

Implementation of documented and written informed consent for clinical trials of communicable diseases: Lessons learned, barriers, solutions, future directions identified during the conduct of a COVID-19 clinical trial

Patricia Woods^a, Maura Flynn^a, Paul Monach^{a, b, c, d}, Karen Visnaw^a, Sara Schiller^a, Erika Holmberg^a, Sarah Leatherman^a, Ryan Ferguson^{a, e, f}, Westyn Branch-Elliman^{b, c, g, h, *}

^a Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) and CSP Coordinating Center, Boston, MA, USA

^b VA Boston Healthcare System, Department of Medicine, Boston, MA, USA

^c Harvard Medical School, Boston, MA, USA

^d Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital, USA

^e Boston University School of Medicine, Boston, MA, USA

^f Boston University School of Public Health, Boston, MA, USA

^g VA Boston Center for Healthcare Organization and Implementation Research (CHOIR), Boston, MA, USA

^h Beth Israel Deaconess Medical Center, Department of Medicine, Division of Infectious Diseases, Boston, MA, USA

ABSTRACT

Background and objective: The communicable nature of many infectious diseases, including SARS-CoV-2, creates challenges for implementing and obtaining regulatory-compliant written informed consent. The goal of this project was to identify and evaluate processes that address these barriers while maintaining clinical and research staff safety.

Methods: We reviewed Federal Drug Administration (FDA), World Health Organization (WHO), and VA Office of Research and Development (ORD) guidance about informed consent during the COVID-19 pandemic, and identified and pilot-tested several mechanisms for obtaining regulatory-compliant consent during our COVID-19 therapeutics clinical trial.

Results: Several processes were identified. These included a standard face-to-face consent with a plan for maintaining a paper copy of the signed consent form, a phone or video chat consent process that included taking a picture of the signed consent form or a screen shot of the signed document during a video chat, integration of the consent forms into software embedded within the electronic health record, and secure software programs with electronic signature. These processes are FDA-compliant but time-intensive, often requiring four or more hours of coordination between the clinical team, research staff, patients, and legally authorized representatives.

Conclusions: Future studies could evaluate how to improve efficiency, and whether some elements of the consenting process, such as the requirement for documented written signed consent, rather than a witnessed oral consent, is an acceptable standard for research participants with communicable diseases.

1. Background

SARS-CoV2 is a novel human pathogen that emerged in China at the end of 2019 and has rapidly spread around the globe [1]. COVID-19, the clinical syndrome caused by the novel coronavirus, is highly infectious with a high mortality rate. Because the disease is new, and with few known effective treatments, there is an urgent need to conduct high-quality research to guide treatment.

However, due to the communicability of SARS-CoV-2 compounded by limited resources, such as personal protective equipment (PPE) [2,3], conducting clinical research among patients with COVID-19 presents unique barriers that require adaptations to typical consenting

processes. Obtaining documented, written informed consent from patients with communicable diseases is inherently more challenging than consent processes for other medical conditions. Additional considerations include 1) the need to protect research team members from a potentially contagious infection, 2) the need to limit the unnecessary use of PPE, particularly when supplies are limited, and 3) the potential for environmental spread of communicable diseases, such as through the transfer of paper. While fomite-based transmission appears to be rare for SARS-CoV-2, environmental and fomite-based spread are important modes of transmission for other pathogens that may be studied in future clinical trials.

* Corresponding author. VA Boston Healthcare System. 1400 VFW Parkway. West Roxbury, MA, 02132, USA.

E-mail address: wbranche@bidmc.harvard.edu (W. Branch-Elliman).

<https://doi.org/10.1016/j.conctc.2021.100804>

Received 28 October 2020; Received in revised form 4 June 2021; Accepted 12 June 2021

Available online 26 June 2021

2451-8654/© 2021 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

The Common Rule, as implemented in the VA, allows waiver of documented informed consent only if “research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.” [4] Although there was hope for a waiver of documented written informed consent for patients with COVID-19, including in the VA Office of Research and Development frequently asked questions released early in the pandemic [5], the US Food and Drug Administration (FDA) issued formal guidance for the documentation of written informed consent in its official statement on COVID-19 clinical research, and these recommendations were adopted by the VA [6,7]. For clinical consents, and for compassionate use of investigational medications, a witnessed consent process, without a requirement for written documentation, was deemed acceptable [6,8].

