



Ethical challenges of prospective clinical trials during the COVID-19 pandemic

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ABSTRACT

Introduction: The COVID-19 pandemic has created an unprecedented opportunity to reimagine clinical research. While much has been written about the challenges associated with generating real-world evidence during the COVID-19 pandemic, comparatively little attention has been paid to the ethical challenges facing patients, clinicians, researchers, and regulatory bodies.

Areas covered: In this manuscript, we examine these challenges through the lens of informed consent and explore how the consenting process changes as our understanding of the disease is altered.

Expert opinion: We also suggest ways to limit these ethical hurdles through the use of embedded pragmatic clinical trials, which generate real-world data without the limitations associated with observational trials or the resources and lack of generalizability that are obstacles to conducting conventional randomized clinical trials. We argue that clinical research must become more nimble, and must include embedded researchers to ensure that relevant questions and ethical issues are properly addressed.

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1. Introduction

The COVID-19 pandemic presents both challenges and opportunities for clinical researchers [1,2]. While the regulatory and logistic hurdles associated with trials that include patients infected with coronavirus are well-documented, the ethical challenges have received comparatively less attention [3]. The pandemic has forced biomedical research investigators to change many long-standing patient-facing research consent and collection methods to comply with COVID-19 related limitations. Although governing agencies, such as the Federal Drug Administration (FDA), have published nonbinding recommendations for the conduct of clinical trials during the COVID-19 Public Health Emergency, they are not all-inclusive of ethical challenges [4]. Specifically, the normative conflict of consenting a patient for an experimental clinical trial to treat COVID-19, when the standard of treatment and available data is constantly evolving, is not explored in depth in the FDA's recommendations [5,6]. Moreover, no literature yet exists on evaluating the consent process for COVID-19 clinical trials using the guidance and framework of the four major principles of biomedical ethics outlined by Beauchamp and Childress: justice, autonomy, beneficence, and nonmaleficence [7,8]. The principles provide a conceptual framework for the adjudication of normative issues encountered in the delivery of health care and medical research. But as the COVID-19 pandemic has revealed, these principles have distinct limitations, and may not meet the needs of the practicing clinician. A more nimble and robust framework is necessary to meet the challenges of the COVID-19 medicine. Below, we review how an evolving understanding of coronavirus has altered the landscape for biomedical researchers, patients, and those charged with maintaining the integrity of clinical trials.

2. Background

In 2020, the Federal Drug Administration (FDA) released non-binding recommendations as part of guidance on the conduct of clinical trials during the 'COVID-19 Public Health Emergency.' Specifically, the FDA recognizes challenges that may arise, including but not limited to, 'quarantines, site closures, travel limitations, interruptions to the supply chain from the investigational product' [9]. The clinical trial's consent process must be altered to comply with the pandemic's limitations. To minimize the opportunity for adverse ethical events on clinical trials, the FDA constructed general guidelines for "assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity [10]. In practice, however, it is difficult to assure a trial volunteer that a novel intervention is safe, especially when randomized data is lacking and the standard of care is changing.

Therapeutic recommendations and evidence for the treatment of COVID-19 have evolved rapidly since 2020, and the FDA oversees not only the regulation of clinical trials but the approval of therapeutics for the treatment of COVID-19 [11,12]. On October 22nd, the FDA approved remdesivir as its first COVID-19 drug following the results of 3 randomized clinical trials showing it to decrease the length of hospital stays and reduce the likelihood that patients will need supplemental oxygen [3,13–16]. However, toward the end of 2020, two monoclonal antibody treatments, bamlanivunab and a combination of casirivimab and imdevimab ('REGEN-COV'), were proven to protect patients from progressing to a more severe form of COVID-19 [3,17,18]. Due to the pace of COVID-19 research and treatment discovery, patients have been given clinical trial treatments that have been later deemed,

Article highlights

- The pandemic has forced biomedical research investigators to change many long-standing patient-facing research consent and collection methods to comply with COVID-19 related limitations.
- While much has been written about the regulatory and logistic hurdles associated with COVID-19 clinical trials, comparatively little attention has been paid to the ethical challenges.
- Informed consent may take on a new meaning when the standard of treatment and available data is quickly evolving.
- In order to properly address complex ethical issues associated with COVID-19 clinical trials, we believe that the clinical research apparatus requires a new priority: embedded pragmatic clinical trials.

