COVID-19 Vaccine Trials (and Tribulations): How to improve the process of clinical trials in a pandemic

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Running Title: Improving Vaccine Clinical Trials

Summary: Vaccine clinical trials have been essential to develop effective SARS-CoV-2 vaccines. The challenges of supply chain disruptions, infection control, study designs, and participant factors that affect trial procedures are reviewed, with specific solutions to streamline the clinical trial process.

ABSTRACT:

Vaccine clinical trials have been essential to develop effective SARS-CoV-2 vaccines. The challenges of supply chain disruptions, infection control, study designs, and participant factors that affect trial procedures are reviewed, with specific solutions to streamline the clinical trial process.

Keywords: COVID-19 vaccine, clinical trials, study design, pandemic preparedness

Background

With the onset of the COVID-19 pandemic, there was an urgency to develop and implement novel and effective SARS-CoV-2 vaccines to reduce disease burden and mitigate the devastating social and economic effects of the pandemic. Randomized controlled trials (RCTs) are a vital component of the vaccine development process and employ both treatment and placebo arms to evaluate the immunogenicity, safety, and efficacy of COVID-19 vaccine candidates in humans. RCTs have been the gold-standard methodology to investigate new therapeutics or preventative agents and are necessary to achieve licensure from regulatory agencies including the U.S. Food and Drug Administration (FDA). Traditionally, vaccine development from discovery to licensure has been a costly, lengthy and risky process, with an average of 10 or more years for a vaccine candidate to come to market and only a 6% success rate for any given product [1,2]. In contrast, the time from discovery of the novel coronavirus in December 2019 [3] to publicly available effective SARS-CoV-2 vaccines via Emergency Use Authorization (EUA) occurred in under a year. In the United States alone, there are now three SARS-CoV-2 vaccines available that have been rapidly implemented, with EUAs issued for Ad26.CoV.2 (Janssen Biotech Inc) for adults 18 years and older, BNT162b2 (Pfizer-BioNTech) for children 11-15 years old, and full Biologics Licensure Application (BLA) approval for BNT162b2 for 16 years and older and mRNA-1273 (ModernaTx, Inc) for 18 years and older [4–6]. While this is a remarkable achievement, with modeling showing that 1.1 million additional COVID-19 deaths were averted because of vaccination campaigns [7], conducting rigorous clinical trials has been challenging during the pandemic for both logistical and scientific reasons. There has been critique that despite the historical speed of the trials, the trials did not move quickly enough or fully answer questions needed to implement public health guidelines, at the cost of SARS-CoV-2 infecting and killing millions of people worldwide [8]. The COVID-19 pandemic has forced clinical trialists and scientists to re-think the usual infrastructure. It is essential that we reflect upon the lessons learned from the COVID-19 pandemic to further improve vaccine clinical trials. In this review, we will

dissect the anatomy of vaccine clinical trials and highlight the challenges that arose, as well as discuss solutions and approaches to improve the scientific process.

Challenges of Conducting RCTs During a Pandemic

At their core, RCTs are laborious and slow, due to the incredible effort required to enroll and monitor thousands of participants to the exacting requirements of a specific protocol over an extended duration of time. These usual tribulations are further compounded by unique challenges of conducting a trial during a pandemic.

Logistical and Site Issues

The need to rapidly accelerate enrollment and procedures was often at odds with the daily realities and logistical technicalities of the clinical trial sites. Clinical trials require direct and indirect support to function. Supplies and materials, especially personal protective equipment (PPE) and swabs, were in global demand, especially at the beginning of the pandemic, with the unpredictable supply diverted to hospitals and healthcare workers on the frontline [9]. These supplies were also needed for the clinical trials to be able to safely conduct participant visits and achieve endpoint goals (e.g., PCR with nasopharyngeal swabs to assess for SARS-CoV-2 infections). Furthermore, even usual equipment that stocks clinical trials spaces, such as band aids, toilet paper, and thermometers, suffered from shipping delays due to the overall supply chain disruptions that were occurring as the pandemic unfolded. The cost and availability of human resources were also greatly disrupted, as staff that usually drive the trials (including research assistants, nursing staff, regulatory affairs managers, pharmacists, and physicians) were diverted to either healthcare responsibilities, contract research organizations (CROs), chose early retirement, or left due to personal safety concerns or family responsibilities (e.g. childcare with the closure of schools). Recruiting new staff to meet the demands became difficult with intermittent hiring freezes from academic institutions and pay cuts, which exacerbated already baseline shortages in clinical

trialists and vaccinologists. Furthermore, even among the employed staff, a chronic understaffing occurred due to potential exposures and frequent quarantining.