Our center lead an open-label, multi-center adaptive, randomized controlled trial within the Veterans-Integrated Service Network (VISN) –1 Clinical Trials Network (NCT 04359901) [9,10]. As part of the operationalization of this trial, conducted in compliance with FDA guidance, we encountered many barriers, particularly to the research informed consent process, and pilot tested and implemented processes to address these barriers. Here, we discuss the barriers and challenges we identified during the conduct of the trial, and how we addressed them. We also highlight challenges and inequities that were insurmountable, leading to considerations for future improvements.

2. Methods

During the period from March to April 2020, we rapidly developed and implemented an open-label, adaptive randomized controlled trial with broad eligibility criteria evaluating the utility of the interleukin-6 receptor inhibitor, sarilumab [11], in addition to standard-of-care, for hospitalized, non-intubated patients with confirmed SARS-CoV-2 infection. As part of the implementation of this clinical trial, several processes that allowed for documentation of signed informed consent documents were evaluated and pilot tested.

2.1. Patient consent processes

Potential informed consent documentation practices are outlined in Fig. 1. The first process utilized a standard signed document on a printed informed consent form (ICF) that was collected and then stored in a paper bag on the nursing unit for four days prior to collection by the study team. As is typical for most clinical studies, both the investigator and the participant sign the same form. If this process is selected, then a photograph of the signed ICF should be taken and provided to pharmacy before temporary storage of the paper documents. In a variation of this process, the signature pages of the ICF could be removed and placed in a clear plastic bag. Then, after leaving the patient room, investigators wipe down the plastic bag (e.g., with an alcohol swab or a disinfecting wipe) and the signature page is photocopied, faxed, or scanned into a file that is then distributed to relevant stakeholders via encrypted email.

The second process included collecting a signature, either electronically or on a paper copy of the consent form, remotely by the person obtaining consent as well as a witness, after the patient indicated intent to enroll and confirmed signing the document. In this process, the patient and the investigator sign different forms, but both are collected. In accordance with federal regulations, this process requires that the person obtaining consent and an impartial witness attest that the patient both consented to participate *and* signed the physical document, and that proof of the patient's signature be captured (e.g., scanning the paper documents after storing them in a clear plastic bag and decontaminating it, or storage of the physical paper document followed by later collection and storage). After this process is complete, the form with the

attestation statement could be printed and stored with other study documents or scanned into the electronic health record (EHR).

Some EHRs include an integrated process for obtaining consent; in our facility, this includes an electronic signature pad that is directly uploaded into a specific platform within the patient record. This fully electronic system was created for clinical consents, but, because it includes a mechanism for obtaining a signature from the patient, is compliant with federal guidelines about documenting consent to participate in research. Due to challenges with cleaning and disinfection requirements, this option was not pursued.

The third process involved collecting a photograph of the patient's signature on the paper informed consent document. This photograph could be obtained using a smartphone, tablet, or other approved *and* encrypted device, and then printed and stored with other study documents, or scanned into the electronic medical record system. Signature by the person obtaining consent and the witness must also be documented in parallel, similar to the processes laid out above. Alternatively, if consent was obtained via video chat, investigators could take a screenshot of the patient holding up the signed consent form, and that would serve as documentation of signature.

A process using DocuSign, or similar electronic signature software, was also explored but not available for implementation and testing during the period our trial was open and enrolling.

