

Review

Pride and Prejudice during the COVID-19 Pandemic: The Misfortune of Inappropriate Clinical Trial Design

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) is a rapidly evolving global pandemic for which more than a thousand clinical trials have been registered to secure therapeutic effectiveness, expeditiously. Most of these are single-center non-randomized studies rather than multi-center, randomized controlled trials. Single-arm trials have several limitations and may be conducted when spontaneous improvement is not anticipated, small placebo effect exists, and randomization to a placebo is not ethical. In an emergency where saving lives takes precedence, it is ethical to conduct trials with any scientifically proven design, however, safety must not be compromised. A phase II or III trial can be conducted directly in a pandemic with appropriate checkpoints and stopping rules. COVID-19 has two management paradigms- antivirals, or treatment of its complications. Simultaneous assessment of two different treatments can be done using 2×2 factorial schema. World Health Organization's SOLIDARITY trial is a classic example of the global research protocol which can evaluate the preferred treatment to combat COVID-19 pandemic. Short of that, a trial design must incorporate the practicality of the intervention used, and an appropriate primary endpoint which should ideally be a clinical outcome. Collaboration between institutions is needed more than ever to successfully execute and accrue in randomized trials.

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1. INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causing the disease Coronavirus Disease 2019 (COVID-19), is a rapidly evolving global pandemic for which a significant number of clinical trials are ongoing. As of May 16th, 2020, there have been more than 4.6 million confirmed cases of COVID-19 worldwide and >3000 deaths [1].

As per the 2016 guidance of the World Health Organization (WHO) on ethical issues in infectious diseases, research is pivotal in finding innovative modalities for prevention, diagnosis, and treatment, during an epidemic [2]. During COVID-19 pandemic, novel, safe, and effective therapeutics, which include treatment drugs and vaccines are emergently needed.

2. CLINICAL TRIALS FOR COVID-19 TREATMENT

Five months into the pandemic, as of May 16th, 2020, more than a thousand clinical trials related to COVID-19 have been registered, the majority of whom are single-center, non-randomized studies

[3,4]. There are large numbers of therapeutic and vaccine trials ongoing to find the best possible prevention and treatment for combating this pandemic, which may take 12–18 months. The majority of the clinical trials for COVID-19 are centered on those countries which have been affected the most over the last 4 months encompassing North America, Europe, Iran, South Korea, and China. Comparatively, a very low number of clinical trials have been proposed in the Middle East, Africa, Central, and South America.

Although, the low- and middle-income countries had initially reported a relatively small number of confirmed cases COVID-19 perhaps due to the non-availability of diagnostic kits, decreased capacity, and weak health care infrastructure, these numbers have escalated exponentially over the past few weeks. Many developing countries are already challenged by the rising incidence of COVID-19 pneumonia, inadequate response capabilities, and protective gears for health care workers leading to significantly increased mortality.

At present, there is no known effective treatment for COVID-19 and thereby none of the drugs have regulatory approval for the treatment of this disease. However, two drugs have received an emergency use authorization for its management, which include tocilizumab (approved by China's National Medical Product Administration) [5], and remdesivir [approved by the United States Food and Drug Administration] [6]. It must be noted that as of the

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writing of this manuscript, the randomized trials on whose basis these two drugs were approved have not been published in peer-reviewed journals.

3. OPTIMUM METHODOLOGY FOR CLINICAL TRIALS

The best course of action to combat this rapidly rising pandemic is to design and execute well thought, innovative, and well-powered clinical trials that are universally accessible beyond political and geographical boundaries. Global, multi-center, Randomized Controlled Trials (RCTs) with clear objectives and endpoints are urgently needed to avoid the collapse of health care infrastructure and prevent a global recession. Though in principle this could be achieved by multi-center collaboration and most investigators agree with this, real-world data has shown that assimilating and executing clinical trials efficiently during an epidemic or pandemic is a very complex phenomenon. A lesson from recent history concerning clinical trials is the use of ZMapp during the Ebola virus epidemic, in which political and media-related factors played a major role in the initial failures of executing and completing clinical trials in Africa [7]. Unfortunately, during the COVID-19 pandemic, many issues due to political, psychological, and social reasons have arisen, and premature results from some clinical trials have stirred enormous controversies. Not only people (by themselves) have over-utilized and misused the drugs projected to “cure” or “prevent” COVID-19, the hype and *prejudice* originating from immature trial results (and propagation by celebrities, physician-scientists, and politicians), has even led to an unaccepted death due to toxicities of drugs (currently in trials) for COVID-19 [8].

