



Human Subjects Research in Bioemergencies

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Introduction

The nature of clinical care in bioemergencies presents distinct ethical and operational challenges for both patient care and research. While the most pressing concern at the onset of a bioemergency is always implementing clinical and public health measures to mitigate impact and stop the spread of disease, research is still needed to support this goal and improve our capacity to respond to the next threat.

As research within the context of containment care (i.e., patient care within a clinical biocontainment unit) remains a relatively new domain, novel and unexpected challenges present themselves as research opportunities that are approached in each new bioemergency. These challenges will vary greatly depending on the type of research being conducted. Understanding basic broad principles of the human subjects research relevant to studies conducted in acute care settings, as well as the growing experiences of investigators in these unique settings, will develop an informed foundation for containment care investigators.

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Recent pandemic threats (severe acute respiratory syndrome (SARS), avian influenza H5N1, pandemic influenza H1N1, and the 2014 Ebola virus disease outbreak) have highlighted the challenges in conducting clinical research in disease outbreaks, particularly involving novel or (re)emerging pathogens, particularly those about which limited systematic or high-quality data are available. Moreover, a debate has arisen regarding the ethical basis of the clinical and public health research being conducted during these emergencies. Research opportunities in bioemergencies are ample, and a number of considerations must be taken into account to ensure patient, public, and care worker safety. Conducting effective research in these environments requires making the distinction between it and public health practice or operational response [1].

Research Opportunities in Clinical Biocontainment Units

Clinical biocontainment units provide a novel but challenging platform for research in bioemergencies. Despite the broadly recognized importance of this research, international and domestic ethics guiding principles, as well as basic human rights, must be upheld and protected. Critical to these efforts is distinguishing the difference between data collection and analysis for effective response and clinical practice in an operational response and human subjects research for generalizable knowledge. To make this distinction, one must address the intent of the activity, which easily becomes blurred during emergencies [1]. For example, in a recent outbreak of Middle East respiratory syndrome coronavirus (MERS Co-V), epidemiologic and clinical data were collected and analyzed to determine the most effective infection control measures. The goal of this investigation was to effectively reduce transmission of MERS Co-V; however, the data will ultimately inform broader research questions outside of the context of the outbreak.

A critical priority for clinical and public health researchers, particularly those who are also practitioners, is understanding how to determine what activities are human subjects research versus a “standard” clinical operational response. To answer this question, the investigator must determine his or her goal. The Health and Human Services Office for Human Research Protections provides guidance on whether an activity is human subjects research [2]. Figure 15.1 demonstrates a decision tree for determining whether or not an individual is performing human subjects research. If the goal of the investigation is to develop or contribute to generalizable knowledge, this is fundamentally research and must progress down the regulatory path associated with research.

Research Types

There are several research activities that can be conducted in bioemergencies. In this chapter, we will focus primarily on clinical research, particularly as it relates to human subjects participation in bioemergencies. Among the various types of