2.2. Legally authorized representative consent process

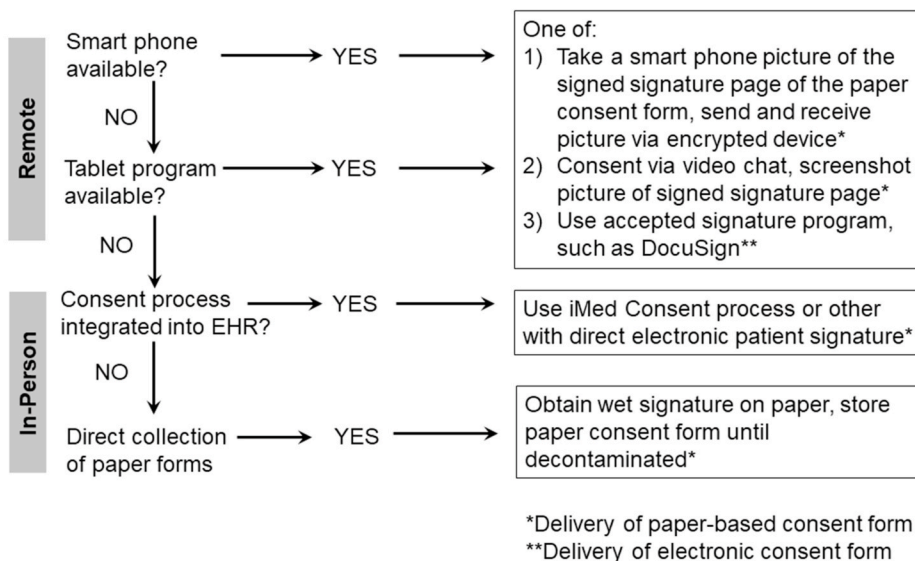
We identified similar processes for obtaining consent via a legally authorized representative (LAR), with some variations given that LARs may not be able to enter facilities due to visitor restrictions implemented during the pandemic, and that LARs, unlike patients, may not pose an infection risk to staff if they are able to consent in person. If the LAR is able to come to the medical center and sign the paper consent form, then typical research processes may be followed, without the need for additional workarounds, PPE use, or concern for contamination. If the LAR is remote, or unable to come to the medical center, then the consent form can be emailed to the LAR using an encrypted email service, and the informed consent process conducted via phone with a witness also on the call. To maintain compliance, the LAR must then print and sign the ICF and return the signature page by email or take a photograph of the ICF document and return it via encrypted software. Either this document is then signed by the person obtaining consent and the witness (to maintain all signatures on one page), or those additional signatures can be on a separate page, as above. Alternatively, the LAR's signature may be witnessed using a video chat platform approved by the institution and compliant with local privacy policies. A snapshot of the ICF is collected, and then the investigator and the witness sign the ICF, attesting that the LAR signed a paper copy of the document remotely.

2.3. Pilot testing and implementation

During pilot testing, we attempted to identify processes that would minimize the need for face-to-face interactions to limit exposure of staff to patients with COVID-19 disease and to preserve PPE, in light of national shortages. Another goal was to limit the amount of physical paperwork that needed to be saved and collected, to minimize the risk of fomite-based transmission, and also to minimize the need for a “decontamination period” wherein the paper copy was stored and then collected at a later time to minimize the risk that relevant study documents would be lost or misplaced. In addition, we sought to estimate the average length of time required to complete the guideline-compliant informed consent process.

Of note, our facility has an iPad program for admitted patients with COVID-19, thus this tool is universally available in our facility for pa-

A. Patient Consent Processes after Delivery of Consent Form



B. Legally Authorized Representative (LAR) Consent Processes

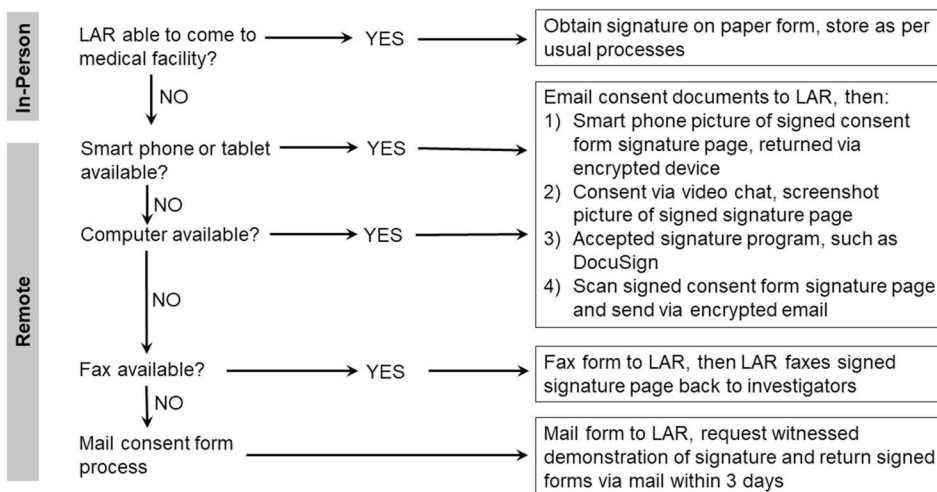


Fig. 1. Processes for obtaining written informed consent for patients with SARS-CoV-2 infection. **Fig. 1A** = Processes for obtaining written informed consent from the patient. **Fig. 1B** = Processes for obtaining written informed consent from a legally authorized representative (LAR).

tients who do not require a legally authorized representative (LAR) to participate in the informed consent process.

3. Results

Several major barriers to the informed consent process were identified; these are presented in **Table 1** and paired with their potential solutions.

Based on these barriers, and FDA regulatory guidance, we identified four independent processes that could be used to collect written informed consent (**Fig. 1**). All strongly emphasized limiting staff exposure and need for PPE use. Critical to all options, in accordance with FDA guidance, either the patient or the LAR required access to a physical copy of the informed consent document. This could be provided in paper form to the patient or the LAR at the treating facility or provided via fax or email to a LAR who was not on-site.

