Overcoming the Challenges of Obtaining Informed Consent During the Pandemic

Synopsis
The COVID-19 pandemic created a public health emergency that has had a profound impact on all aspects of the clinical trial industry.

Quarantine requirements, and limited access to hospitals and clinics made it very difficult for investigators and site staff to conduct in-person informed consent discussions with potential clinical trial participants. It was also hard to identify and contact participants' legally authorised representatives (LARs), when they were unable to provide consent themselves.

The United States Food and Drug Administration (FDA) responded rapidly, supplementing its existing regulations covering informed consent with additional guidance to address the new realities facing sponsors, clinical research organisations, and sites. It also promptly published responses to frequently asked questions (FAQs) from the industry.

This healthcare crisis hastened the clinical trial industry's adoption of remote and e-consent approaches, creating challenges and benefits in the process. This article will discuss that industry transition and address some of the questions and issues it provoked.

COVID-19's impact started being felt in the clinical trial field in March 2020, when businesses and local governments began to shut down, and our Institutional Review Board (IRB) received an avalanche of questions about how to proceed not only with clinical trial conduct, but also interpreting the regulations in the context of the pandemic. Fortunately, there were several existing and new resources that we could draw upon for reference.

FDA's Code of Federal Regulations (CFR) Title 21 Section 50.20 states that before investigators can involve a human being as a participant in research covered by those regulations, they must obtain "the legally effective informed consent of the subject or the subject's [LAR]. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimise the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in a language understandable to the subject or the representative."

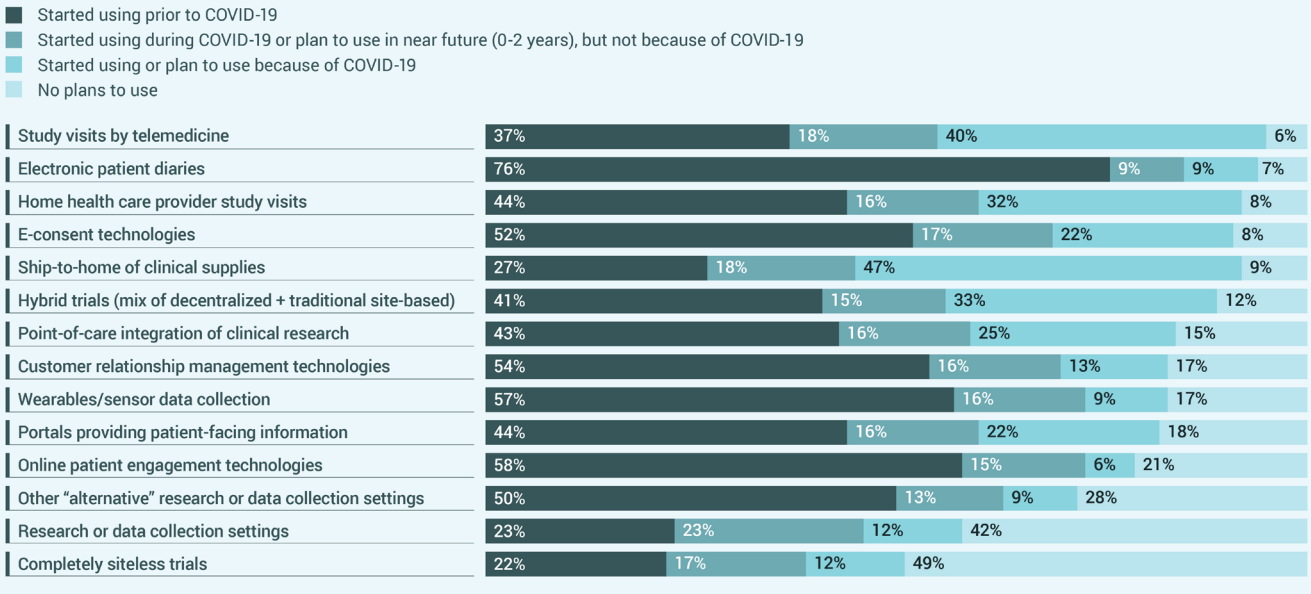
Furthermore, 21 CFR 50.27 (a) states that a written consent form approved by the IRB, should be signed, and dated by the participant or their LAR at the time of consent, and a copy given to the person signing the form.

The regulations do not specify that informed consent requires a wet ink signature. They are quite flexible in that regard. Neither do the regulations stipulate how informed consent should be obtained, they just define the elements it should contain.

There was also existing Department of Health and Human Services (HHS) and FDA e-consent guidance upon which to draw, including the "Use of Electronic Informed Consent: Questions and Answers," which was published in December 2016.

In response to the pandemic, the FDA issued new guidance for sponsors and investigators on the "Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency" in March 2020. The Agency also issued updates as either new information became available, or it received additional questions. The most recent update was issued in August 2021.

Decentralized Trial Activities and Patient Engagement Technologies



Source: WCG Avoca

Another resource that we relied upon was FDA's email address ClinicalTrialConduct-COVID19@FDA.HHS.gov, which allowed the Agency to provide very quick responses.