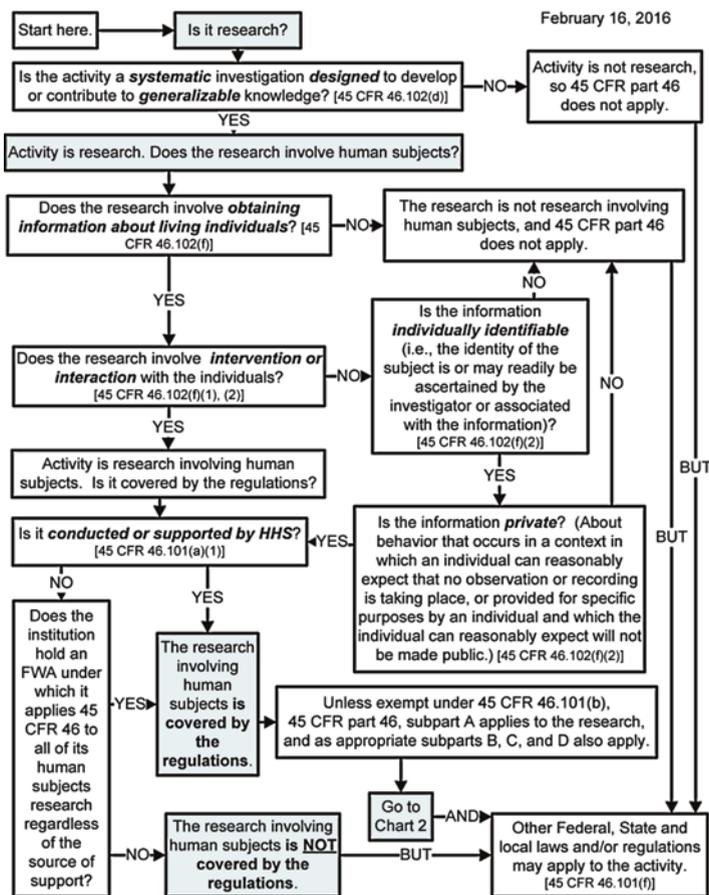


Fig. 15.1 Decision chart to determine if an activity is research involving human subjects. (From: Human Subject Regulations Decision Charts [Internet]. HHS.gov. 2016 [cited 26 October 2017]. Available from: <https://www.hhs.gov/ohrp/regulations-and-policy/decision-charts/index.html#c1>)

clinical research, treatment studies are the most likely, as they generally involve analyzing the effects of a countermeasure, therapeutic, or other intervention on affected or at-risk individuals.

Additionally, research related to vaccine or postexposure prophylaxis development and trials in an at-risk population, such as healthcare workers, may be conducted, with the goal of developing therapeutics and other tools for prevention of future outbreaks/infections. Other examples of research may involve collection of biospecimens for use in future research efforts or quarantine or containment research to understand infection and transmission dynamics. Research specimens are highly valuable in informing downstream laboratory analysis for better understanding of infectious diseases. Finally, diagnostic and screening research seeks to detect specific diseases or individuals afflicted by them. These studies offer new information

on a critical component of research in outbreaks and pandemics, as it focuses on preventing further spread of the infection.

Other research is necessary for an effective clinical and public health response beyond clinical research. Operational or implementation research in bioemergencies often focuses on real-time improvements to the clinical or health system response. This may include epidemiological studies focused on identification of causes, effects, or simply cases of a specific infection and may include looking for patterns during an outbreak for improved response, and many of these cases may not constitute human subjects research.

Regulatory Oversight of Human Subjects Research in Bioemergencies

The basic protections for human subjects of research are promulgated in the Common Rule, published in 1991, and based on the HHS regulations at 45 Code of Federal Regulations [CFR] part 46 [3]. The Common Rule applies to research conducted or supported by any of the departments and agencies that are signatories to the rule. Additional regulations at 21 CFR 50 (Protection of Human Subjects) and 21 CFR 56 (IRBs) cover clinical investigations using FDA-regulated products and differ only slightly from the HHS regulations.

These rules generally lay out the specific requirements for Institutional Review Board (IRB) operations and the conditions under which human subjects research may occur. This includes, among other things, the specific criteria for approval of research by the IRB, the process of obtaining informed consent from human subjects, and the elements of information that must be part of that process.

The IRB must assure that certain conditions are met before approving human subjects research. These criteria for approval are based on the ethical principles of respect for persons, beneficence, and justice, as laid out in the Belmont Report [3]. The IRB must judge that risks to subjects are minimized, that the risks are reasonable in relation to anticipated benefits to subject or to society, that subject selection is equitable, that informed consent is obtained, and that additional safeguards have been included to protect the vulnerable subjects, as well as other requirements.

Research conducted in the setting of a bioemergency presents challenges to both the investigator and to the IRB in assuring that these ethical and regulatory requirements are met so that critical research can be conducted.

Risk/Benefit

Research must be conducted in a manner that minimizes risk to participants. The investigator must design the protocol to limit potential harms, must monitor subjects throughout the protocol, and be prepared to adjust study parameters or design to assure that the subjects are not exposed to unnecessary risk. At the same time the protocol must be designed to maximize the possibility of direct subject benefit and

of more general scientific value. This may be particularly difficult in the setting of a disease process with an unknown natural history while using interventions of unproven (and, in many cases, only theoretical) efficacy.

Subject Selection

In all research, the ethical principles of the Belmont Report and HHS and FDA regulations require that selection of subjects must be fair and primarily based on scientific validity but also distribute risks and benefits equitably. This is particularly true in the case of therapeutic research during bioemergencies.

