Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Cancer Cell

CellPress

Letter

Translating inspiration from COVID-19 vaccine trials to innovations in clinical cancer research

Noura J. Choudhury,[1] Gregory J. Riely,[1,2] Paul J. Sabbatini,[1,2] and Matthew D. Hellmann[1,2,*]
[1]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York City, NY 10065, USA
[2]Department of Medicine, Weill Cornell Medical College, New York City, NY 10065, USA
*Correspondence: hellmanm@mskcc.org
https://doi.org/10.1016/j.ccell.2021.05.001

The operational efficiencies which led to the rapid approval of effective vaccines for COVID-19 inspire lessons in innovation from which clinical cancer research may benefit. In this letter, we provide a framework for achieving this progress, including articulation of societal value of trial participation, maximizing design efficiency, and increasing transparency.

Clinical trials to evaluate approaches to treatment and prevention of COVID-19 showed the peaks and valleys of what clinical research can deliver for patients and society at large. At its peak, the development of multiple effective vaccines for SARS-CoV-2 in less than a year is one of the greatest achievements of modern clinical research. These successes were realized in part by the unprecedented scale and operational efficacy of the vaccine trials. In 3 months, nearly 74,000 volunteers were recruited for the Pfizer-BioNTech BNT162b2 and the Moderna mRNA-1273 vaccine trials (Baden et al., 2020; Polack et al., 2020); 44,000 additional volunteers were recruited for the Johnson & Johnson Ad26.COV2.S vaccine trial in 3 months (Sadoff et al., 2021). The RECOVERY trial, one of the most notable therapeutic trials for COVID-19, randomized 11,000 patients in 3 months, using an efficient platform design to deliver conclusive findings for multiple COVID-19 treatments (RECOVERY Collaborative Group, 2020). These remarkable operational and scientific successes stand in contrast to the many valleys of underpowered, observational, and duplicative COVID-19-related trials, which were unlikely at inception to produce meaningful or conclusive results (Bugin and Woodcock, 2021).

Inspiration from the extraordinary vaccine and RECOVERY trials—in scale, pace, generalizability, interpretability—punctuating an otherwise chaotic landscape of COVID-19 clinical research highlights lessons in potential innovations for cancer clinical trials. In many ways, the spectrum of COVID-19-related research, featuring both exceptional breakthroughs as well as well-intentioned but uncoordinated efforts, mirrors the current state of clinical cancer research. This status of research may be more understandable for COVID-19 in the context of an unprecedented global crisis; the circumstances in oncology, however, are long-standing. Despite >600,000 deaths each year in the United States from cancer, therapeutic trials often carry an inherent expectation that results will take years to achieve, burdened in part by the relatively slow pace of accruals and complex protocols that are expensive and laborious to execute. Seeking lessons from the RECOVERY and SARS-CoV-2 vaccine trials, we propose a framework (Figure S1) for accelerating progress in cancer clinical research.

Articulate and deliver societal value

There is substantial room for improvement in the scale of patient participation in cancer clinical research. In relative terms, only 2%–8% of adults with cancer participate in clinical trials (Unger et al., 2019). As one measure of the absolute scale, a total of 35,000 patients with cancer participated in clinical trials that led to new U.S. Food & Drug Administration approvals for oncology indications between 2015 and 2019 (U.S. Food & Drug Administration, 2021). In contrast, the rapid accrual of volunteers for COVID-19 vaccine trials in just a few months suggests that broad participation in clinical research is possible when the context, necessity, and potential value are effectively communicated. For many, COVID-19 engendered a deep sense of shared responsibility and recognition that progress was predicated upon completion of randomized clinical trials. As an emotionally weighted diagnosis, cancer similarly inspires altruism and action, yielding tremendous fundraising for cancer research and advocacy campaigns for early detection and awareness. Clinical cancer research would still benefit from public-facing articulation of the societal value for trial participation as a critical and necessary engine of progress. Of course, such messaging is dependent upon actual delivery of societal value, which can be achieved through developing novel therapies as well as rapidly completing studies of derivative interventions that provide clear conclusions.