Embedded studies may enable a more nuanced discussion of informed consent and generate real-world evidence without the limitations associated with observational studies.

in some cases, harmful, such as in the case of causing cardiac arrhythmia [19–22]. COVID-19's relatively new prevalence in the world has created this wide-scale challenge for treatment discovery, given that there have been over 181 million cases and nearly 4 million deaths globally as of June 2021 [23].

Within this issue, we should also consider how there are some treatments that carry vastly different perspectives between investigators and the FDA. There is perhaps no better example than the drug hydroxychloroquine, which is widely used to treat malaria and systemic lupus erythematosus, and has sustained continued attention since the beginning of the COVID-19 pandemic [24,25]. While believed to be an effective primary treatment by the FDA, COVID-19 patients at hundreds of sites around the world were consented and given the treatment of hydroxychloroquine [26–29]. It was later found to be ineffective [28,29], and in some cases harmful as detailed above, and therefore, an inappropriate treatment for hospitalized COVID-19 patients [30–32].

The overall ethical tension lies in whether consenting a patient for a COVID-19 clinical trial in severe cases of COVID-19 is ethically appropriate when little has been understood about COVID-19 given its relative infancy, and the best available treatment for it is constantly evolving and being updated by the FDA [11]. In short, we must ask how clinical researchers can obtain informed consent when information is constantly changing. Hydroxychloroquine serves as a tantalizing case study [33–35].

2.1. Hydroxychloroquine

Chloroquine is an anti-malarial drug that belongs to the group 4-aminoquinolines, and through increasing endosomal pH required for virus-cell fusion and glycosylation of cellular receptors, can block the virus [24,27,36]. In addition, it has immunomodulating capabilities and is widely distributed throughout the body [30,37]. Chloroquine and Hydroxychloroquine, in vitro, caused changes in size and morphology of early lysosomes and endolysosomes [28]. It was hypothesized that endosome maturation was blocked by lack of acidification, and therefore virions may have been blocked for release [38]. Hydroxychloroquine is a less toxic version of chloroquine and therefore used in the treatment of humans infected with COVID-19 [37,39]. Chloroquine

became popularized after it was found to be effective in vitro, and initially a favorable drug candidate for COVID-19 due to its cost and accessibility [24,39–45]. Given its initial predicted potential, researchers that yielded these in vitro results called for clinical investigation of hydroxychloroquine in COVID-19 patients [38].

The novelty of COVID-19 and lack of frame of reference has created a rush to create clinical trials and publish literature on the topic, and methodology and scientific standards have been overlooked with this urgency [26], especially in the case of hydroxychloroquine. In 2020, the popularized drug treatment of Hydroxychloroquine had over 200 single-arm trials over about 200 centers [26,27]. These single-arm trials were improperly designed: at least 32 of them had sample sizes of 100 or less, at least 10 had no control group, at least 12 were nonrandomized, and only 50 were multicenter [26]. Single-arm trial (see 'Role of Clinical Trial Design in Evolving Therapeutic Recommendations: Single-arm Trial vs Randomized Control Trial') and overall study design flaws were key contributors to the misconceptions and inaccurate results originally produced by several early hydroxychloroquine clinical trials [26,28,46].

Combined with poorly designed clinical trial studies, hydroxychloroquine also amassed a confusing public narrative throughout the time it was being given to patients in clinical trials. A 2020 paper published in the *Lancet* titled 'Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis' [47] claimed that hydroxychloroquine was harmful to patients hospitalized with COVID-19, which sparked a call from major public health bodies to suspend hydroxychloroquine clinical trial recruitment [48]. It was later discovered that the paper had major data discrepancies, and the journal was unable to verify the data in the database [48]. Whether the claim that hydroxychloroquine was harmful to hospitalized COVID-19 patients was true or false, there was no credible data provided in the article to assess this, nor reason to suspend clinical trials using the drug.

After confusion created by this pivotal study, hydroxychloroquine was eventually deemed ineffective in the treatment of hospitalized COVID-19 patients with moderate to severe disease after the results of a study conducted by the National Heart, Lung, and Blood Institute PETAL Clinical Trials Network was published [28,29]. 479 patients were randomized to receive hydroxychloroquine (400 mg twice daily for 2 doses, and then 200 mg twice daily for 8 doses) ($n = 242$) or placebo ($n = 237$). Clinical status measured on a 7-category ordinal scale at 14 days, and none of the 12 secondary outcomes (which included 28-day mortality) showed that there was no significant difference between the placebo and experimental group [28,29].