These supply issues of both physical equipment and human resources posed great challenges for how to safely conduct study visits on-site. At a time when little was known about the transmissibility of SARS-CoV-2 or infection control measures, clinical sites were required to adapt their trial spaces to abide by the ever-changing public health guidance for the safety of both the participants and staff. Some sites were able to creatively find solutions – acquire office space that was no longer in use during the pandemic or create outdoor spaces with tents for participants' visits – although some sites without this luxury had to either decrease the number of participants in a day or expand the work hours with early and late hours, as well as weekend openings, to reduce crowding and maintain infection control policies.

Study Design: Phases, Outcomes and Endpoints, and Participants

Although RCTs are designed to be the simplest path to demonstrate efficacy of a new drug product, the development from the pre-clinical stage to licensure is lengthy, with each phase (1-4) conventionally progressing in a stepwise fashion and requiring months to years to complete each phase. Clearly this laborious and protracted process is misaligned with the pandemic induced urgency to rapidly develop a preventative agent. At the beginning of the COVID-19 pandemic, even the pre-clinical data were intrinsically limited since there were no validated SARS-CoV-2 animal models. To address this issue, preclinical and toxicology data from related vaccines (SARS-CoV and MERS-CoV candidates) were used to expedite much of the pre-clinical vaccine development work [10]. The clinical trials were further designed to have overlapping phases. Indeed, manufacturers began large-scale production of vaccines prior to the accumulation of data and results from the phase III trials, which was financially risky since the vaccine product may have failed for either safety or efficacy reasons.

Design considerations for the primary endpoints of the phase 1-3 studies were especially challenging. At a time when little was known about SARS-CoV-2 pathogenesis and disease, even less was known about appropriate laboratory assays, with no validated tools to measure clinical outcomes. Furthermore, study endpoints had to be defined based on limited data, with reliance on home questionnaires (via Smartphone applications), home oxygen monitoring, and sampling kits that could be sent by mail. Identifying a reliable and practical molecular target for primary end point analysis was problematic, with several types of assays in development and insufficient data initially to know the validity of a given test. In addition, the testing materials and reagents had to be both scalable and available for all the clinical trial sites to maintain consistency across study procedures. How should a clinical trial be designed with meaningful endpoints when knowledge is simultaneously building and shifting the targets? As researchers grappled with this task, heterogeneous targets and different assays were selected across different vaccine candidate trials, which later limited the ability to compare outcome measures across vaccine products.

Recruitment and enrollment of participants, especially for phase 3 vaccine trials that require 30,000-40,000 participants, is often difficult even under the best circumstances. Unlike volunteers who suffer from disease and seek trials for therapeutic benefits, volunteers for vaccine trials are healthy individuals who may not have a direct health benefit from the study product (or may receive placebo) and are exposed to potential harm from the product [11]. Identifying high-risk and willing participants was problematic due to many of the issues described above, including staffing issues (resulting in decreased recruitment efforts) and ability to maintain COVID-19 infection control practices, as well as ensuring safe transportation and study flow for the participants. In addition, with misinformation equally as viral as SARS-CoV-2 transmission and an overflow of data and publications (followed by an unprecedented number of retractions and redactions) highlighted in the media [12], overall trust in science among the public was low. This directly impacted the trials and outreach efforts. Many of the

communities most affected by COVID-19 had concerns about COVID-19 vaccines and the trial process, which limited participation [13,14]. Another criticism of the trials involved the exclusion of special populations, such as pregnant women, immunocompromised individuals, and children. Paradoxically, these vulnerable populations are traditionally protected from phase 3 vaccine trials, although if the vaccines are efficacious, these individuals eventually receive the vaccine without significant data to support their use in these populations. Clinical trials for the pediatric population were initiated in March 2021 after the initial efficacy and safety signal in adults, with special considerations for dosing and side effects [15]. However, for other special populations such as pregnant women and immunocompromised individuals, the vaccines were mostly studied using observational cohort studies or real-world evaluations, which often have many confounding variables.