The RECOVERY trial—which demonstrated the benefit of steroids in hospitalized patients with severe COVID-19 relatively early in the pandemic—is a real-world case study of these principles and opportunities. In the UK, public officials reiterated to hospitals nationwide that enrollment in RECOVERY was the standard of care for hospitalized patients with COVID-19 (https://www.nytimes.com/2020/09/01/opinion/coronavirus-clinical-research.html); the delivery of rapid and conclusive results reinforced public trust in those efforts. Clinical cancer researchers, through partnerships with government and advocacy groups, can similarly prioritize opportunities to articulate—and deliver—the value of clinical research.

Efficient trial design and lowering barriers to entry

To augment recruitment, clinical investigators and industry and regulatory stakeholders can also fundamentally change how we conduct cancer trials. Cancer trial

protocols are often operationally complex, and many target arbitrarily specific patient populations that can delay completion and limit generalizability of results to routine settings. We should design trials to be simpler to execute and more likely to transfer the degree of impact to standard care. Minimizing non-crucial eligibility criteria and protocol assessments, especially in later phases of development, will expand the pool of eligible patients (Liu et al., 2021) and help to dispel the myth that clinical research is appropriate for only very fit, well-resourced, or desperate patients. In COVID-19 vaccine trials, in-person study visits were minimal, with two in-person visits after each injection for the BNT162b2 trial (Polack et al., 2020), easing the burden of participation. By similarly minimizing the time commitment of trial participation, cancer trials could be completed more efficiently and simultaneously recruit a more diverse patient population.

The efforts of the phase 3 vaccine trials, which publicly committed to recruiting populations disproportionately impacted by severe COVID-19, suggest that focused efforts to lower barriers to entry and include representative patients may also improve the translatability of benefit to real-world settings. Moderna targeted clinical research sites more likely to recruit underrepresented populations and published weekly demographic statistics tracking this progress. While still not reflective of the US population, its phase 3 COVE study population was 10% Black, 20% Hispanic, and 25% patients age >65, exceeding the diversity often seen in cancer clinical trials (U.S. Food & Drug Administration, 2021). Perhaps in part as a result, early data have already demonstrated that mRNA vaccines perform in real-world settings with nearly the same efficacy as reported in the phase 3 trials (Dagan et al., 2021). In oncology, however, there is often substantial expectation of attrition of benefit observed in clinical trials when transferred to the real-world setting (Phillips et al., 2020). In addition to increased pace and efficiency, efforts to recruit representative patients may also increase generalizability of results in oncology and realistically appraise the benefit of new therapeutics in real-world settings.

Transparency of trial protocols and regulatory deliberations

Conscious of the need to rapidly build confidence in forthcoming results from COVID-19 vaccine trials, many vaccine developers publicly released the detailed trial protocols and statistical analysis plans ahead of outcomes being met. The FDA also released anticipatory guidelines in June 2020 detailing the evidence needed to approve COVID-19 vaccine candidates in an effort to proactively build public trust in the process. This transparency differs from routine approach in oncology trials, in which publicly available details of protocol design, regulatory guidance, and interpretation are often scant. The effectiveness of such proactive transparency could be seen as a new opportunity to seek a similar partnership with the public trust in patients with cancer, which can expedite the completion of clincal trials and the integration of results into practice.

From a regulatory perspective, the publicly accessible analyses of the vaccine results and FDA open session for Emergency Use Authorization deliberations contributed to expediting broader understanding and establishing clinical confidence. In cancer clinical research, public Oncologic Drug Advisory Committee (ODAC) meetings are generally convened only for controversial or complicated decisions. In ostensibly more straightforward approval decisions, there is often little insight about regulatory decision-making, nuanced data considerations, or invitation for public participation. It may be valuable to re-evaluate the opportunity for regulatory stakeholders to engage clinicians, industry, and lay public in all regulatory decisions in an effort to engage the greater public in clinical research efforts.