Where availability of interventions is limited, priorities should be dictated by ethical principles such as fairness between countries and among populations within countries (i.e., distributive justice) and the likelihood of a positive impact on both individual and public health outcomes. In addition, investigators should consider issues of reciprocity and social usefulness. Reciprocity refers to the obligations of healthcare workers during a pandemic and the obligations of society to them in return; that is, the acceptance of a healthcare provider's risk taking care of a patient with a highly communicable disease engenders reciprocal duties on the part of the community to them. Social usefulness refers to the idea that healthcare workers preferential access to prophylaxis and treatment would be directly associated with the continued ability of the healthcare system to provide interventions to everybody else [4].

Informed Consent

The investigator must design the study, and the IRB must also be assured that subjects will provide their voluntary and valid informed consent before participating in the research and that such consent is based on adequate, understandable information presented in a manner that minimizes the possibility of confusion, coercion, or undue influence. The conditions surrounding a bioemergency do not easily lend themselves to the provision of time for thoughtful consideration by a subject nor can the investigator be sure of the risks associated with his or her interventions, much less clearly explain them to a subject.

Further, subjects may be too ill to meaningfully or practically participate in the process of informed consent (particularly with some of the special pathogens such as Ebola virus that can contribute to substantial cognitive impairment). Under these circumstances, it may be necessary to utilize a legally authorized representative to provide "consent" (more accurately, "permission") for the patient to participate in the research.

Waiver of consent for participation in research is allowed under FDA and HHS regulations in very limited circumstances. FDA regulations allow that informed consent may be waived if the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing that (1) the human

subject is confronted by a life-threatening situation necessitating the use of the test article; (2) informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject; (3) time is not sufficient to obtain consent from the subject's legal representative; and (4) there is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject [5]. While potentially applicable to treatment studies of novel interventions for incapacitated persons in a bioemergency, such waiver would not be appropriate for collection of biospecimens or epidemiologic studies.

In addition FDA allows for exception from informed consent requirements for emergency research [6]; however, conducting research under these regulations requires extensive preparation and investigator and IRB responsibilities. For example, the regulations require consultation with representatives of and public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation. They also require public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study. As well, the regulations require that an independent data monitoring committee exercises oversight of the clinical investigation. These additional protections make use of this method unsuitable for most bioemergency situations.

It is important to stress that consent to participate in therapy research during a bioemergency is different from consent in the clinical treatment setting. In the clinical setting, for patients who are incapacitated, in need of a lifesaving intervention, and who cannot provide consent, "implied consent" is acceptable practice. "Implied consent" is not valid in the research setting.

Additional FDA Considerations

Under FDA regulations, the use of an FDA-unapproved drug, device, or biologic on a human subject requires, except under very limited circumstances, prior IRB approval. The use also requires informed consent (except as described above).

The usual process requires that the FDA grants an investigational new drug (IND), or an investigational device exemption (IDE) designation, which allows the drug or device to be used before it is legally marketed. Considering the use of unapproved drugs, most commonly, an investigator or a sponsor submits an IND to propose studying an unapproved drug or an approved product for a new indication or in a new patient population. In contrast, an emergency use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for the usual IND process. It is also used for patients who do not meet the criteria of an existing study protocol or if an approved study protocol does not exist. Finally, a treatment IND may be submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place [7].

Research utilizing drugs under any of these three types of INDs requires IRB approval. As described above, the IRB must determine that the criteria for approval are met, that informed consent is obtained, and that the rights and welfare of the subject are protected.

Under very specific and limited circumstances, unapproved drugs may be used without prospective IRB approval. FDA regulations allow for use of an investigational drug or biological product in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval [8]. The regulation allows for one emergency use of a test article without prospective IRB review; subsequent use of the investigational product at the institution has prospective IRB review and approval. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a single individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue. Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative (except as has been described above).

A second mechanism for use of unapproved drugs in a bioemergency involves the issuance of an emergency use authorization (EUA) [9]. The FDA may allow 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 biological agents (like Ebola or anthrax) when there are no adequate, approved, and available alternatives. The EUA must be issued by the commissioner based on a determination by the secretary of Homeland Security, Defense, or HHS, that a domestic, military, or public health emergency exists. Products approved under an EUA must meet a (lower) standard of effectiveness, must address a serious or life-threatening disease or condition, must have a favorable risk-benefit assessment, and must have no adequate, approved, and available alternative. The EUA is valid for up to 1 year from the date of the declaration of emergency or for as long as the emergency is in effect, whichever is shorter.

