COVID-19: REGULATORY GUIDANCE AND FLEXIBILITIES FOR THE CLINICAL RESEARCH COMMUNITY

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U.S. Health Care Alert

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INTRODUCTION

The COVID-19 outbreak has placed an unprecedented burden on the global health care community and caused significant disruption to numerous aspects of operations, including ongoing clinical research programs. The exceptional operational challenges presented by the pandemic have prompted the federal government and states to provide regulatory flexibility in order to stem the spread of the disease and mitigate interruptions in critical sectors.

For sponsors, institutions, and investigators engaged in clinical research, the COVID-19 outbreak has required significant adjustments to many vital processes and procedures. Social distancing requirements and concerns for patient and personnel safety limit the ability to conduct study visits and study monitoring. Further, global supply chain disruption and scarcity in certain health care products limits the availability of resources for clinical trials. With strained clinical supply chain resources being diverted to support emergency care for COVID-19 patients, clinical research stakeholders may face difficulty securing ongoing access to investigational drugs and devices, as well as peripheral supplies, including personal protective equipment (PPE) required for the protection of study personnel. Coupled with study personnel and subjects being under shelter-in-place orders in most parts of the country, investigators and institutions are increasingly turning to remote patient monitoring, evaluation and continued investigational interventions to prevent interruption or delays in ongoing studies.

The federal government has taken certain steps to address and support the clinical research community during the COVID-19 outbreak by, among other things, offering guidance related to the ethical conduct of clinical research studies during the public health emergency, providing waivers of certain remote treatment restrictions, encouraging interstate reciprocity of pharmacy licenses that may otherwise be required for interstate dispensing of investigational drugs, and offering federal grant funding to health care providers that can be used to support research operations.

This alert highlights several key actions taken by the federal government and state boards of pharmacy to support the continuance of clinical research studies in the midst of the COVID-19 pandemic.

OHRP GUIDANCE

The U.S. Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP) issued a guidance document on 8 April 2020, that clarifies certain regulatory flexibilities the research community can rely upon during the COVID-19 emergency in regard to compliance with the human subjects research protection regulations at 45 C.F.R part 46.[1] Though the guidance document is broadly applicable, OHRP notes that the circumstances particular to each research institution should ultimately guide that institution's decision-making during the emergency period.

OHRP first reiterates that actions not taken for research purposes do not require Institutional Review Board (IRB) approval. Specifically, public health or clinical actions with no research component, such as mandatory screening for persons coming to a research institution, do not require IRB review. Under 45 C.F.R 46.102(l)(2), certain types of public health surveillance are excluded from the definition of research and thus may be operationalized without IRB approval. This provision specifically exempts:

> *[T]he collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority [when necessary] . . . 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).*[2]

OHRP also indicates that investigators may follow state or federal public health authority mandates on collecting, analyzing, and reporting COVID-19 test results, even if such reporting is in conflict with the research study's consent form. This includes studies for which the Secretary of HHS has issued certificates of confidentiality under 42 U.S.C. § 241(d). OHRP states, however, if required reports are made, research participants should be informed by the investigator.

OHRP clarifies that investigators may make immediate changes to approved research when required to reduce or eliminate apparent immediate hazards without prior review and approval of the changes by the IRB. Such changes could include not conducting study visits in person or on schedule. Visits could also be canceled to reduce the risk of COVID-19 transmission. However, when possible, these changes should be reported to the IRB. Additionally, for changes that are submitted to the IRB, expedited review procedures may be utilized if the changes are minor. Research suspensions or terminations initiated by the investigator or institution due to COVID-19 do not need to be reported to OHRP. However, if a termination or suspension is instituted by the IRB, it must still be reported.

OHRP also notes that its 2018 guidance on disasters may be applicable in the current COVID-19 context.[3] This guidance emphasizes the discretion OHRP will exercise in considering the particular circumstances of a research study disrupted by an emergency. The 2018 guidance is primarily focused on what steps should be taken in the event a disaster prevents an IRB or research study from conducting its operations, including utilizing alternative IRBs and collaborating with investigators in other locations — though certain of these measures may be infeasible in the context of a public health emergency with national (versus local) impacts.