Study procedures had to constantly adapt to the vicissitudes of the pandemic itself. The protocols underwent multiple revisions to address new data, align with product and endpoint kit availability, and react to shifting realities of the pathogen with new circulating variants. Amid these adaptations, the participant's perceptions and expectations had to be considered as well. For example, as seen in the mRNA-1273 and BNT162b2 trials, an early efficacy signal was seen less than six months into the trial. At the core, trial participants must be protected and allowed access to the product if shown to be efficacious; this is essential to maintain trust and transparency with the study participants and the community. However, how should new information and knowledge be incorporated into the study design, in a rationale and ethical manner, while maintaining scientific rigor? For most of the phase 3 efficacy trials, an unblinding phase was introduced mid-trial when this efficacy signal was confirmed and the vaccine granted EUA by the FDA. This allowed for participants to remain in the study and have additional data collected, although at the cost of losing the placebo-controlled value of the study [16]. The EUA approval of the mRNA-1273 and BNT162b2 vaccines in December 2020 further influenced the

other vaccine candidate trials, manufactured by Janssen and Novavax. Many participants left these studies in favor of obtaining an EUA approved vaccine, thus compromising the results from those trials.

Solutions and New Approaches

The challenges affecting the COVID-19 vaccine clinical trials offers a unique opportunity to reflect upon the clinical trial process. Many solutions were developed in "real-time" and reactionary to immediate demands. However, a thoughtful exploration of these challenges can yield novel ideas and approaches for future conduct of trials that will expedite regulatory and administrative affairs, engage a more diverse range of participants, streamline the study visits, encourage data sharing and transparency, and allow for flexible trial designs (Table 1).

Partnerships and Shared Platforms

Public-private partnerships should be established immediately (such as the COVID-19 Prevention Network, or CoVPN) with clear organizational structures, roles, and responsibilities with the goal of fast-tracking vaccine RCTs by offsetting financial and operational risks typically associated with vaccine development. Under this organizational umbrella, efficacy trials would benefit from common Data and Safety Monitoring Board (DSMB), common lab assays (even across different industry sponsored products), public sharing of protocols and informed consent documents, and to the extent possible, common protocol templates and data systems [17]. Funders should rely on well-established clinical trial sites and networks, such as the Division of AIDS (DAIDS) funded Clinical Trial Units (CTUs) and Division of Microbiology and Infectious Diseases (DMID) funded Vaccine and Treatment Evaluation units (VTEUs), to implement trials quickly, and leverage surge capacity areas when feasible, such as the NIH funded Clinical and Translational Science Awards (CTSA). At the local level, it is essential to secure early institutional buy-in and establish Rapid Response teams (Biosafety, Office of Clinical Research, contracts, and Institutional Review Boards) to ensure prompt institutional approval on RCTs. Establishing this

infrastructure not only would allow for rapid initiation of trials, but also would allow for consistency across vaccine candidate protocols and management.

Rethinking Trial Designs: Adaptive and Flexible Models

Flexible and adaptive trial designs are critical to success, especially in the context of a new pathogen. As described, overlapping the preclinical, phase 1, 2, and 3 was necessary to expedite discovery and clinical testing, with some studies even incorporating all three phases into one protocol (e.g., NCT04368728). However, future study designs should carefully determine appropriate transition points; for example, determine the level and quality of data required to advance from phase I to phase 2 and 3. Traditionally, phase 2 has served to further refine and optimize the dosing and schedule. With a more fluid and adaptive model, this important step could be better integrated into phase 1 investigations. Designing each phase with earlier interim analyses and ongoing safety evaluations throughout may aid in acquiring relevant data in an expedited fashion.