We also posted answers rapidly on our IRB website to the large volume of questions we were receiving. Many university IRBs and hospital IRBs also posted guidance for their investigators, which provided local context.

Obtaining Remote Consent

For this article, remote consent refers to instances in which informed consent was obtained at a distance and then the handwritten, signed consent form was sent back to the site or investigator.

FDA's guidance outlined many different scenarios in which consent could be obtained remotely in an FAQ document. The methods most frequently employed were as follows:

The consent form was sent to a prospective participant via email, US mail or a courier, such as UPS or FedEx. The potential participant reviewed the consent form remotely, and then asked questions of the site staff or investigators either by telephone or video conference call before deciding whether to give consent.

If the potential participant agreed to join the study, they signed the consent form and returned it. The guidance described several ways in which the form could be returned. For example, the participant could print the form, sign it, then photograph their signature on the document and return that image via email. Alternatively, they could print, sign, scan and email the consent form back, or return the signed hard copy via courier or US mail. Many sites started providing a stamped return envelope so that participants could sign the consent form and send it back easily.

If a participant could not print the consent form, the FDA guidance allowed documentation of verbal consent, but recommended that a witness be present.

Alternatively, the participant could send an email stating that they consented to join the study and would sign the consent form during their next on-site visit.

Another option was to record the phone call or video call, to provide verbal or visual documentation of consent.

Documentation is key for successful implementation of the remote consent process. Sites should implement a Standard Operating Procedure (SOP) describing their remote consent process to ensure their staff know the organisation's expectations and that consent is approached in a consistent manner.

When sites or sponsors contacted our IRB and asked about remote consent, we recommended that they create checklists or forms so that their documentation was standardised and consistent and could be more easily compiled for future audits. That way, they would not have some remote consents with a witness and others without or some that had the investigator sign the remote consent process and others that just noted their name.

We also recommended that any recordings, emails, signed consent forms, and other communications be filed in the appropriate participant's folder for audit purposes.

Obtaining E-consent

There are two types of e-consent. There are digital storyboards, which usually involve animation or interactive sections where a potential participant can click and get answers to their questions and then sign their consent to join the study electronically. Then, there is simply an electronic version of the consent form.

This article focuses on the second type of e-consent because during the pandemic, especially at the beginning when companies started shutting down, there was an urgent need to obtain consent in a safe way due to the risks of exposure. The easiest, most accessible approach was to create an electronic version of the paper consent form.

From a regulatory standpoint, the FDA guidance states: "Systems used to generate electronic signatures…including informed consent documents, during the COVID-19 public health emergency, must comply with the requirements outlined in FDA regulations at 21 CFR part 11." The pandemic does not exempt sites or sponsors from complying with the part 11 requirements for obtaining e-signatures.

Before establishing or certifying a participant's or LAR's electronic signature, site staff must verify the individual's identity using an official document such as a driver's license or passport, answers to security questions, or their username and password combination.

During the e-consent process, the organisation must still give potential participants suitable opportunity to ask questions and provide them with a record of the e-consent. Electronic records must also be available for inspection.

The e-signature tools that our IRB has seen employed most often include FDA's COVID MyStudies app, Adobe Sign, DocuSign, and REDCap. Adobe Sign and DocuSign scan documents as PDFs and then send them out for e-signature. REDCap allows some customisation, enabling investigators to add checkboxes or buttons, for example.

But even though those technologies are available, sites and sponsors are still responsible for ensuring that they are part 11 compliant. Some versions of Adobe Sign and DocuSign, generally the free versions, have non-part 11 compliant components. There are separate, paid part 11 compliant versions of the systems.

In addition to determining that the e-signature tool it plans to implement is part 11 compliant, the site also must define how the sponsor, monitors, and inspectors will have access to review the e-consent documents. That information should be outlined either in training procedures or SOPs. Part 11 also requires documented staff training on those systems prior to implementation.

Identifying LARs

An LAR is defined under 21 CFR 50.3(1) as "an individual, or judicial, or other body authorised under applicable law to consent on behalf of a prospective research subject to the subject's participation in the procedure(s) involved in the research." Some state laws differ on who can act as an LAR or give surrogate consent.

When HHS revised the Common Rule in 2018 (45 CFR 46.102 (i), it clarified that "in jurisdictions where there is no applicable law for allowing an LAR to provide consent on behalf of a prospective research subject, LAR means an individual recognised by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective research subject to the subject's participation in the procedure(s) involved in the research."

Therefore, if there is no applicable law for allowing an LAR, then the institutional policy determining who is allowed to consent for a patient who is incapacitated in a hospital setting also applies in the research setting.

For example, as COVID-19 had such a severe impact on an individual's respiratory function, there was heightened concern about having to consent patients who were intubated and on ventilators and who did not have the capacity to consent.

There was also the challenge of identifying the patient's LAR because many hospitals were at capacity and limiting who was allowed to be with the patient or even enter the hospital.