Benefits of the first process, which involved a standard paper consent form and a non-remote consenting process, included that the signed form is able to be copied and provided directly to pharmacy

without concern for contamination. Short turnaround time between obtaining documentation of consent and provision of documentation to pharmacy speeds the process of release of study drug and ultimately administration of the study drug to the patient. Downsides of this process include the need to use limited PPE to enter the patient's room, unnecessary possible exposure of providers and investigators to SARS-COV-2, and the potential to lose the physical copy of the document during the storage and future collection process; however, this may be mitigated if the document is able to be decontaminated and quickly scanned into an electronic format, as is the case if a clear plastic bag is used. A benefit of this adapted standard approach is that it may be the fastest mechanism to obtain consent, as few technological transfers are required.

The second process, involving remote consent, was the most commonly used strategy (13/15 consents). During the conduct of our trial, we found that, given inherent challenges on the closed inpatient COVID-19 unit, this process was substantially more feasible after we introduced informed consent packets, which included all regulatory documents and a pen, stored in a plastic bag on the unit for easy distribution to the patient and cleaning.

Table 1
Barriers to collecting written informed consent and potential solutions.

Barrier	Solution(s)
Need to preserve personal protective equipment, and need to limit staff and investigator exposures and room entries.	Video or teleconferencing-based consent. Consideration of alternative mechanisms for obtaining signatures, such as DocuSign or other similar software programs.
Requirement for documentation of signed, written consent.	Photograph of informed consent document, sent via encrypted software. Screenshot of video conference, with patient or legally authorized representative holding up the informed consent document. Collection of potentially contaminated paper hours to days after consent is obtained.
Limited availability of technology to support informed consent process to patient or legally authorized representative (e.g., LAR lacks a printer, scanner, smart phone, computer, or a fax machine).	We were not able to identify a solution. Witnessed phone consent was a possibility, however, is only currently accepted for clinical consents and not for participation in a clinical trial.
Distribution of paper copy of informed consent to the patient.	Consent forms pre-printed and available on nursing units. Distribute consent forms to all patients admitted to COVID-19 units. Provide informed consent documents to treating teams to distribute during morning rounds, to limit the need for additional room entries and exists and personal protective equipment use.
Patients gravely ill/too ill to provide consent.	Screen and consent patients prior to eligibility.

Electronic consenting platforms already integrated into the EHR, were not used in our facility. A barrier to using this process for obtaining consent for participation in research was the need to minimize contamination, cleaning and disinfection of portable electronic systems, which might be used by many different patients, and therefore pose an infection control risk if SARS-CoV-2 patients used the system directly. Although we did not pursue this approach, a benefit of this strategy is that a note is automatically generated within the EHR and serves as documentation that the process occurred. However, because signing with an “X” on behalf of the patient is only permitted for compassionate use, challenges about cleaning and decontaminating the portable electronic system remain.

The third process involved obtaining a photograph of the patient's signature on the paper informed consent document. We found that challenges of this strategy included: 1) available iPads did not have picture-taking capability, thus were of limited utility for obtaining proof of written consent, and 2) pictures taken were often of low-quality, making discerning of signatures difficult, and/or did not include the IRB stamp and approval date in the picture field, requiring additional documentation attempts prior to receiving adequate documentation of written consent for compliance with research regulatory procedures. Additionally, many of the patients enrolled in our trial were quite ill, and were often weak and trembling, making collection of a regulatory-compliant photograph challenging.

A final option we explored was the use of DocuSign [12] or similar electronic signature systems to obtain signed consent, either from the patient or from their LAR. Due to regulations and information security controls within the VA while our trial was open and enrolling, we were not able to use this process in our facility; however, its use for both COVID and non-COVID research may be a possibility for other institutions with access to this software or similar software [13]. Such signature systems can be used on any smart phone or electronic device, including computers; thus, many potential participants will have access and be able to participate. As with the other options presented, this is

also a touchless system that does not require the use of additional PPE, or the need to place staff at risk, in order to obtain a legal signature. For an off-site LAR, access to technology at the level of a smart phone or email is necessary, but email access is also needed to deliver the informed consent form, so use of an approach like DocuSign is not an additional barrier. In addition, an actual physical copy of the paper document is not required, as the system is fully electronic and thus there is no potential exposure to clinical or research staff, and no need for additional PPE.