3. Role of clinical trial design in evolving therapeutic recommendations

3.1. Single-arm trial vs randomized control trial

The novelty and infancy of COVID-19 has sent the medical and scientific community around the world scrambling to find a treatment to mitigate the effects of, or provide some control over, the effects of COVID-19 on humans [30,37]. Many of the

initial COVID-19 trials were observational, and lacked the scientific rigor to answer relevant clinical questions [27].

As a result of the urgency associated with an expanding pandemic, a great majority of COVID-19 clinical drug trials have been conducted as single-arm trials [27,49,50]. Evans, 2010 defines a single arm trial as being ‘a sample of individuals with the targeted medical condition is given the experimental therapy and then followed over time to observe their response’ [51]. Single-arm trials are usually conducted when spontaneous improvement is not anticipated, a small placebo effect exists, and a randomization to a placebo is unethical [27,49,51]. Although understandably employed due to urgency in the circumstance of COVID-19, a single-arm trial should only be used when the aim of the trial is to obtain preliminary evidence and safety data, and should not be used as a conclusive measure for efficacy of a drug [50]. In the case of COVID-19, a majority of clinical trial sites around the country have conducted single-arm trials [50], which retrospectively has provided complicated and inefficient results for certain drugs, such as hydroxychloroquine [21].

By contrast, randomized control trials (RCT) can allow for a multicenter and simultaneous investigation of several drugs, rather than just one [52,53]. In these platform trials, subjects are randomly assigned to two groups: the experimental group (receiving the intervention being tested) and the comparison or control group (receiving an alternative conventional treatment) [52,53]. Randomization is the centerpiece of an RCT [52,53]. Unlike in single-arm trials, randomization is the only way to be able to measure whether there is a significant difference between the two groups [52,53].

The widespread reliance on single-arm trials to identify a drug for the treatment of COVID-19 significantly contributes to the ethical tension of whether consenting a patient for a COVID-19 clinical trial in inpatient cases of COVID-19 is ethically appropriate when little has been understood about COVID-19, and the best available treatment for it is constantly evolving [19,28,48]. Because of the limitations of a single-arm trial, the urgency of treatment exploration and use of a single-arm trial versus the most appropriate study design of an RCT, must be weighed against one another.

4. Ethical issues

4.1. Informed consent

The informed consent process occurs before enrolling a patient in a clinical trial and allows for the investigator to provide the patient with education to assess the risks and potential benefits of a procedure or treatment [9,11]. The required elements of ‘(1) nature of the procedure, (2) the risks and benefits and the procedure, (3) reasonable alternatives, (4) risks and benefits of alternatives, and (5) assessment of the patient’s understanding of the elements 1 through 4’ must be documented, per the Joint Commission.

In the consent process for a COVID-19 clinical trial, patients are entitled to the same requirements discussed above. However, patients are also provided the understanding that their participation in the study is important to learn more about the drug and their safety in patients experiencing

adverse effects from COVID-19 [12]. Aquino and Cabrera, 2020 highlighted three ethical concepts – (1) evidence-based practice, (2) sustainable allocation, (3) meaningful consent, all of which must be protected when testing the efficacy of COVID-19 drugs in clinical trials.

In practice, the consenting process may differ widely between investigators and study sites. For patients with moderate-to-severe COVID-19, patients typically require hospitalization and supplemental oxygen may be necessary. In some cases, patients may not feel comfortable deciding on the value of enrolling in a clinical trial with an experimental medication to treat a disease that didn’t exist a short time ago [54]. In these moments, potential volunteers may defer to family, friends, or outpatient clinicians. Researchers and their study teams must be prepared for this inevitability and must ensure that legally-authorized representatives are given full access to the potential advantages and drawbacks of enrollment in a clinical trial.

4.2. Bioethical principles

Historically, medical practitioners have evaluated the moral and ethical impact of medical procedures using the four bioethical principles of justice, autonomy, beneficence, and non-maleficence [7,8]. In this paper, we evaluate the role of the evolving therapeutic recommendations and clinical evidence when consenting patients for COVID-19 experimental clinical trials through the lens of these four bioethical principles.