Use of a drug or device under an EUA requires neither IRB review nor informed consent (though a "fact sheet" for healthcare providers and recipients is required).

IRB Review

As discussed above, IRBs are responsible for protecting the rights and welfare of human subjects of research, a responsibility shared, obviously, with the investigator. The IRB must determine that the regulatory criteria for approval are met. Typically, the IRB receives a written application describing the research, as well as the investigator's description of how the investigator will assure that risks are minimized, the risk-benefit relationship is acceptable, subject selection is equitable, and so on. The IRB reviews this information (along with the full sponsor protocol, the informed consent documents, the investigator's brochure, and any additional materials) at a full convened meeting. After due deliberation, the board may approve the research conditional upon minor modifications or return the application to the investigator

for clarification or modifications needed to satisfy the regulatory criteria for approval. In addition, review and approval by other committees (scientific review, Pharmacy and Therapeutics, Sponsored Programs and Contracts, Institutional Biosafety) may be needed. Eventually, the protocol is approved, and the investigator may begin recruiting potential subjects. The process is thoughtful and protective but does not typically lend itself to the urgent timeline associated with a bioemergency.

Several approaches to this problem have been utilized. For example, the Ethics Review Board for Médecins Sans Frontières (MSF) has described a process of review and approval of a generic pathogen or intervention agnostic master research protocol in advance of a bioemergency; the details related to the specifics of the outbreak are then amended to the protocol when known [10].

Another approach has been the creation of national or regional central IRBs, with focus on public health emergencies, including bioemergencies. The HHS Public Health Emergency Research Review Board (PHERRB) is one such body and can serve as the IRB of record for any institution (such as a state health department, academic medical center, or community hospital) that is engaged in the conduct of the protocol [11].

A third approach is the utilization of a “Rapid Response IRB” such as that developed at the University of Nebraska Medical Center (UNMC). This fully constituted IRB was created to allow for review of clinical protocols on an expedited timeline, utilizing extensive prereview of protocols and consent documents in an iterative process, and close collaboration with the investigator. The UNMC Rapid Response IRB (RR-IRB) was used successfully to review research protocols associated with several investigational drugs and interventions targeting patients with Ebola virus disease hospitalized in the Nebraska Biocontainment Unit at UNMC/Nebraska Medicine.

The RR-IRB at UNMC also serves as the central IRB for the entire National Ebola Training and Education Center (NETEC) Special Pathogens Research Network, consisting of UNMC and the nine additional NETEC regional treatment center sites [12]. To facilitate this single IRB process, the network utilizes the reliance agreements modeled by the NIH SMART (Streamlined, Multisite, Accelerated Resources for Trials) IRB Platform [13].

Practical Issues

One of the biggest challenges of conducting research in bioemergencies is that they often involve novel disease-causing agents or pathogens. When the pathogen is novel, predetermined study design and pre-identification of affected populations and countermeasures is almost impossible [14]. This challenge represents situations where research, particularly clinical studies, is most needed as novel diseases often do not have associated therapeutics that are far enough down the drug discovery pipeline. Because of this, there are often not preapproved drug or treatment clinical trial protocols in place, ready to be implemented.

Innovations in Trial Design

In bioemergencies, the standard approach to generating evidence for informing medical practice may not be appropriate or feasible. There is growing interest in developing adaptive protocols that allow for flexibility and adaptability in study design through the use of ongoing data analysis and modeling to inform design structure. This approach has a twofold benefit of increasing the likelihood of obtaining usable, high-quality data from a variable and fast-paced study environment and reducing the cost-prohibitive price tag of traditional clinical trials.

In addition, trial networks that form around specific clinical areas of interest and capitalize on each other's existing research infrastructure are becoming increasingly common. They develop to share the burden of research infrastructure needs across multiple sites. Often, this is accomplished with common master or model protocols, central IRBs, central biorepositories, and innovative approaches to sharing resources [15].