3.1. Processes used

In total, after the FDA issued updated guidance about the informed consent process for COVID-19 clinical trials, we conducted informed consent remotely with 13 patients and 2 LARs at our facility; documentation of written consent was obtained using the scanning method for 7 participants, 3 participants took a photo of the signed documents and emailed them back to study staff and for 5 participants study staff took a photo of the consent forms. A summary of the benefits and downsides to different processes is presented in Table 2.

3.2. Personal time required and other process and feasibility challenges

Overall, we found that the informed consent discussion with the patient for the study required approximately 10 minutes, with 5 additional minutes for questions. However, the entire process for documenting and completing informed consent took on average 4 h, as a result of difficulties with providing a physical copy of the ICF to the patient, identifying the appropriate LAR and then coordinating with that individual, and transferring the materials required to demonstrate proof of written informed consent. Of note, regulations at our facility included a provision that the patient be allowed to decline contact by the research team before receiving informed consent documents and receiving more detailed information about the study from study team members, which also contributed to prolonging the consenting process.

Due to the nature of the fully remote research program prior to widespread availability of vaccination, the research team primarily depended on nursing staff to provide the paper packet to patients. This was essential for minimizing risk of infection to research staff, however, inherently introduced additional delays into the consent process, leading to substantial personnel resources dedicated to the fully remote consenting process.

Even the seemingly small task of providing patients with the paper packets required close coordination with their nursing and clinical teams. During the period when the unit was a closed COVID-19 unit, this process was fairly straightforward, however, it was more complicated when the unit was not fully dedicated to COVID-19, and providing research regulatory documents to patients required an additional room entry with full donning and doffing of PPE, or waiting until the clinical care providers were planning to enter the room for another reason. This delay was often compounded by the fact that clinical teams often rounded on the COVID-19 ward last, or later in the day, and the study team was not permitted to contact potential participants until after the clinical team received permission for members of the research team to contact the patient and then conveyed that permission to the study team. Additional causes for delays in the informed consent process included that patients were often very tired and worn out due to their underlying diagnosis and admission processing, and thus not up to reviewing research documents when they were initially approached. Other delays may have been caused by other activities, such as meals, which patients preferred not to have interrupted. When LARs were involved in the consenting process, they were often compelled to consult with other family members prior to making a decision about enrolling their loved one in the study, also leading to additional phone calls and lengthening the process. Finally, after the patients consented to enroll-

Table 2
Pros and cons of different strategies for obtaining informed consent documentation remotely.

	Process	Pros	Cons
Patient	In-person consent/signed form inserted in clear plastic bag and a copy collected	<p>Face-to-face interaction may engage the patient more effectively in the informed consent process.</p> <p>Study staff may be able to better communicate with patient and gauge their understanding of study information.</p> <p>Study staff were able to assess the patient's physical condition and ability to tolerate the timing of the informed consent process (some patients were easily fatigued or coughing).</p> <p>No technology hurdles to overcome.</p> <p>A more positive/satisfying experience for patient.</p> <p>Study staff were not put at risk of potential exposure to SARS-COV-2.</p> <p>Process provided a successful option for conducting the informed consent process and meet the FDA/VA requirements for obtaining documentation of informed consent.</p>	<p>Study staff using personal protective equipment (PPE) that was limited in supply and prioritized for clinical use.</p> <p>Potential exposure of study staff to SARS-COV-2.</p>
	Remote Consent conducted by phone or video with a photograph or scan of the signed informed consent signature page	<p>Valuable option to engage LARs (who due to COVID could not be present with their family member) and provide their loved one an opportunity to participate in a research study.</p>	<p>Consent conducted by phone may be less personal and limits the ability of study staff to assess the patient's condition and non-verbal response to the information presented.</p> <p>Technical challenges: identifying available resources, learning the use of equipment, determining permitted methods to transfer documents.</p> <p>Reliance/added burden on nursing staff to support research staff; access to iPad, providing consent form to patient, removing signed form from patient's room.</p> <p>Hearing Impairment – some patients were unable to hear on the phone.</p> <p>Logistical challenges encountered with coordinating/scheduling calls with patients/LARs/witnesses.</p> <p>More burdensome on patient – asking patient to place signed documents in plastic bag or instructing patient to take a photo of the signature pages and send to study staff via encrypted email.</p> <p>Quality of photo/scanned document was poor and required repeating.</p> <p>More difficult to guide patient in completing form particularly amongst those of advanced age.</p> <p>Study staff may not note discrepancies in completing the document at the time of consent, e.g., incorrect date or date placed in wrong location on form.</p> <p>Technical barrier – LAR needed to have access to email and a printer. (In one instance, staff drove to LARs location to provide documents and obtain signature).</p> <p>More burdensome to LAR – LAR needed to print, sign and scan/take photo of signed document and return to study staff via encrypted email.</p>
Legally Authorized Representative	Remote Consent conducted by phone or video with a photograph or scan of the signed signature page	<p>Valuable option to engage LARs (who due to COVID could not be present with their family member) and provide their loved one an opportunity to participate in a research study.</p>	<p>Technical barrier – LAR needed to have access to email and a printer. (In one instance, staff drove to LARs location to provide documents and obtain signature).</p> <p>More burdensome to LAR – LAR needed to print, sign and scan/take photo of signed document and return to study staff via encrypted email.</p>

