Nebraska Isolation and Quarantine Manual

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Clinical Research in the HLCC Setting
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Introduction
Providing safe and effective care to patients in a high-level containment care (HLCC) setting poses unique challenges to both clinicians and researchers. Diseases managed in the HLCC setting, particularly novel, rare, or emerging infectious diseases such as Ebola virus disease (EVD), often lack proven effective (licensed) therapeutic options. In addition, disease management may be challenged further by the lack of approved diagnostic tests. Furthermore, access to diagnostic equipment for clinical management may be limited by the risk of device contamination or inaccessibility of the device in an HLCC setting. Finally, effective screening and proven postexposure management strategies are limited in the absence of available opportunities to study novel and emerging infectious diseases in a rigorous scientific manner. Despite these challenges, the HLCC setting offers opportunities for clinical research to advance scientific knowledge amid a paucity of high-quality clinical data for certain special pathogens and emerging infectious diseases. Appropriately designed protocols are imperative to answer questions related to safety and efficacy of potential therapeutic interventions, diagnostics platforms, and prevention strategies, including vaccines.
Human Subjects’ Protection and Good Clinical Practices in HLCC Clinical Research

It is important to distinguish between that which constitutes clinical care and those activities that constitute research in a patient care environment. Much of the care administered in an HLCC setting with the sole intention of enhancing the well-being of a patient is considered treatment within the context of medical practice. However, systematic data collection with the intent to develop or contribute to generalizable knowledge is research. The Office for Human Research Protections (OHRP) provides guidance to establish whether an activity is human subjects research, so clinicians can be mindful of their obligations to uphold the Belmont Report’s ethical principles and follow guidelines for the protection of human subjects and comply with the US Department of Health and Human Services (HHS) Code of Federal Regulations (CFR) Title 45 Part 46 (45 CFR 46) Protection of Human Subjects.

Notably, the HHS Federal Policy for the Protection of Human Subjects, also known as the Common Rule, underwent revisions in 2017, and investigators conducting HHS-regulated research must comply with the new requirements as of January 21, 2019. The revised Common Rule contains significant updates including, among other changes, (1) new requirements regarding the information that must be given to prospective research subjects as part of the informed consent process; (2) allowing the use of broad consent (i.e., seeking prospective consent to unspecified research) from a subject for storage, maintenance, and secondary research use of identifiable private information and biospecimens; (3) establishing a requirement for US-based institutions engaged in cooperative research to use a single institutional review board (IRB) for the portion of the research that takes place within the United States, with certain exceptions.

Additional regulations related to clinical research and use of products regulated by the Food and Drug Administration (FDA) include 21

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1 The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, published in 1978 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, is a widely accepted summary of the ethical principles of research in humans.
Clinical Research in the HLCC Setting

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CFR 50 (Protection of Human Subjects), 21 CFR 56 (Institutional Review Boards), and 21 CFR 312 (Investigational New Drugs). These regulations allow for specific exemptions when conducting emergency research and may apply to clinical research in HLCC settings. Investigators conducting clinical research should adhere to the standards of good clinical practice as outlined in the International Council for Harmonization Integrated Addendum E6(R2) to E6(R1). It is ultimately the responsibility of the investigator to guarantee the safety and welfare of participants in clinical research and to ensure that study subjects are adequately protected while maintaining their rights, autonomy, and personal dignity.

**Treatment Research: Investigational Therapeutics and Devices**

In the absence of licensed therapies, clinicians caring for patients in an HLCC setting may seek use of investigational products that are in a preclinical or early clinical phase, and which have not yet been vetted through the lengthy drug development process and the scientific rigor of clinical trials. When considering use of an investigational drug or biological product, investigators must deliberate on and weigh the risk of potential harm against the potential benefit of an intervention to the subject. Ideally, an option with a favorable risk-benefit ratio can be determined prior to seeking use of an investigational therapeutic. Such an assessment may be particularly challenging when clinicians are faced with managing a life-threatening disease for which data regarding interventions are limited to preclinical trials and may not be publicly available.

Subpart I of 21 CFR 312 provides for expanded access to investigational drugs for treatment of immediately life-threatening conditions for which there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient’s disease or condition. Section 310 of this regulation delineates specifications for emergency use in individual patients, provided the physician determines that the probable risk to the person from the investigational new drug (IND) is not greater than the probable risk from the disease or condition and the FDA determines that the patient cannot obtain the drug under another IND or existing protocol. Treatment is generally limited to a single course of therapy for a specified duration unless the FDA expressly authorizes multiple courses
or chronic therapy. The licensed physician or sponsor must explain how
the expanded access use will meet the requirements of §§312.305 and
312.310 and must agree to submit an expanded access submission to the
FDA within 15 working days of FDA’s authorization of the use.