Specimen Collection for Research Purposes

When conducting clinical research, it may be necessary to collect biospecimens from human subjects. Specimens may be collected for clinical purposes and used to inform a research study or may be collected specifically for research purposes. The Common Rule governs the collection of biological specimens from any living subject; in addition specific states and organizations may have their own rules regarding human samples. Specimen collection, retrieval, and practices will vary depending on type of research activity, nature of the specimen, and particular infectious disease of the patient. For example, a serum sample of a highly viremic Ebola virus disease patient will be addressed and handled differently than the nasal swab of a patient with an unidentified influenza-like illness. There are several best practice guidance documents regarding the handling of research specimens. For more information, see the laboratory chapter of this text (Chap. 6).

Storage and Future Use of Specimens and Data

Once collected, there is an option to store and maintain biological specimens and associated data for unspecified future use in a biorepository. A biorepository is a collection of any human biological materials and/or data that is intended to be used for research purposes, even if the purposes are not yet known. The data and specimens may be identifiable or de-identified (either coded or anonymous). This process is especially useful in a bioemergency as patients able to be enrolled in research studies may be sporadic or small in numbers. The OHRP provides specific guidance on the use of identifiable existing specimens and data in their guidance on Coded Private Information or Specimens Use in Research [2, 16–18].

Repository activities involve three components: the collection, storage, and distribution of materials and/or data. Specific IRB approval and continuing oversight are required for banking of specimens. The decision to store specimens and data for future use should be approved in advance of their collection. Federal regulation requires separate consent for the storage of biological materials. Subsequent research use of identifiable materials may require additional informed consent from subjects. Alternately, the consent provided at the time of banking of the information or specimens may have been sufficiently descriptive of what the stored specimen would be used for (i.e., consent to use may have already been obtained) that no additional permission would be required. Finally, separate consent for use of the specimens could be waived if the research is minimal risk, will not affect the rights and welfare of the subjects, and the research not be practicably carried out if additional consent were required (under HHS regulations) 45 CFR 46.116(d).

It is the responsibility of the investigator to maintain and protect human subjects records and specimens, and the resulting data, until they are properly destroyed. Federal regulations require research data to be retained for at least 3 years after the completion of the research [3]; however, many institutions have minimum amounts of time for keeping data upon completion of the research, so it is important to be aware of local requirements for both storage and (if necessary) appropriate destruction of data (and specimens.) As long as the researcher can guarantee that research data are secure, they can be kept indefinitely.

Participant Privacy

As noted above, collaboration is necessary for effective research in many bioemergencies as often times the disease may be rare and cases may be sporadic, particularly early in the emergency. This creates unique challenges around protecting the privacy of human subjects, particularly given the high level of media attention surrounding these events. For example, during the 2014–2016 Ebola virus disease outbreak, there was public awareness of the names of the few individuals treated in the USA. While formal measures for protecting and maintaining patient privacy should always be followed, they may not be sufficient in this context, and awareness of this is critical to reducing the risk of inadvertent participant identification [18–20].

Dissemination of Research Findings

While the goal of research is to inform generalizable knowledge, research data may be critical to response in the context of an unfolding public health emergency. Although publishing data is vital to the research process, it may delay dissemination of findings and potential beneficial changes in clinical practice or public health actions. In the wake of the Ebola outbreak of 2014–2016, the World Health Organization issued a consensus statement noting the need for more efficient and effective sharing of data and results in public health emergencies. Following this,

several journals made sweeping changes to improve researchers' ability to share data, without negatively impacting their ability to publish resulting manuscripts [21, 22].

When conducting research in bioemergencies, investigators should be cognizant of the need for both timely information sharing and publication of formal results. Conflict can arise among study team members regarding priority and approach to both of these areas, and discussion of a dissemination plan should occur early in the development of a research study whenever possible.

Conclusion

Researchers are responsible for maintaining the public's confidence and upholding this trust through appropriate conduct of research, and this is especially important in the role of clinician scientist. The stakes are particularly high in the context of a bioemergency, a setting with opportunities for conducting clinically novel and critical research but also considerable challenges. Affected populations are inherently vulnerable, and all aspects of conducting research in this emergency environment are challenging. Careful adherence to the high standards set for human subjects research helps to ensure that the rights and welfare of individuals are protected in bioemergencies and that all persons maintain trust in the research relationship and process.

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