COMMENTARY

A Public Option for Clinical Trials? Lessons from Convalescent Plasma

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Abstract: The case of clinical trials for convalescent plasma during COVID-19 illustrates important lessons for realizing public sector approaches to biomedical research and development. These lessons, centering on mission, transparency, and spillover effects, can be translated to wider efforts to develop a "public option" for clinical trials.

Clinical trials play a critical role in generating evidence that informs regulatory decisions as well as clinical and public health practice. The conditions under which clinical trials occur — typically driven by private actors and with proprietary knowledge — carry enormous implications for the development and use of medical products. Despite the importance of privately sponsored trials, their application to practice poses inherent limitations beyond their escalating costs, including issues with representation and generalizability, a push towards less clinically meaningful "surrogate" endpoints, and selective publication and results reporting.[1] Yet the conventional wisdom is that a viable alternative for clinical trials would not be feasible, with the public sector often deemed to lack the entrepreneurial capabilities to generate the rigorous and timely evidence needed to inform practice for the large number of medical products in use.

Grundy et al.'s detailed analysis of convalescent plasma during the pandemic, however, adds to a growing counterpoint to this conventional wisdom. A search for new models of funding and organizing clinical trials has been inspired in part by the significant public sector involvement in developing COVID-19 technologies, including diagnostic tests, therapeutic drug and device interventions, and vaccines.[2] Among these medical products, convalescent plasma is novel for its unusual legal status — a non-patentable therapeutic intervention derived from blood donations by volunteers who have recovered from the illness and thus offered the authors a chance to gain insights into an alternative model of research and development. In their qualitative case study, Grundy et al. purposively sampled 8 prominent clinical studies of convalescent plasma during 2020-2021, spanning Canada, the US, Argentina, the United Kingdom, India, and China. They performed a content analysis related to these studies, ranging from study protocols to media accounts and scientific reports. What they found was a striking story of the potential of public sector-driven strategies for biomedical innovation marked by at least three central features: mission-orientation, transparency, and spillovers.

First, Grundy et al. describe the "mission-orientation" of governments in shaping the directionality *and* velocity of clinical trials for convalescent plasma. By

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explicitly prioritizing the need for rigorous and reliable evidence, for example, British authorities enabled the rapid design and implementation of clinical trials, rather than pursuing observational studies. With this direction, the RECOVERY study in the UK moved "at unprecedented speed," going from ideation to enrolling 7500 patients within weeks with the support of British public agencies. Second, transparency was a critical enabler for this mission-orientation. The authors document numerous instances from within countries like India and across transnational networks of scientists in which rapid and open sharing of clinical trial resources spurred higher quality efforts to evaluate the safety and efficacy of convalescent plasma for the treatment of COVID-19. Finally, this mission-orientation and transparency created the potential for under-appreciated "spillover" effects that impact public health more broadly. One highlighted example is the development of novel public blood services infrastructure in countries like Argentina, where clinical studies of convalescent plasma motivated the government to create a national program for blood plasma donation with potential benefits far beyond COVID-19.

This study adds weight for an aspirational idea that has been long debated: the need to build substantial public sector infrastructure — a "public option" — for clinical trials beyond health emergencies.[3] A public option would be a government financed and administered option that competes alongside traditional private ones, much in the American tradition of the US postal service or public libraries co-existing with FedEx and Amazon.[4] Proposals calling for clinical trials spearheaded by public agencies devoted to late-stage product development would ostensibly enable government to direct science towards population and public health goals, while also enabling the generation of transparent and high-quality evidence at lower costs.[5]

But any such aspiration would need to account for the serious hurdles facing public-sector approaches. A first-order challenge is that most marketed medical products are commercialized and proprietary, with publicly funded biomedical research contributing to products ultimately owned by pharmaceutical and biotechnology companies.[6] While public-private partnerships are much touted, they have often been marked by substantial deference to private sector imperatives, even when governments make large-scale investments.[7] This pattern was visible with Operation Warp Speed; while the US government pushed for greater clinical trial transparency, it was unable to use its leverage to get manufacturers to conduct head-to-head studies that would have produced more pragmatic evidence.[8]

In the face of these challenges, lessons from convalescent plasma offer the seeds of a more robust "public option" for clinical trials. One lesson is the crucial role of publicly funded networks of experienced clinical trialists. Platform trials, including RECOVERY in the UK, enable a decentralized, adaptive approach across trial sites coupled with strategies to reduce organizational barriers such as centralized institutional review boards and integration of clinical research into clinical care.[9] Similar efforts were launched by the US National Institutes of Health during the pandemic: the ACTIV platform.[10] Beyond the pandemic, a normative orientation towards transparency in these networks can enable trust, which is a vital ingredient for large-scale and rapid clinical trials. Full disclosure of trial design, protocols, and results also establishes buy-in from research and community institutions that are on the frontlines of executing trials and instills confidence in the ultimate users of the evidence: clinicians and patients.