Some facts must be considered to decipher the applicability of clinical trials being conducted currently for COVID-19. Investigators in most of the countries (both developed and developing) are conducting predominantly single center and single-arm trials. For example, more than 200 centers are currently engaged in hydroxychloroquine or chloroquine trials. Single-arm trials have several limitations, including complicated interpretation of trial results that would not yield quantifiable and measurable outcomes (particularly efficacy and safety), and are incapable of differentiating the impact of therapeutic intervention, placebo-effect, and natural history. Additionally, construing the response without a frame of reference for comparison has been a constant challenge. Such trials are most suited for diseases with well understood natural history, non-existent or minimal placebo effects, and in a situation where placebo control is not an ethical requirement. Single-arm trials may be conducted in cases where spontaneous improvement is not anticipated, small placebo effects exist, and the randomization to a placebo is not ethical [9]. However, there has been a flurry of single-arm trials for COVID-19 since many investigators are trying to conduct trials at their institution which has obvious advantages such as having control over the trial design and operations, rapid pace of execution, and authorship recognition in publications. However, sub-consciously, this psychology of “me too” or preference of “my institution” can sometimes create a false sense of *pride* which, unfortunately, can lead to confusion in the applicability of scientific literature as well as an inefficient use of resources (due to duplication of efforts).

Such small scale, single-center trials are certainly not conducive to fill the knowledge gap to find the best possible remedies in

combating the COVID-19 pandemic when multiple novel drugs are on the horizon for treatment. Currently, the results from single-arm trials (or retrospective studies) for many drugs being used off-label currently for the treatment of COVID-19 have been published [10–20]. Instead of single-arm, single-center trials, there is an urgent need to conduct large, multicenter, and multi-arm, randomized controlled trials to support prevention and clinical management guidelines and to find solutions for many unanswered questions. Expedient remote initiation and monitoring of such ethically sound RCTs, without overburdening already overstretched health care systems could help minimize morbidity and mortality due to COVID-19. The best practices and lessons learned from the landmark clinical trials done in West Africa, during the 2013 Ebola outbreak could be applied to COVID-19 trials to expedite the headway [21–24] with the caveat of the real-world issues mentioned above.

In an emergency where saving lives takes priority over executing a “perfect” trial, we believe that it is ethical to rapidly conduct a trial with any scientifically proven design as long as safety checks are in place. A classic 3 + 3 + 3 phase I design execution is not necessary if initial reports from different groups have established the safety of a drug that has some efficacy *in vitro* or *in vivo*. A phase II or III trial can be conducted with appropriate checkpoints and stopping rules directly in cases of a pandemic like COVID-19.

COVID-19 has two management paradigms – treatment for the disease itself (i.e. with antivirals, e.g. remdesivir, oseltamivir, favipiravir, etc.), or treatment of its complications which include acute respiratory distress syndrome, macrophage activation syndrome, pneumonia, or hemophagocytic lymphohistiocytosis thus multiple hypotheses can be tested concurrently for the sake of urgency to prevent mortality. Simultaneous assessment of two different treatments can be done using 2 × 2 factorial schema by randomly assigning each patient to intervention arm 1, to intervention arm 2, to both intervention arms, or neither intervention arms. This design allows for comparing each intervention with the control, comparing each intervention with the other, and possible interactions between them. The efficiency of the large-scale clinical trials is enhanced by such trials by measuring an effect that otherwise might not be apparent. However, the loss of power is possible in case of sufficiently severe interaction [25].

Multiplicity adversely affects the trial outcome in cases where investigators are inclined to test myriads of hypotheses simultaneously. In such cases (comparing investigational drug versus placebo; primary and secondary outcomes; sub-stratification by age, race, gender, baseline characteristics, etc.), the probability of false-positive error is higher than 5%. As the best practice, testing the single important hypotheses at a given time reduces the probability of false results. Significant results obtained through multiplicity require proper adjustment (e.g. Bonferroni or Scheffe), and validation with independent data. The results of non-significant tests should also be reported for the statistically significant outcomes to be construed in the framework of multiplicity to control false-positive error [26].

Keeping in view wide variation in commitments, provisions, equitable and affordable access among developed and a developing country, a worldwide research consortium is warranted to conduct cutting edge multi-center clinical trials involving multi-disciplinary subject matter expertise. Such a consolidated effort

Table 1 | Primary endpoints used in selected trials for COVID-19

Primary endpoint	Trial drugs
Time to clinical improvement, two steps in a Six-category ordinal scale: 1 (discharged) to 6 (death), censoring at day 28.	Remdesivir
To evaluate the antiviral efficiency of five FDA-approved drugs including ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine, and two well-known broad-spectrum antiviral drugs remdesivir and favipiravir against a clinical isolate of 2019-nCoV <i>in vitro</i> .	Ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine and remdesivir and favipiravir
Time to clinical improvement, defined as the time from randomization to either an improvement of two points on a seven-category ordinal scale or discharge from the hospital, whichever came first	Lopinavir–Ritonavir
To describe the epidemiological and clinical characteristics of Novel COVID-19 infected pneumonia	Oseltamivir
Time of viral clearance	Favipiravir versus Lopinavir/ritonavir
Treatment response	Tocilizumab
To assess the safety of baricitinib combined with antiviral (lopinavir/ritonavir) in terms of serious or nonserious adverse events incidence rate	Baricitinib
Clinical recovery rate of day 7	Favipiravir versus Arbidol
To evaluate the role of hydroxychloroquine on respiratory viral loads	Chloroquine and hydroxychloroquine
	Azithromycin
To assess virologic and clinical outcomes of COVID-19 patients	Hydroxychloroquine and azithromycin
Assess outcome improvement in COVID-19 pneumonia (various outcome measures)	Mesenchymal stromal cells