Furthermore, while RCTs are the current gold standard, alternatives to placebo-controlled trials should be considered. Human challenge studies [18], non-inferiority studies, and immunogenicity studies (once correlates of protection (CoP) have been established) are more efficient and less costly. Indeed, early analysis and identification of a correlate of protection is essential to allow for rapid iteration and allow bridging of immunogenicity data, which would be useful to evaluate efficacy in populations that were not strictly studied in the trials, determine efficacy quickly (and at less cost compared to RCTs) of novel vaccine candidates, and investigate efficacy of vaccines against new variants as they emerge [19].

The regulatory processes as they relate to early data from clinical trials is also an important component. The FDA's role is to evaluate the full body of evidence and determine safety and efficacy for a novel product; full approval and licensure should not be expedited and thorough evaluation is necessary to maintain this important safeguard. However, with the expeditious nature of the vaccine

clinical trials, the FDA utilized the EUA mechanism to rapidly enable availability of COVID-19 vaccines to the public. By definition, the EUA allows for authorizations based on limited evidence, with consideration of direct risks and benefits in the context of a public health emergency [20]. While the EUA was overall beneficial and allowed for rapid distribution of COVID-19 vaccines earlier in the pandemic, further refinements and criteria for EUAs should be addressed, with improved transparency [21]. In addition, independent reviews by experts (e.g., the Vaccines and Related Biological Products Advisory Committee) are essential to address decisions regarding the EUA and to provide a platform for open communication with scientists and the public allowing increased trust and confidence in the process by the public. Perhaps further expansion or increased frequency of these independent review committees would aid the FDA in being able to iteratively reflect upon emerging data and reassess interventions as pandemic conditions change (e.g, in response to variants of concern or waning of immunity and considerations to deploy booster immunizations). Educating the public and clinicians on the differences between EUA and full licensure is also warranted, since confusion about terminology can lead to further misunderstandings and mistrust of vaccines and the regulatory processes that govern approval [22].

Clinical Trial Management and Visits: Streamlining the process

Visits should be streamlined favoring online consenting, telemedicine visits, use of Smartphone apps for safety monitoring, and provision of home thermometers, oximeters, and testing kits for participant's self-monitoring. Utilizing these technologies will not only reduce in-person visits and directly address many of the logistical barriers described above, but also will use more cost-effective and efficient tools, with the benefit of more fully engaging the participants [23]. However, with technological adaptations, researchers should also evaluate strategies that are inclusive for elderly populations and people with low health literacy who may not be as facile in e-Health tools. Other approaches are warranted as well, which can both reduce the burden of on-site visits and expand access to trial

participation. For example, hiring personnel for home visits or partnering with home health agencies to conduct research visits at alternative locations to the research site are important strategies to pursue.

Building Trust and Engaging the Community

Recruitment should reflect the population we serve. While central registries can be very beneficial, involving local leaders as well as neighboring healthcare systems are crucial strategies for success. By local outreach efforts to communities about vaccines in particular and research in general, a more successful partnership can be developed and nourished. Strategies to improve communication with the public is also essential to combat widespread misinformation. While sharing of information has been conducted mainly through press release, timely manuscript write-up, transparent review process and prompt publishing of papers (e.g utilizing pre-print servers, online posting after peer review or reporting results on clinicaltrials.gov) should be prioritized. Tackling misinformation is of utmost importance, and clear and continuous communication with the community, scientists, and the participants regarding evolving information is essential to allow for iterative feedback of scientific developments and perceptions. A coordinated Learning Immunization System [24] is one model by which to involve key stakeholders, including the communities most affected, to begin to open effective communication and build trust. Such targeted methods can begin to address mistrust and misperceptions regarding vaccines and clinical trials.