ment, there was a wait period to compile and transfer research regulatory documents, and a waiting period for a study team member to go to the medical center, don PPE, collect the form, doff PPE, and then scan or take a picture of the paper form.

4. Discussion

In the setting of a global pandemic with a highly transmissible and potentially fatal novel infection, there is a significant burden on clinicians, investigators, patients, and their LARs in obtaining written signed informed consent that is fully compliant with current federal guidance. World Health Organization (WHO) Guidance for Managing Ethical Issues in Infectious Disease Outbreaks includes a provision that research should not drain critical health-related resources [14]. In conducting our clinical trial, we found that the process of requiring paper documents and written informed consent required an average of 4 h of logistical coordination by clinical and study staff, a substantial burden on an already overwhelmed system. This time was primarily spent identifying ways to gather proof of a “wet signature,” and transfer and store paper and electronic documents. The WHO guidance recommends that patients in isolation have the time and opportunity to discuss clinical

trial options with their loved ones, which is critical for informed participation in research, however, the delays in our trial were due to time spent addressing administrative and process barriers, not counseling patients or their family members.

A major reason the informed consent process is undertaken is to ensure that patients understand that the treatment being investigated may or may not be beneficial. This principle is critical for avoiding therapeutic misconception for patients participating in clinical trials, however, there is no reason to believe that documentation of a wet signature on a piece of paper mitigates this risk, and, as we found, identifying ways to maintain compliance with FDA guidance places a substantial burden, including risks of infection, on clinicians and investigators caring for COVID-19 patients. Notably, the United States has been criticized recently for limited enrollment in clinical trials [15,16] – a problem not encountered in the United Kingdom, where a less cumbersome verbal consent process without the need to document wet signatures on potentially contaminated paper was approved, in the event that methods to secure proof of a wet signature were not feasible [17]. It would be educational to learn how many patients were consented for large trials in the UK and US using different consenting methods.

In addition to typical challenges in conducting and implementing a clinical trial, patients with COVID-19 are in isolation units, gravely ill, and often elderly and unable to provide informed consent themselves, and therefore must rely on a LAR. Further complicating matters, the LAR is prohibited from visiting the hospital. Beyond the administrative barriers, it is inappropriate and unethical to ask study staff who are not involved in patient care to expose themselves to the risk of infection purely for the purposes of gathering the necessary regulatory documents. Many IRBs stipulate that investigators are not permitted to enroll patients for whom they are caring clinically, presenting an additional challenge and potentially additional use of PPE; a particularly large ethical challenge when PPE supplies are limited. These numerous barriers impede the conduct of critical research required to advance our understanding of how to improve outcomes among COVID-19 patients and may have contributed to the comparatively low rates of clinical trial recruitment in the United States.

Current FDA guidance mandates that written informed consent be documented for interventional research studies [6], but allows a witnessed oral consent process for clinical consent, including consent for investigational and unapproved medications without proven benefit and unknown harms, such as remdesivir, which was available under a compassionate use program prior to the opening of large clinical trials [18]. Initial ORD guidance suggested that a similar process could be applied to research studies for patients with COVID-19,⁴ however, subsequent statements did not permit a process without written documentation of informed consent [5,7]. This documentation requirement creates substantial barriers to conducting clinical trials evaluating the effectiveness of treatments for COVID-19, which are desperately needed to advance our understanding of this novel infection. Instead, an unintended consequence of these regulations may be the off-label use of potentially promising medications outside of a clinical trial setting. Although it is widely acknowledged, including by clinical societies such as the American Thoracic Society, that off-label use may be ethically sound for patients who are critically ill with few other options [19], complicated and logistically challenging documentation requirements limits the research community's ability to collect sound data on which to base future clinical decisions, as demonstrated by the controversies surrounding observational studies of hydroxychloroquine [20–23]. Furthermore, there is not a rational basis for allowing a clinical consent process for medications that are fully unproven and untested, such as remdesivir [8], while requiring a more cumbersome consent documentation process for medications that are already FDA-approved with known side effect and safety profiles and simply because they are being administered in the setting of a clinical trial. We also note that the early experiences of the remdesivir compassionate use program were collected, analyzed, and presented as an observational research investigation in a premier medical journal to support the future clinical use of the medication, despite not being classified as “research” for the purposes of informed consent documentation practices [18]. Thus, ultimately, patients participating in the compassionate use program were subject to the same risks as those receiving the drug in therapeutics trials. Further, in trials in which use of other medications is not prohibited, patients randomized to standard of care are not subject to greater risk than patients who are not involved in any trial or compassionate use program. We do not argue that the process of informed consent to participate in research should be compromised, but rather that its documentation should not be made more arduous – for the patient – than it is for open-label use of an unapproved drug.