Autonomy is intended as a guiding bioethical principle so that patient decision-making is uninterrupted by coercion or coaxing by investigators [7]. This ensures that a patient is making a decision without the influence of external research motivations, and purely on behalf of their own thoughts, intentions, and actions. Jahn, 2011 derives the moral regulations of truth, respect of privacy, protection of confidential information, and consent for intervention, from the principle of autonomy [8]. In a COVID-19 Clinical Trial, with the assumption that the patient has been extended appropriate autonomy to develop independent thought, intention, and action in regard to making a treatment decision, autonomy is potentially disrupted by this moral regulation of truth. While not intentional, truth is tainted by the fact that COVID-19’s investigational drug history is limited and as seen in the case of hydroxychloroquine, unreliable [20,24,29].

When looking at this particular issue, the violation of justice is not of any central concern. To our knowledge, there is no evidence to suggest that patients, despite their status in society, were not given equal access to hydroxychloroquine. Assuring beneficence and non-maleficence in COVID-19 clinical trials is what we identify to be at the root of the ethical tension given the complexity of the information and pace of treatment discovery of COVID-19.

Beneficence ‘requires that the procedure be provided with the intent of doing good for the patient involved’ [7]. In the case of hydroxychloroquine trials, any potential benefit to the patient could not be assured given that it was repeatedly threatened by an inconsistent and confusing clinical trial history. The FDA still approved emergency authorization off-label

use for the drug despite limited available data [3,24]. The American Medical Association Code of Ethics states that off-label use must be justified by 'sufficient evidence' [55]. Evidence not produced by Randomized Control Trials (RCT) is seen as supported, suppositional, and investigational [24,56]. The lack of appropriate clinical trial evidence about hydroxychloroquine puts the integrity of this in question. At time of consent, known potential risks of the treatment being administered are declared, yet there is no declaration of the limited knowledge about the drug and its relationship to COVID-19.

Non-maleficence is heavily related to beneficence, and for the purpose of this analysis, does not need to be considered independently.

We must learn from our mistakes in clinical research. Past instances in biomedical research have revealed major discrepancies in the results of a single-arm trial versus a RCT [15, Boardman et al, 2015], and this example provides all the more evidence for designing a trial to have a RCT design rather than a single-arm trial design. While time to conduct an RCT is of concern, in past public health crises (such as the H1N1 Pandemic of 2009 [Wang et al, 2011]), albeit not as impactful and widespread amongst the population, RCTs have been successfully conducted [Zhaori et al, 2020].

5. Expert opinion

The COVID-19 pandemic has revealed the extraordinary resourcefulness of clinical researchers tasked with addressing evolving questions that are directly relevant to patient care. However, our rapidly changing understanding of a novel virus has presented unique ethical hurdles. In order to properly address these issues, we believe that the clinical research apparatus requires a new priority: embedded pragmatic clinical trials [57]. These studies, which are integrated into standard medical care using routinely collected clinical information, generate real-world evidence without the limitations associated with observational studies or the time, expense, and lack of generalizability that are barriers to conducting conventional randomized clinical trials [58–60].

In order to create a generation of researchers capable of conducting these trials, we must change the way biomedical research is conducted [61,62]. In most cases, there is a firewall between full-time clinicians and full-time researchers. We need more people who can do both. By incorporating basic research methods into medical training, clinicians will be equipped to conduct nimble studies that address crucial research questions.

The National Institutes of Health (NIH) Health Care Systems Research Collaboratory already supports these types of studies, which typically target conditions that affect large numbers of patients and are designed to improve quality-of-care measures and demonstrate benefit over a short period [63]. By placing research in the hands of practicing clinicians, these studies may be able to alleviate some of the ethical hurdles described above.

Practicing clinicians were able to witness firsthand the futility of hydroxychloroquine as a therapeutic intervention long before clinical trial results were available. This enabled

embedded researchers to provide a more nuanced discussion of treatment options while consenting patients for COVID-19 studies. Patients and potential research volunteers were able to learn about the virus from someone on the frontlines who was familiar with the knowns and unknowns of a potentially lethal virus for which there was (and is) no cure.

There is an urgent need to build upon the network of COVID-19 clinician-researchers who have been a part of these embedded trials, in both developed and developing countries. For this to succeed, several barriers clinicians' and patients' aversion to research participation, and liability concerns, will have to be addressed [63]. The first step is to acknowledge these concerns, and to speak openly about the ethical challenges facing stakeholders involved in COVID-19 research so that we are prepared for the next pandemic.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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