would synergize ongoing initiatives. The WHO's SOLIDARITY trial is a perfect example of the global research protocol which was launched on March 18, 2020, a global study of highly effective and probable management options for the definitive treatment of COVID-19 in the Middle East, Africa, Asia, Europe, and the Americas [27]. The WHO coordinates this trial through measures of performance and effectiveness. The guidance to ensure critical coordination and information sharing are provided by the WHO COVID-19 Scientific Advisory Group. The WHO plays a pivotal role in assessment, monitoring, evaluation of the new scientific information generated by the trials, and in producing new guidelines [28]. It must be noted, however, that the SOLIDARITY trial does not include an arm with hydroxychloroquine and azithromycin combination, which is currently being used in clinical trials as well as for off-trial management in some centers.

A common mistake by investigators is to repeat single-arm trials without realizing that single-arm trials are happening globally with the same agent for the same disease (in this case for COVID-19). Thus before establishing a clinical protocol, the investigators must gather adequate information to prevent duplication of efforts. To pursue this, continuously updated databases that have information on the trials being conducted globally are needed. *clinicaltrials.gov* is only one of many databases containing this information and is inadequate for investigators who are contemplating embarking upon clinical trials for a pandemic of this scale. An artificial-intelligence-powered, multi-domain, and real-time dashboard of COVID-19 clinical trials has been established to collate live information from all possible COVID-19 trials, encompassing global COVID-19 research registries and initiatives [29].

The current pandemic has revealed another real-world issue in the clinical trial domain which is the definition of the primary endpoint. The primary outcome variable needs to be selected very carefully to promote and accelerate any clinical trial for the desired end states (safety, efficacy, risk communication) of new modalities against SARS-CoV-2, globally. For management, research should focus primarily on minimizing mortality rather than response rates or laboratory factors. The primary endpoint should ideally be a clinical outcome and can be achieved by expedited approval by

the Institutional Review Board (IRBs), agile importation of investigational drugs, standardized data management, and data sharing. Unfortunately, the scientific community is currently dealing with multiple variables as primary endpoints in various clinical trials being conducted for COVID-19 (Table 1). These endpoints range from COVID-19 disease severity scales, to test parameter negativity [e.g. rates of reverse transcription polymerase chain reaction (RT-PCR) negativity concerning the number of days]. This is most unfortunate since the results from clinical trials with hugely disparate endpoints cannot be interpretable for choosing the most optimal strategy for treatment. Master protocols that have predefined rules for the structure of the trial and the release of data can be utilized for the sake of conducting urgent clinical trials. Such protocols have been developed by various agencies or investigators for various diseases, and we endorse the “core protocol” formulated by the R&D Blueprint (sponsored by the WHO) [30].

Lastly, as soon as a clinical trial on the treatment of a pandemic is complete or prematurely terminated (by data monitoring committee/data safety monitoring board), the results should be published in an expedited fashion, so that investigators contemplating studies using the same drugs can potentially benefit. An example is the evaluation of the lopinavir–ritonavir combination for severe COVID-19 patients in a randomized placebo-controlled 1:1 trial, the results of which (negative trial) were published promptly [31].

4. CONCLUSION

Ideally, one trial for the whole world can be accomplished by bringing together the expertise of the clinicians, scientists, regulatory authorities, and policymakers to augment WHO's initiatives to combat the COVID-19 pandemic, but in the real world, it may not always be possible; nonetheless, an effort to acquire a WHO initiated trial should be made. Seeking collaborations to establish randomized trials would require a sacrifice of both the institutional and the identity *pride* which is currently needed more than ever, at least during this pandemic!

“It is very often nothing but our own vanity that deceives us.” – Jane Austen

CONFLICTS OF INTEREST

None of the authors declare any *relevant* conflicts of interest. SKH has received honoraria from Novartis, Pfizer, Janssen, and Mallinckrodt. SKH has received travel grants from Sanofi, Gilead, and Takeda.

AUTHORS' CONTRIBUTION

FH and SKH wrote the first draft. All authors contributed substantially to the conception, acquisition, analysis, and interpretation of the data for the work and approved the final approval of the version to be published.

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