HRPP-Related Federal Guidance on COVID-19: Year in Review

Introduction

Research institutions have needed to adapt to a new research landscape during the COVID-19 pandemic. In an effort to provide additional resources to investigators and institutional review boards (IRBs) involved in the conduct and oversight of human research, various federal agencies have released a substantial amount of guidance to address the new realities and challenges faced by these institutions. The full list of federal guidance can be found on Huron's COVID-19 HRPP Toolkit Supplemental Documents Release webpage.

This article aims to provide IRB professionals with a selection of highlights from the human research-related federal guidance released over the past year, in order to focus attention onto those topics that continue to be most impactful. The following highlights are presented roughly in order of their importance and their current impact to IRBs at the present time, in Huron's opinion. We recognize that the research landscape continues to shift during this pandemic, and the impact of these guidance documents will continue to evolve over time.

HRPP COVID-19-Specific Policies and Procedures

Human research protection programs (HRPPs) are encouraged to establish (and continually update) their policies and procedures as it relates to participant safety and well-being during COVID-19.

IRBs were encouraged to establish or alter policies and procedures to address participant safety and well-being during COVID-19 public health control measures. The U.S. Food and Drug Administration (FDA) outlines some examples of these procedures in its guidance, however, doesn't mandate or require any specific policies to be implemented. Across the nation, IRBs implemented guidance and policies based on the individual needs of their institutions and researchers in order to minimize COVID-19 transmission. Some of the examples of policies and procedures seen during the COVID-19 pandemic included or addressed:

1. Eliminating or reducing the amount of in-person contact between researchers and participants.
2. Prioritizing and accelerating the approval of COVID-19 research and COVID-19-related amendments.
3. Participant screening procedures.
4. Nontherapeutic research holds.

With vaccinations becoming more widely available and state-mandated restrictions changing, these procedures will likely need to be assessed on a constant basis to determine when they require alterations and when COVID-19 restrictions can be revised or lifted. IRBs are encouraged to continue to review current Centers for Disease Control and Prevention (CDC) guidelines and state requirements

as they may impact institutional and IRB policies regarding in-person research contact and reduction of research activity holds.

Minimizing or Eliminating Hazards to Human Subjects

Study procedures should be altered to mitigate the transmission of COVID-19. The implementation of procedures to eliminate hazards or protect research participants can be implemented before IRB approval has been obtained.

In the FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency, the FDA recognizes that there "may be unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 public health control measures." Sponsors and investigators are encouraged to alter procedures to mitigate the transmission of COVID-19 by reviewing the following:

1. Consent form procedures
2. In-person procedures that could take place via video or phone
3. The implementation of COVID-19 screening procedures

Although the FDA encourages sponsors and investigators to prospectively discuss any amendments to their procedures, both the FDA and Office for Human Research Protections (OHRP) regulations allow for the implementation of procedures that "minimize or eliminate immediate hazards or protect the life and well-being of research participants" before receiving IRB approval for the changes. The reasons for any study changes should be documented by the sponsor or investigator and reported to the IRB of record.

Informed Consent With COVID-19 Patients

The FDA included in its guidance numerous ways that investigators can obtain informed consent during the COVID-19 pandemic when the traditional way of obtaining informed consent is not feasible.

In its FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency, the FDA outlines informed consent procedures for subjects in quarantine, recognizing that it's not always feasible to obtain consent in the traditional fashion (i.e., paper consent or electronic consent). The methods of consent provided in this guidance include specific instructions and requirements for documentation. The IRB and researchers should review the guidance when exploring options for participants who may still not be able to sign a traditional consent form.

Furthermore, regardless of the method of informed consent chosen as most appropriate by the study team, the informed consent form should still be documented and archived, either using paper copies or certified electronic copies, and retained according to the appropriate regulations and funding requirements. Consent must also be documented (and obtained prior to study procedures), and a copy of the consent form must be provided to the research subjects. In cases where it is not feasible to obtain written consent before FDA-regulated study procedures take place, the study team should have

"the prospective trial participant or legally authorized representative confirm verbally during the consent interview that the participant or legally authorized representative has signed and dated the form."

IRB Review of Expanded Access

An increase in single subject expanded access requests warrants creating or updating IRB review procedures for these submissions.