A proposed vision for such networks in the US would be further investment in resources like CTSA (Clinical and Translational Sciences Awards), a consortium of medical research institutions across the nation, to build clinical trial networks across a broad range of diseases with large medical centers collaborating with community practitioners in the enterprise.[11] Another direction for engagement could be Patient Centered Outcomes Research Institute (PCORI), which has established a network of health systems for pragmatic clinical trials

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but has thus far shied away from comparative testing of brand name medical product interventions.[12]

A frequently cited barrier for implementing such a vision, however, is budgetary constraints. Thus, another lesson is the importance of investing in public sector organizations required to build clinical trial enterprises. While there are ample reasons to be doubtful of major change in the current political environment, recent efforts point to opportunities. The US federal government is investing, via Project Next Gen, in building a network of "at-ready" trials with flexibility to pivot to new vaccines as they mature. And the recent launch of Advanced Research Projects Agency for Health (ARPA-H) offers the potential for the government to take an entrepreneurial role in late-stage product development beyond COVID-19 and other public health emergencies. This renewed interest in reviving public ambition and industrial strategy may in turn build momentum beyond public health emergencies for a critical need: public options for clinical trials.

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References

1. National Academies of Science, Medicine, and Engineering. *Envisioning a Transformed Clinical Trials Enterprise for 2030: Proceedings of a Workshop* (National Academies Press; 2022), doi:10.17226/26349; J. S. Ross, et al., "Promoting Transparency in Pharmaceutical Industry — Sponsored Research," *American Journal of Public Health* 102, no. 1 (2012): 72-80, doi:10.2105/AJPH.2011.300187.
2. Q. Grundy et al., "A Most Equitable Drug': How the Clinical Studies of Convalescent Plasma as A Treatment for SARS-Cov-2 Might Usefully Inform Post-Pandemic Public Sector Approaches to Drug Development," *Journal of Law, Medicine & Ethics* 52, no. 1 (2024): 80-97.
3. T. R. Lewis et al., "The Case for Public Funding and Public Oversight of Clinical Trials," *The Economists' Voice* 4, no. 1 (2007), doi:10.2202/1553-3832.1123.
4. G. Sitaraman and A. Alstott *The Public Option: How to Expand Freedom, Increase Opportunity, and Promote Equality* (Cambridge: Harvard University Press; 2019).
5. A. Sarpatwari, D. Brown, and A. S. Kesselheim "Development of a National Public Pharmaceutical Research and Development Institute," *Journal of Law, Medicine & Ethics 48, no. 1* (2020): 225-227, doi:10.1177/1073110520917023; D. Baker "The Benefits and Savings from Publicly Funded Clinical Trials of Prescription Drugs," *International Journal of Health Services* 38, no. 4 (2008): 731-50, doi: 10.2190/HS.38.4.i, PMID: 19069290.
6. E. Galkina Cleary, et al., "Comparison of Research Spending on New Drug Approvals by the National Institutes of Health vs the Pharmaceutical Industry, 2010-2019," *JAMA Health Forum* 4, no. 4 (2023): e230511, doi:10.1001/jamahealthforum.2023.0511.
7. M. Mazzucato and V. Roy, "Rethinking Value in Health Innovation: From Mystifications Towards Prescriptions, "*Journal of Economic Policy Reform* 73, no. 2 (2018): 1-19, doi:10.1080/17487870.2018.1509712.
8. A. Kapczynski et al., "How Not to Do Industrial Policy," *Boston Review*, Published online October 2, 2023, *available at* <https://www.bostonreview.net/articles/how-not-to-do-industrial-policy/> (last visited March 5, 2024).
9. S. L. T. Normand, "The RECOVERY Platform," *New England Journal of Medicine* 384, no. 8 (2021): 757-758, doi:10.1056/NEJMe2025674.
10. J. S. Ross and P. Malani, "Learning from the Success of the ACTIV Platform," *JAMA* 330. No. 24 (2023): 2363-2364, doi:10.1001/jama.2023.24087.
11. P. Eisenberg et al., "Developing a Clinical Trials Infrastructure in the United States," *NAM Perspectives*, Published online May 11, 2012, doi:10.31478/201205g.
12. Patient Centered Outcomes Research Institute, Pragmatic Clinical Studies, Published August 1, 2016, *available at* <https://www.pcori.org/research/about-our-research/pragmatic-clinical-studies> (last visited March 5, 2024).

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