Lavori PW, Dawson R. Adaptive treatment strategies in chronic disease. Annu Rev Med **2008**; 59:443–53.
4. Pallmann P, Bedding AW, Choodari-Oskooei B, et al. Adaptive designs in clinical trials: why use them, and how to run and report them. BMC Med **2018**; 16:29.
5. Rogers E. Diffusion of Innovations. 5th ed. New York: Free Press; **2003**.
6. Regeneron and Sanofi Provide Update on U.S. Phase 2/3 Adaptive-Designed Trial of Kevzara® (sarilumab) in Hospitalized COVID-19 Patients [press release]. **2020**. Available at: https://investor.regeneron.com/news-releases/news-release-details/regeneron-and-sanofi-provide-update-us-phase-23-adaptive. Accessed 27 April 2020.
7. Tocilizumab improves significantly clinical outcomes of patients with moderate or severe COVID-19 pneumonia [press release]. **2020**. Available at: https://pipelinereview.com/index.php/2020042874458/Antibodies/Tocilizumab-improves-significantly-clinical-outcomes-of-patients-with-moderate-or-severe-COVID-19-pneumonia.html. Accessed 28 April 2020.
8. Butler-Laporte G, Cheng MP, Thirion DJ, et al. Clinical trials increase off-study drug use: a segmented time series analysis. In: Open Forum Infectious Diseases; **2020**.
9. Chambers DA, Feero WG, Khoury MJ. Convergence of implementation science, precision medicine, and the learning health care system: a new model for biomedical research. JAMA **2016**; 315:1941–2.