Furthermore, some LARs were in quarantine because they were suspected of having been in contact with an infected person.

That said, it was rare for a patient to arrive at the hospital and need to be intubated immediately. There was usually a window of time after the patient was admitted to the hospital before their condition was serious enough to warrant intubation and being put on a ventilator.

It is also important to remember that obtaining LAR consent for a participant who is incapacitated is not new. That type of situation occurs with research into stroke drugs, or studies on epilepsy. There

are existing regulations and guidances on conducting research in an emergency setting (21 CFR 50.24).

Included below are some of the questions that our IRB frequently received at the start of the pandemic.

Can the IRB Waive Documentation of Consent During the Pandemic?

No, the FDA did not grant any special exemptions from obtaining informed consent or signatures for informed consent during the pandemic. However, it did issue guidance on all the different ways consent could be documented.

The FDA and HHS have specific criteria that must be met for a waiver of documentation of informed consent to be allowed: the study must be no more than minimal risk; the waiver or alteration would not adversely affect the rights and welfare of participants; and the clinical investigation could not practicably be carried out without the waiver or alteration. Even if a signature is not required, verbal consent should still be obtained. Whenever appropriate, the participants should be provided with additional pertinent information afterwards.

If Government Mandates Require all Non-Essential Companies to Shut Down, and Participants Cannot Come in for Visits or to Sign New Consent Documents for Changes, What Should We Do?

FDA regulations (21 CFR 56.108(a)(4)) allow changes to be made to research without prior IRB approval to eliminate immediate hazards to human participants.

Changes to the protocol to reduce visits or changes to the consent form to allow for remote consent or e-consent to reduce potential exposure to COVID-19, could be seen as actions to eliminate possible immediate hazards to participants. Therefore, IRBs were very flexible in allowing that and communicating that to sponsors and investigators.

However, although the regulations allowed those actions to be implemented prior to IRB approval, sponsors and investigators still had to report them to the IRB. Documenting the deviations and rationale were critically important.

Do We Have to Revise our Consent Form to Allow for Remote Consent and Remote Monitoring?

The regulations do not require informed consent forms to be changed. Our IRB allowed "Dear Participant" letters or informed consent form addendums to be sent to participants. We recognised that making informed consent revisions can be quite a lengthy process and permitting those options would eliminate some of the burden of having to obtain reconsent signatures. At that time, many people were struggling to obtain signatures at all.

Of course, the absence of a reconsenting signature on the consent form does not mean participants cannot withdraw from the study. It is simply a way of communicating new information. If a participant learns about new procedures and decides to withdraw, they certainly can, and quite a few did.

In terms of remote monitoring, if the informed consent form states that the sponsor, its representatives, the IRB, and regulatory team will have access to personal health information, then the consent form does not need to be updated to allow for remote monitoring, since it already adequately discloses that they will have access. However, if the consent form specifically limits access to personal health information to on-site monitoring, then informed consent form revisions are required.

Do We Have to Obtain IRB Approval for Moving to Remote or E-Consents?

Yes, the regulations require that the IRB reviews and has authority to approve and disapprove all research activities. That includes the responsibility to ensure an adequate, informed consent process.

The move to e-consent or remote consent during the pandemic could be made prior to IRB approval because it fit the category of removing immediate risk of harm, but it still needed to be submitted to the IRB.

Benefits and Challenges

The pandemic spurred the adoption of remote and e-consent processes, producing both expected and unexpected benefits.

E-consent tools helped to ensure that the most up-to-date version of the consent form was used, and flagged missed fields such as checkboxes, dates, and signatures.

While e-consent provided a lot of flexibility, it also placed a cost and implementation burden on sites because they had to obtain an e-consent technology, train staff, and implement SOPs quickly. Many sites and e-consent companies were overwhelmed with purchase and implementation requests.

Introducing these remote processes also highlighted the difficulty of working with underserved populations, which often had difficulty accessing technology, limited access to internet, or experienced trouble with technical literacy.

In addition, it underscored the challenge for potential participants of interfacing with long, complex consent documents, which might require scrolling through 30 pages of information. It emphasised the importance of communicating key information – per HHS' Revised Common Rule in 2018 – which can help a potential participant decide whether to participate in a study.

Perhaps surprisingly, some sites and participants reported increased interactions during the informed consent process when videoconferencing and teleconferencing were employed. Those participants had a greater opportunity to ask questions than previously when they were just given the consent form, told to read it, and come back if they had questions.

Also on the positive side, we have seen increased diversity and growing enrolment of non-english speaking participants in clinical trials. Requests to our IRB for informed consent form translations jumped from 2,300 in 2019 to 3,700 in 2020.

Conclusion

The COVID-19 pandemic presented significant challenges to obtaining informed consent from clinical trial participants. Fortunately, the FDA and IRBs provided prompt, clear guidance, which built upon existing regulations, and provided a framework within which clinical research could continue, enabling breakthroughs to be made with COVID-19 vaccines and therapies.

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