In identifying ways to address the barriers posed by the need for documented consent, we found that coordination with the clinical teams caring for COVID-19 patients was even more important than usual, for several reasons. First, the treating clinicians were aware of which patients were eligible, and which might become eligible for participation. Second, the treating teams were donning PPE and seeing the patient anyway, so the additional burden of providing potentially eligi-

ble patients a paper copy of a consent form while on rounds was minimal. Indeed, given the very limited treatment options for patients with COVID-19, we found our clinical partners to be highly engaged and enthusiastic supporters of the research study and that they were willing to facilitate the process. A barrier to this process was the frequent change and turn-over on clinical teams. To address this, the study team reached out to attendings as they rotated onto the COVID-19 service, introducing them to the study, and clarifying their role. Despite this intervention, we found variable support with different teams and attendings, impacting both the time required to obtain informed consent and also receipt of permission from patients to contact them about the study.

Importantly, due to the rapidly progressive nature of COVID-19, we included a provision that patients could be screened and consented before meeting eligibility for randomization. This was a critical facilitator for enrolling patients because the informed consent process was time-intensive, and patients with COVID-19 may decompensate quickly. Thus, there was a short window in which patients met eligibility criteria without being too sick to engage in the research study. In addition, we found that obtaining informed consent, due to the processes involved, was often challenging for patients who were critically or near-critically ill; thus, it was less burdensome for the patient to complete the informed consent process prior to eligibility, and then to randomize patients if they clinically worsened to the point they were eligible for participation in our trial.

Although we were able to identify many work-arounds, we were not fully able to address the case of patients who were unable to provide informed consent themselves, and who either did not have a LAR, or had a LAR who did not have access to the relevant technology (e.g., no smart phone, tablet, computer, printer, or fax machine), and who were not able to travel to the medical center to participate in a traditional paper consenting process. Under the current federal guidance supporting documented signed consent, patients whose LAR lacks amenities such as a printer, scanner, or mobile phone able to send and receive encrypted images, are unable to participate, or undue burden is placed on the LAR to seek access to the relevant technology. Although consent forms could be sent via mail, this option leads to additional delays providing any treatments to the patient, which may ultimately render them ineligible for the clinical trial. As noted above, because COVID-19 is a novel disease process, there are limited treatment options available outside of clinical trials. Thus, beyond challenges to conducting clinical research, current FDA requirements are a substantial barrier—and health inequity—that must be addressed in future iterations of federal guidelines.

5. Conclusion

While the informed consent processes presented above were developed specifically for use in a COVID-19 environment, reuse of such remote processes may confer benefit in the development of future clinical trials where face-to-face informed consent is not possible, and may be applied to the study of other communicable diseases that may pose a risk of transmission to research study staff, or for environmental or fomite-based spread of disease for other pathogens. Issues of inequities and access require additional consideration and modification to ensure access to clinical trials for all patients who may benefit and wish to participate.

Funding

WBE is supported by National Heart Lung and Blood Institute 1K12HL138049-01.

Declaration of competing interest

All authors have no conflicts of interest to report.

Acknowledgements

We would like to thank all of the providers and staff at VA Boston Healthcare System who helped us work through barriers and assisted with the informed consent process, and the VA Boston Institutional Review Board and Research Service for their assistance navigating barriers and identifying solutions. We would also like to thank the VSN-1 Clinical Trials Network members and the staff of the VA Boston CSP Coordinating Center for their support of this study and assistance with implementation and operationalizing this study, and our collaborators at the participating sites for their ongoing collaboration and support of this project.

The views expressed are those of the study authors and do not imply endorsement of the US Federal Government.