Conclusion

The initial COVID-19 vaccine trials are a remarkable testament to how, under the right conditions and with exceptional operational execution, clinical trial results can be delivered with clarity and pace. The vaccine trials had powerful, global incentive to produce effective vaccines quickly. We, too, have powerful incentives to produce results for our patients with cancer. Academic institutions, clinical investigators, and industry and regulatory stakeholders all have the opportunity and the responsibility to articulate and harness this urgency to further accelerate expeditious progress for our patients.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2021.05.001.

DECLARATION OF INTERESTS

G.J.R. reports institutional research funding from Roche, Pfizer, Novartis, Millennium, Mirati, and Merck; non-financial support from Pfizer, Roche, and Takeda; and travel expense reimbursement from Daiichi and Merck. P.J.S. reports institutional research support from BMS. M.D.H. reports research grant from BMS; personal fees from Achilles, Arcus, AstraZeneca, Blueprint, BMS, Genentech/Roche, Genzyme, Immunai, Instil Bio, Janssen, Merck, Mirati, Natera, Nektar, Pact Pharma, Regeneron, Shattuck Labs, and Syndax as well as equity options from Arcus, Factorial, Immunai, and Shattuck Labs. A patent filed by Memorial Sloan Kettering related to the use of tumor mutational burden to predict response to immunotherapy (PCT/US2015/062208) is pending and licensed by PGDx.

REFERENCES

Baden, L.R., El Sahly, H.M., Essink, B., Kotloff, K., Frey, S., Novak, R., Diemert, D., Spector, S.A., Rouphael, N., Creech, C.B., et al. (2020). Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N. Engl. J. Med. *384*, 403–416. https://doi.org/10.1056/NEJMoa2035389.

Bugin, K., and Woodcock, J. (2021). Trends in COVID-19 therapeutic clinical trials. Nat. Rev. Drug Discov. https://doi.org/10.1038/d41573-021-00037-3.

Dagan, N., Barda, N., Kepten, E., Miron, O., Perchik, S., Katz, M.A., Hernán, M.A., Lipsitch, M., Reis, B., and Balicer, R.D. (2021). BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N. Engl. J. Med. *384*, 1412–1423. https://doi.org/10.1056/NEJMoa2101765.

Liu, R., Rizzo, S., Whipple, S., Pal, N., Pineda, A.L., Lu, M., Arnieri, B., Lu, Y., Capra, W., Copping, R., and Zou, J. (2021). Evaluating eligibility criteria of oncology trials using real-world data and AI. Nature *592*, 629–633. https://doi.org/10.1038/s41586-021-03430-5.

Phillips, C.M., Parmar, A., Guo, H., Schwartz, D., Isaranuwatchai, W., Beca, J., Dai, W., Arias, J., Gavura, S., and Chan, K.K.W. (2020). Assessing the efficacy-effectiveness gap for cancer therapies: A comparison of overall survival and toxicity between clinical trial and population-based, real-world data for contemporary parenteral cancer therapeutics. Cancer *126*, 1717–1726. https://doi.org/10.1002/cncr.32697.

Polack, F.P., Thomas, S.J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J.L., Pérez Marc, G., Moreira, E.D., Zerbini, C., et al. (2020). Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N. Engl. J. Med. *383*, 2603–2615. https://doi.org/10.1056/NEJMoa2034577.

RECOVERY Collaborative Group (2020). Dexamethasone in hospitalized patients with Covid-19. N. Engl. J. Med. *384*, 693–704. https://doi.org/10.1056/NEJMoa2021436.

Sadoff, J., Gray, G., Vandebosch, A., Cárdenas, V., Shukarev, G., Grinsztejn, B., Goepfert, P.A., Truyers, C., Fennema, H., Spiessens, B., et al. (2021). Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. N. Engl. J. Med. https://doi.org/10.1056/NEJMoa2101544.

Unger, J.M., Vaidya, R., Hershman, D.L., Minasian, L.M., and Fleury, M.E. (2019). Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. J. Natl. Cancer Inst. *111*, 245–255. https://doi.org/10.1093/jnci/djy221.

U.S. Food & Drug Administration (2021). 2015–2019 drug trials snapshot summary report: five-year summary and analysis of clinical trial participation and demographics, Report of the U.S. Food & Drug Administration https://www.fda.gov/media/143592/download.