In June 2020, the FDA released recommendations for procedures and factors that the IRB or designated reviewer should consider for individual patient expanded access submissions during the COVID-19 pandemic. During the early days of the COVID-19 pandemic, there was a noticeable increase in expanded access submissions at many IRBs. There is likely still an increase in these submissions as treating physicians work tirelessly to help their patients who present with severe disease by utilizing investigational drugs or devices that are not approved for this indication. These recommendations should be reviewed and used to streamline reviews of these types of IRB submissions.

IRBs should consider creating procedures for a single IRB member to review expanded access submissions for individual patients when the physician requests a waiver of full IRB review (Form FDA 3926 Box 10.b).

Reviewer(s) should also focus on the risks and benefits for the patient. This can be completed by a thorough review of the patient history and treatment plan (details included in Form FDA 3926 should be sufficient).

Other aspects that reviewers should consider are physician qualifications, consent and assent plans, and a required statement about the investigational nature of the drug for COVID-19 treatment.

Exception to Single IRB Review Requirements During COVID-19

An exception to the requirement to use a single IRB of record has been granted for certain studies that are conducted or supported by the Department of Health and Human Services (HHS).

On Oct. 8, 2020, as specifically permitted by 45 CFR 46.114(b)(2)(ii), the OHRP issued in the Federal Register its determination of Exceptions to Use of a Single IRB During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (OHRP COVID-19 Exception Determination). The determination states that, for certain studies that are conducted or supported by HHS and subject to the 2018 requirements, and for purposes of 45 CFR 46.114(b)(2)(ii), an exception to the requirement to use a single IRB is appropriate for cooperative research that meets the following criteria:

1. The cooperative research is "ongoing or initially reviewed by the IRB during the Coronavirus Disease 2019 (COVID-19) public health emergency, as declared by the Secretary of Health and Human Services."
2. "Reliance on a single IRB would not be practical."
3. "The HHS division supporting or conducting the research approves of the use of this exception."

For as long as OHRP's determination is in place, the National Institutes of Health (NIH) will not require use of a single IRB for NIH-funded research that qualifies for an exception. Approved exceptions apply for the duration of the NIH-conducted or supported research.

EUA Overview

An emergency use authorization (EUA) is a pathway for unapproved medical products or unapproved uses of approved medical products to be used in an emergency setting when certain criteria are met.

The EUA authority, under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), allows for unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by chemical, biological, radiological or nuclear (CBRN) threat agents when there are no adequate, approved and available alternatives.

Researchers and IRBs should be aware that the FDA's EUA authority is separate and distinct from the use of a medical product under an investigational application (i.e., investigational new drug application (IND) or investigational device exemption (IDE)), section 561 expanded access authorities, and section 564A emergency use authorities. Therefore, once the FDA issues an EUA, then subsequent use of the drug or device in the clinical setting is not considered research and subject to IND/IDE requirements or IRB review.

The FDA also added question 27 to its Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency, which asked:

> Q27. Certain clinical trial protocols have an exclusion criterion for receipt of another "investigational medical product." If a participant receives a vaccine or other medical product for the prevention or treatment of COVID-19 authorized under an Emergency Use Authorization (EUA), would FDA consider this receipt of an investigational medical product?

The FDA stated that when a medical product is being used under an EUA, the FDA does not consider receipt under an EUA as receipt of an investigational product, but that there may be valid scientific reasons to have an exclusion (and even a discontinuation) criterion for a medical product, whether that product was used under an EUA or not.

Public Health Surveillance Activities

IRB professionals are reminded that activities that meet the definition of public health surveillance activities do not require IRB review.

With the revised Common Rule, there were four categories under 45 CFR part 46.102(l) that were "deemed not to be research." Public health surveillance activities was one of these four activities. 45 CFR part 46.102(l)(2) reads as follows:

> Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease

> outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

IRB professionals are reminded to keep the above noted public health surveillance activities definition in mind as some activities related to COVID-19 will likely fall within this category. As a reminder, it is the recommendation of the Secretary's Advisory Committee on Human Research Protections that the public health authority and public health surveillance activities exclusion be interpreted narrowly such that research that is subject to the Common Rule is reviewed properly.

Conclusion

In the early weeks and months of the pandemic, the phrase "when things go back to normal" was widespread. It is now clear that things may never return to the way they were before the pandemic. All areas of the research enterprise have had to be nimble during the COVID-19 pandemic. This means adjusting research design and approach, the methods used to protect research participants, and keeping the past year's guidance in mind while reviewing human subjects research in light of a pandemic. Huron's team of certified IRB professionals and HRPP experts have been working with institutions to help navigate all the above topics, and we continue to develop guidance and institutional considerations that organizations can use during this challenging time.

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