During the 2014–16 West Africa Ebola outbreak, 15 facilities in the
United States and Europe provided care to 27 patients with EVD, 23 of
whom received at least one investigational therapy. However, there were
very limited data available to clinicians and researchers to guide the se-
lection, administration, and monitoring of existing therapeutic options.
In addition, lack of a coordinated research network led to institutions
independently seeking the best available treatment options for their in-
dividual patients. The use of investigational therapeutics with heteroge-
neous clinical data collection and lack of standardized protocols across
institutions limited the ability to make conclusions as to whether the
therapeutic provided clinical benefit. In addition, use of multiple inves-
tigational therapeutics simultaneously precluded definitive conclusions
related to efficacy or potential harm from any individual drug. Despite
these limitations, data reported from these clinical observations can
generate knowledge and can inform the design of future randomized
clinical trials.

**Investigational Devices**

While providing HLCC care, lack of approved diagnostic tests may se-
verely limit a clinician’s ability to manage their patients appropriately.
Use of a medical device that has not yet been approved or cleared by
the FDA is considered investigational and generally should only be used
in human subjects if it is approved for clinical testing under an investi-
gational device exemption (IDE). Investigational devices, including in
vitro diagnostic tests, may be considered for use in clinical care under
the provisions of a treatment IDE if the device is intended to treat or
diagnose a serious or immediately life-threatening disease or condition
for which there is no comparable or satisfactory alternative device, the
device is under investigation in a controlled clinical trial for the same use
under an approved IDE, and the sponsor of the investigation is active-
ly pursuing marketing approval/clearance of the investigational device with due diligence.

**Additional Clinical Research Opportunities in a HLCC Unit**

In addition to treatment research, HLCC offers critical opportunities in other areas of clinical research to enhance knowledge and understanding of novel and emerging infectious diseases. Such research may include diagnostics, screening and prevention research, disease natural history, and epidemiological studies.

Reliable diagnostic assays are critically important to identify individuals infected with a particular pathogen accurately and may be necessary to monitor their response to treatment. Often in the setting of an emerging infectious disease outbreak, diagnostic tests may be limited only to those available in research settings or reference laboratories, thus reducing a clinician’s ability to make timely management decisions for their patients. During the care of the first patients with EVD in the United States, the Serious Communicable Diseases Unit at Emory University and the Nebraska Biocontainment Unit at the University of Nebraska Medical Center/Nebraska Medicine evaluated a diagnostic assay not yet approved for clinical use. This study demonstrated comparable performance of a research-use-only FilmArray® Biothreat-E panel when compared to the more complex molecular assays available at the time through the Centers for Disease Control and Prevention (CDC), suggesting a more accessible and easier-to-use assay with a rapid turnaround time. During the course of this study, the FDA subsequently issued an emergency use authorization (EUA) to allow use of this assay in the clinical setting.

Laboratory analysis of biospecimens during the course of a patient’s illness may support findings from animal models and inform future preclinical research. Comprehensive laboratory investigations, such as kinetic analysis of biomarkers, can lead to basic science discovery and improved understanding of the pathogenesis of rare and emerging infectious diseases. A main challenge of these studies is the ability to perform these types of investigations with samples classified as Category A or
select agents. These cannot be performed at the clinical institutions, and the shipping and storage of these is regulated by the Division of Select Agents and Toxins at the CDC. The sponsors of the investigational drug or devices may need to collaborate with a BSL-4–capable research laboratory to overcome some of the regulatory challenges.

Screening and prevention research should be prioritized in the midst of a public health emergency to identify potentially infected individuals accurately and to implement protective measures rapidly. Safe and effective pre- and postexposure prophylaxis options, such as vaccines, drugs, and biological products, are needed for individuals potentially exposed to Ebola virus or other special pathogens. Vaccine trials conducted during the West Africa Ebola outbreak provided vitally important data on vaccine safety and immunogenicity and informed the design and execution of future vaccine studies necessary to assess efficacy, including during later Ebola outbreaks in 2018 and 2019 in the Democratic Republic of the Congo.