NIH GUIDANCE FOR CLINICAL TRIALS AND HUMAN SUBJECTS STUDIES

On 16 March 2020, the National Institutes of Health (NIH) published guidance for recipients of NIH funds on the flexibilities available during the COVID-19 emergency.[4] In this guidance, NIH reiterates that the health and safety of both research participants and staff is its primary concern. Therefore, NIH advises that recipients "consult with their IRB and institutions about potential measures" to protect participants and staff. NIH specifically suggests measures such as:

- Limiting study visits to those needed for participant safety or coincident with clinical care
- Conducting virtual study visits
- Arranging flexibilities for required laboratory tests or imaging needed for safety monitoring to occur at local laboratories or clinics
- Canceling large gatherings of 50 or more people
- Limiting or suspending unnecessary travel

Additionally, due to the delays researchers may face due to COVID-19, NIH provides details on a variety of flexibilities funding recipients have, including:

- Financial and progress reports may be submitted late[5]
- Unobligated balances on active grants may be carried over without requesting prior approval
- The final budget period of the approved project on active grants may be extended one time for up to 12 months without requesting prior approval
- Recipients may seek additional extensions for awards supporting NIH-funded clinical trials and human subjects research, including mid-project period extensions, through the awarding Institute or Center (IC)
    - For extensions related to COVID-19, project periods may be extended beyond the seven-year limit for awards supporting clinical trials and other human subjects research

In addition to increased flexibilities, recipients may request administrative supplements from the awarding IC to account for unanticipated costs when unobligated balances are not available to reallocate. ICs will grant additional funding on a case-by-case basis. Unanticipated costs that may warrant administrative supplements include:

- Costs incurred to arrange for participants to receive care at their local sites or virtually, rather than the study site, for required visits
- Supply chain disruptions
- Personnel disruptions due to illness or closure of facilities
- Additional lab testing (e.g., for COVID-19)
- Increased transportation costs

FDA CLINICAL TRIAL GUIDANCE

The federal Food and Drug Administration (FDA) likewise released a guidance document on 18 March 2020, for clinical research stakeholders engaged in FDA-regulated clinical trials during the COVID-19 outbreak.[6] The guidance document provides additional details on changes to research studies that can or should be implemented during the COVID-19 emergency and instances in which such changes may be made without first seeking IRB or FDA approval.

In the guidance document, FDA encourages clinical trial sponsors to engage with IRBs to determine whether continuing the conduct of a clinical trial may put participating patients at undue risk or whether the study design may be modified to minimize the risk of harm to patients and participants. For example, FDA suggests that clinical trials might be adjusted to incorporate remote patient monitoring and assessment or mail order delivery of study drugs that are of a type typically distributed for self-administration. If clinical trial sponsors and overseeing IRBs determine that appropriate modifications will not adequately mitigate the risk of harm to study subjects and personnel, FDA suggests that the conduct of the study should be delayed or cancelled until the study can proceed in a safe manner.

FDA reminds sponsors and clinical investigators that while modifications to a clinical trial protocol may not typically be implemented before review and approval by the IRB, or by FDA, as required, clinical trial sites may implement urgent or emergent changes necessitated by the COVID-19 emergency without prior IRB or FDA approval, so long as the changes are reported to the appropriate body afterwards.[7] Nevertheless, FDA encourages the clinical trial community to engage with IRBs as early as possible when such changes are anticipated.

OTHER REGULATORY FLEXIBILITY

In addition to the foregoing, there are other federal and state regulatory flexibilities that clinical researchers may wish to rely on during the COVID-19 public health emergency. For example, the federal Drug Enforcement Agency (DEA), has announced several exceptions to applicable regulatory requirements intended to facilitate the remote dispensing and prescribing of controlled substances to avoid unnecessary travel or patient-provider contact during the COVID-19 emergency. Further, on 25 March 2020, to facilitate the widespread adoption of licensure reciprocity, DEA announced that it is granting an official exception to the requirement that health care practitioners hold a controlled substances registration in each state in which the practitioner prescribes or dispenses controlled substances.[8] Correspondingly, many state boards of pharmacy have begun to offer reciprocity to health care practitioners licensed in other states.[9]

In the research context, these exceptions may allow a study requiring the dispensing or administration of controlled substances indicated by the study protocol to a patient domiciled or isolated across a state line, regardless of whether the investigator holds a controlled substances registration in the state where the patient is located. In such an instance, where an in-person patient-practitioner encounter would present undue risk, the investigators, clinical research institution, and sponsor (as applicable) may have the flexibility to modify the study design to allow for remote evaluation and prescribing.