Conclusions

The speed and successes of the COVID-19 vaccine trials have been remarkable and have altered the course of the pandemic. Clinical trialists and scientists have proven that the traditionally slow machinery of RCTs is not necessarily warranted, and a safe and rigorous process can be achieved in a more efficient manner. However, further refinement and novel strategies are necessary. New pathogens will continue to emerge, and pandemics will continue to plague our global ecosystem. Investing in preparedness is essential. Continuous investment in global research and training the next generation of vaccinologists (e.g., through nationally funded vaccinology T32 training grants) is a priority. Furthermore, with the COVID-19 pandemic particularly affecting under-represented minorities, we must also focus on increasing diversity of our research staff and faculty and promote continuous training in cultural competency. Through these actions, we will ensure safe, collaborative, and inclusive clinical trial processes that will continue to advance our scientific knowledge.

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NR's institution receives funds from Sanofi, Quidel, Merck, Pfizer, Lilly.

Potential Conflicts of Interests

ACS is involved in HIV, COVID and other vaccine clinical trials conducted in collaboration with the NIH, HIV Vaccine Trials Network (HVTN), COVID Vaccine Prevention Network (CoVPN), International AIDS Vaccine Initiative (IAVI), Crucell/Janssen, Moderna, and Sanofi. NR is the International co-Chair for the Sanofi COVID-19 vaccine efficacy trial (CoVPN 3005), site PI for CoVPN 3001, and a member of the Coronavirus Prevention Network (CoVPN). NR serves on safety committees for ICON and EMMES. NR's institution also receives funding from Quidel, Merk, Pfizer, and Lilly. LRB is involved in HIV, COVID and other vaccine clinical trials conducted in collaboration with the NIH, HIV Vaccine Trials Network (HVTN), COVID Vaccine Prevention Network (CoVPN), International AIDS Vaccine Initiative (IAVI), Crucell/Janssen, Moderna, Military HIV Research Program (MHRP), Gates Foundation, and the Ragon Institute. LBR has received funding from NIH, NIAID, NCATS, Wellcome Trust, and the Gates Foundation, in addition to holding a Data Safety Monitoring board or advisory board position with the NIH and FDA.

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1 **Table 1.**

Challenges	Solutions/Approaches
Recruitment/Enrollment -Including at-risk individuals -Expanding access to clinical trials	-Centralized registry -Involvement of community leaders -Cultural competency training at the trial site level to appropriately engage under-represented minorities -Disseminate updated information regarding open RCTs to healthcare providers and neighboring healthcare systems
Regulatory processes -Limited staffing -Administrative slow downs -Legal/institutional contracts	-Expedited Institutional Review Board and Institutional Biosafety Committee reviews -Standardized contracts -Early engagement of the Office of Clinical Research -Rapid response administrative teams
Study Visits -Difficult to manage on-site due to infection control management and staffing -Long study visits with extended procedures -Limited physical space of research sites	-Expand use of telephone/online platforms to limit in-person visits and attract individuals who are restrained by time or geography -Engage home health agencies in research -Hire personnel for home visits
Study Design -Inflexible study protocols, difficult to adapt with new data or evolving pathogen -Slow, stepwise preclinical to phase 3 processes -Lack inclusion of key populations (e.g., immunocompromised, pregnant women)	-Adaptive trial designs -Overlapping pre-clinical and clinical phases -Iterative data reviews -Increased interim analyses and reviews -Transparent data sharing within a network -Protocols that contain all phases -Common DSMB -Early identification of a correlate of protection to allow for bridging of immunogenicity data
Laboratory assessments -Difficulties of primary endpoint determination	-Common laboratories and templates -Increase capacity for biosafety labs (e.g., BSL3) -Early validation of endpoint assays

-Validation of new assays -Availability of equipment and trained staff	-Consistent assays across different protocols -Uniform laboratory training protocols -Institutional investment in laboratory training for pandemic preparedness
Communication and Community Relationships **-**Misinformation and mistrust of community members -Frequent redaction of scientific papers -Media as only source for information	-Establishing relationships with the community -Clear and continuous communication of expectations -Engaging community leaders -Community engagement and education to understand vaccine hesitancy -Training of clinical trial staff in cultural competency -Preprints, accelerated peer review, open-access manuscripts to quickly share data and scientific developments -Secondary, independent review boards such as the Vaccines and Related Biological Advisory Committee (VRBPAC) with public forums to enhance transparency

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