**Special Pathogens Research Network**

The West Africa Ebola outbreak highlighted key gaps of research infrastructure necessary to implement scientifically sound, ethical clinical trials rapidly in the midst of a public health emergency. In response, the National Ebola Training and Education Center (NETEC), funded by the Assistant Secretary for Preparedness and Response (ASPR) and the CDC, established the Special Pathogen Research Network (SPRN) in collaboration with federal and academic partners to develop infrastructure for cohesive, coordinated clinical research efforts related to Ebola and other special pathogens. Key deliverables of the SPRN include creation of a master protocol for research, operationalization of a central IRB, development of universal case report forms, and web-based clinical data capture to facilitate collation and interpretation of data to inform clinical management, potentially in real time during an outbreak. The SPRN has established a medical countermeasures working group to develop guidance on therapeutics and prophylaxis measures, which will facilitate prompt and efficient awareness of potential investigational interventions. The SPRN is also developing a network biorepository fo-
cused on special pathogens with policies and procedures for processing and storage of specimens. A biorepository offers valuable opportunities for future research, particularly when the number of patients affected by rare and emerging infectious diseases enrolled in clinical research may be limited.

**Practical Considerations**

Even in state-of-the-art, well-resourced facilities, conducting clinical research in an HLCC unit poses significant challenges. There are practical considerations that investigators should anticipate in preparing for clinical research in such a setting. Ensuring that valid informed consent is obtained from a study participant, a critical component of human subjects protection, may be especially challenging when patients are suffering from a life-threatening illness for which there are no apparent alternative treatments. Patients who are critically ill may have decreased lucidity and awareness, rendering them unable to fully comprehend the proposed therapeutic benefit and potential associated risks of an investigational therapy. In such circumstances, or in other situations when a patient is unable to consent for themselves, locating a legally authorized representative in a timely fashion within a potentially narrow therapeutic window may be difficult. Finally, there may also be challenges communicating effectively with patients during the informed consent process simply due to personal protective equipment (masks, PAPRs) causing sound muffling.

Documenting informed consent and maintaining other source documents in an HLCC setting may pose added challenges. Inability to fully decontaminate items from a patient care area may render use of paper documents impractical or prohibitive. Investigators may utilize alternate means, such as electronic documentation or photographs of documents that may be securely transmitted from a contaminated area, as long as the IRB is made aware of and approves of this plan.

A sponsor of an investigational therapeutic may require specific monitoring procedures, such as electrocardiograms, or serial laboratory tests that are not readily available or accessible. Investigators should develop policies and procedures to safely conduct necessary monitoring as
required by the sponsor, but investigators and the sponsor should also consider which interventions are absolutely required versus optional to minimize risks to patients and staff alike.

Finally, health care workers providing HLCC to a patient may not be trained in clinical research. Conversely, research staff may not have prior experience with high-level personal protective equipment (PPE) to safely operate in an HLCC environment. Investigators may seek staff who have experience or familiarity with both clinical research and HLCC operations. Alternatively, research staff may receive just-in-time PPE training for safe and effective interaction in the HLCC unit, or provide training to HLCC health care workers on good clinical practices and protection of human subjects to conduct clinical research.

**Reporting and Dissemination of Findings**

Investigators conducting clinical research must comply with reporting requirements to the IRB, the FDA, and the sponsor. In addition, timely data sharing and dissemination of findings are critical to advance scientific knowledge and inform future investigations rapidly. In some cases, knowledge gained in real time could have an invaluable impact on the care of other patients during an outbreak. One must also consider the crucial aspect of respecting the privacy of the individual in the reporting, given that the number of cases evaluated may be few. This can be accomplished by obtaining consent from the individual, who may agree to the dissemination of their information, or by publishing in aggregate reports that include results from other patients or studies. In September 2015 the World Health Organization (WHO) convened a consultative meeting of international stakeholders to promote the sharing of data and results during public health emergencies. The WHO subsequently published a statement encouraging researchers in both public and private sectors to share data and quality-controlled preliminary results to advance public health, prevent illness, and save lives. Several prominent journals concurred in a consensus statement declaring that journals should encourage public sharing of relevant data and that authors should not be penalized for sharing data in the interest of resolving an urgent situation prior to manuscript submission.
Conclusion

In summary, clinical research is an important element in the management of patients cared for in the HLCC setting, especially when there are no licensed interventions. Knowledge gained, if managed effectively, has the potential to improve the care of subsequent patients, even as the outbreak unfolds. Research in this setting provides additional challenges, above and beyond the usual challenges of conducting clinical research, related to obtaining patient consent, managing records, collecting laboratory specimens, and maintaining patient confidentiality. However, by being prepared in advance to conduct research efficiently and in the spirit of collaboration, researchers can provide significant benefit to patients immediately and in the long term.