References

- [1] W. Guan, Z. Ni, Y. Hu, et al., Clinical characteristics of coronavirus disease 2019 in China, *N. Engl. J. Med.* (2020).
- [2] D. Kamerow, Covid-19: the crisis of personal protective equipment in the US, *BMJ* 369 (2020).
- [3] M.L. Ranney, V. Griffith, A.K. Jha, Critical supply shortages—the need for ventilators and personal protective equipment during the Covid-19 pandemic, *N. Engl. J. Med.* 382 (18) (2020) e41.
- [4] Human Subjects Protection Issues Related to COVID-19: Frequently Asked Questions, 2020.
- [5] Development VOoRa, Human Subjects Protection Issues Related to COVID-19, Webinar, 2020 Session 4/2/2020.
- [6] US Food and Drug Administration, FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards, 2020.
- [7] VA Office and Research and Development, Spring Research Town Hall, 2020.
- [8] Mayo Clinic Emergency Access Program, Frequently Asked Questions, June 2020 Update, 2020.
- [9] W. Branch-Elliman, L.S. Lehmann, W.E. Boden, R. Ferguson, P. Monach, Pragmatic, adaptive clinical trials: is 2020 the dawning of a new age?, *Contemp Clin Trials Commun* 19 (Sep 2020) 100614, <https://doi.org/10.1016/j.conctc.2020.100614>.
- [10] W. Branch-Elliman, A.R. Elwy, P. Monach, Bringing New Meaning to the Term “Adaptive Trial”: Challenges of Conducting Clinical Research During the Coronavirus Disease 2019 Pandemic and Implications for Implementation Science, *Open forum infectious diseases* 7 (11) (2020, November) p. ofaa490. US: Oxford University Press.
- [11] M.G. Raimondo, M. Biggioggero, C. Crotti, A. Becciolini, E.G. Favalli, Profile of sarilumab and its potential in the treatment of rheumatoid arthritis, *Drug Des. Dev. Ther.* 11 (2017) 1593.
- [12] J.E. Natale, R. Lebet, J.G. Joseph, et al., Racial and ethnic disparities in parental refusal of consent in a large, multisite pediatric critical care clinical trial, *J. Pediatr.* 184 (2017) 204–208. e1.
- [13] P. Saberi, Research in the time of coronavirus: continuing ongoing studies in the midst of the COVID-19 pandemic, *AIDS Behav.* (2020) 1–4.
- [14] World Health Organization, *Guidance for Managing Ethical Issues in Infectious Disease Outbreaks*, 2016.
- [15] J. Baumann, Reams of useless COVID data drive reckoning on clinical trials, *Bloomberg News*. September 30 (2020) Accessed 10/14/2020 <https://news.bloomberglaw.com/health-law-and-business/reams-of-useless-covid-data-drive-reckoning-on-clinical-trials>.
- [16] C.M. North, M.L. Dougan, C.A. Sacks, Improving clinical trial enrollment — in the covid-19 era and beyond, *N. Engl. J. Med.* 383 (15) (2020) 1406–1408, <https://doi.org/10.1056/NEJMp2019989>.
- [17] Nuffield Department of Public Health, Recovery Trial FAQ for Sites, Oxford University, 2020 <https://www.recoverytrial.net/for-site-staff/site-set-up-1/recovery-trial-faq-for-study-sites/#identification>. (Accessed 14 October 2020).
- [18] J. Grein, N. Ohmagari, D. Shin, et al., Compassionate use of remdesivir for patients with severe covid-19, *N. Engl. J. Med.* 382 (24) (2020) 2327–2336, <https://doi.org/10.1056/NEJMoa2007016>.
- [19] K. Wilson, S. Chotirmall, C. Bai, J. Rello, COVID-19: Interim Guidance on Management Pending Empirical Evidence, 2020, p. 3 Last updated April.
- [20] J. Geleris, Y. Sun, J. Platt, et al., Observational study of hydroxychloroquine in hospitalized patients with covid-19, *N. Engl. J. Med.* (2020), <https://doi.org/10.1056/NEJMoa2012410>.
- [21] J. Magagnoli, S. Narendran, F. Pereira, et al., Outcomes of Hydroxychloroquine Usage in United States Veterans Hospitalized with Covid-19, *medrxiv*, 2020.
- [22] M.R. Mehra, S.S. Desai, F. Ruschitzka, A.N. Patel, Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis, *Lancet* (2020).
- [23] Mehra MR, Ruschitzka F, Patel AN. Retraction—hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet* doi:10.1016/S0140-6736(20)31324-6.