CARES ACT PROVIDER RELIEF TERMS AND CONDITIONS

As a component of the Coronavirus Aid, Relief, and Economic Security (CARES) Act, the HHS Centers for Medicare & Medicaid Services (CMS) is empowered to issue US$100 billion in grant funding to Medicare-participating institutions to help defray the financial cost of responding to the COVID-19 emergency. Indeed, as of the writing of this alert, CMS has already begun dispersing the first US$30 billion.[10]

Recipients of this funding under the CARES Act must accept terms and conditions similar to those required of recipients of federal research funding (e.g., that the funds will only be used for COVID-19-related purposes, that the institution will not use the funds to reimburse other expenses or losses that have received or are expected to receive reimbursement from other sources).[11] Notably, entities that use CARES Act funds for research components of their operations "must provide satisfactory assurances of compliance with the participant protection requirement of [OHRP] prior to implementation of those research components."[12]

The Secretary of HHS is empowered to require that recipients submit reports to ensure compliance with the terms and conditions. Moreover, on a quarterly basis, entities who receive more than $150,000 from the federal government as part of the COVID-19 response[13] must submit a report of the funds received and how they were used. If used to support COVID-19-related research components, these reporting obligations would require a research institution to report funds allocated to research projects and any sub-grants made to collaborating sites or investigators. Records and cost documentation[14] must also be maintained to substantiate reimbursement of costs as designated in future program instructions. Researchers should also note that the terms and conditions prohibit the use of these CARES Act funds for embryo research.[15]

Full detail of the CARES Act grant funding payment terms and conditions is available in a separate K&L Gates alert, available here.

CONCLUSION

COVID-19 has significantly disrupted most aspects of daily life and workforce activities. The clinical research community is no exception, and safety concerns, public health requirements, and a lack of resources has led to institutions modifying, delaying, or cancelling clinical trials. Federal and state regulators have sought to mitigate some of this disruption by granting and clarifying regulatory flexibility for sponsors, institutions, and investigators to make COVID-19-driven protocol modifications and to continue aspects of studies remotely where it is safe to do so. Researchers may take advantage of these flexibilities, and in doing so, they should continue good documentation and subject communication practices.

K&L Gates LLP has created a HUB webpage to address the legal implications of the COVID-19 outbreak on businesses generally and health care providers in particular. K&L Gates' health care and FDA practice can provide guidance to providers and suppliers on these regulatory pronouncements and other regulatory flexibilities available as a result of the COVID-19 pandemic.

FOOTNOTES

[1] U.S. DEP'T OF HEALTH & HUMAN SERVS., OFFICE FOR HUMAN RESEARCH PROTS., OHRP GUIDANCE

ON COVID-19 (8 April 2020).

[2] 45 C.F.R § 46.102(l)(2).

[3] U.S. DEP'T OF HEALTH & HUMAN SERVS., OFFICE FOR HUMAN RESEARCH PROTS., EFFECTS OF DISASTERS ON HUMAN RESEARCH PROTECTIONS PROGRAMS GUIDANCE (14 May 2018).

[4] NAT'L INSTS, OF HEALTH, GUIDANCE FOR NIH-FUNDED CLINICAL TRIALS AND HUMAN SUBJECTS STUDIES AFFECTED BY COVID-19, NOT-OD-20-087 (16 March 2020).

[5] See also NAT'L INSTS. OF HEALTH, FLEXIBILITIES AVAILABLE TO APPLICANTS AND RECIPIENTS OF FEDERAL FINANCIAL ASSISTANCE AFFECTED BY COVID-19, NOT-OD-20-086 (12 March 2020).

[6] A full copy of the FDA guidance document is available here.

[7] See 21 C.F.R. §§ 56.108(a)(4), 56.104(c), 312.30(b)(2)(ii), 812.35(a)(2).

[8] A full copy of 25 March 2020 announcement from DEA describing the scope of the exception for interstate controlled substances registration during the COVID-19 emergency is available here. DEA's COVID-19 information page, which details additional exceptions and regulatory guidance the agency has offered is available here.

[9] See, e.g., N.C. BD. OF PHARMACY, EMERGENCY SERVICES WAIVER, Pa. Dep't of State Bureau of Prof'l & Occupational Affairs, Licensed Health Care Practitioners Can Provide Telemedicine Services to Pennsylvanians During Coronavirus Emergency (18 March 2020).

[10] DEP'T OF HEALTH & HUMAN SERVS., CARES ACT PROVIDER RELIEF FUND (13 April 2020).

[11] DEP'T OF HEALTH & HUMAN SERVS., Relief Fund Payment Terms and Conditions, 1 (Apr. 13, 2020)

[12] Id.

[13] Reports are required from entities receiving more than $150,000 total from all federal COVID-19 funding legislation, including the CARES Act (Pub. L. No. 116-136), the Coronavirus Preparedness and Response Supplemental Appropriations Act (Pub. L. No. 116-123), the Families First Coronavirus Response Act (Pub. L. No. 116-127), or any other act primarily making appropriations for the COVID-19 response and related activities.

[14] Including as required by 45 C.F.R. § 75.302 and 45 C.F.R. § 75.361–.365.

[15] Pub. L. No. 116-94, H.R. 1865, Sec. 508 (Dec. 20, 2019).

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