**Chapter 45  
Informed consent for EMS research**

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**Development of uniform requirements for the protection of human subjects**

Today’s vast medical knowledge is built upon years of research efforts involving human subjects to delineate the causes and most effective treatments for injury and disease. Regulations regarding the ethical conduct of human subject research in the United States have developed over recent decades, informed largely by multiple instances of research misconduct. The 1974 National Research Act was the first public bioethics policy in the United States [1]. It was, in part, a response to the atrocities uncovered in the Tuskegee syphilis study [2], an experiment in Tuskegee, Alabama, in which treatment was withheld from 400 African American men with syphilis so that scientists could study the course of the disease. The National Research Act was the impetus for the creation of the Belmont Report [3] which led to the development of the first guidelines for human subject research and also defined institutional review boards (IRBs) [1].

**The Belmont Report**

The Belmont Report, published in 1979, identified the ethical principles of beneficence, justice, and respect for persons as the primary concepts comprising ethical research conduct. Today’s informed consent and research subjects selection process are based on these principles ([Table 45.1](https://jigsaw.vitalsource.com/books/9781118990827/epub/OPS/Vol2/c45.xhtml#c45-tbl-0001)).

[**Table 45.1**](https://jigsaw.vitalsource.com/books/9781118990827/epub/OPS/Vol2/c45.xhtml#R_c45-tbl-0001) Central principles of the Belmont Report and application to research

| **Ethical principle identified in Belmont Report** | **Standard for conduct of human subject research** |
| --- | --- |
| Respect for persons | *Concept: Ensure subjects have free choice to participate in research*The right to make an informed free choice to participate in research ANDThe need for special protections for those potential research subjects with diminished autonomy (children, prisoners, pregnant women, and those in subordinate positions) |
| Beneficence | *Concept: Do no harm while maximizing potential benefits and minimizing potential risks*Potential risks to subjects (physical, psychological, legal, economic, or social) should be as minimal as possible while accomplishing research objective ANDPotential benefits may be difficult to quantify, and are often greatest for society or future patients. When possible benefits should be maximized |
| Justice | *Concept: Promote fair study recruitment*Risks should be distributed so that all populations both bear risks and receive potential benefits. Risks must not be borne by one population (such as economically disadvantaged individuals) while benefits are received by a different (such as economically advantaged) population |

Respect for persons, beneficence, and justice were the principles used to inform development of the US Department of Health and Human Services (HHS) human subject protection regulations [4]. They continue to define ethical conduct for both biomedical and behavioral research involving human subjects.

**The Common Rule**

Harmonization of the many different federal human subject protection rules authored by various federal departments and agencies was accomplished in 1991. Fourteen agencies adopted a uniform set of rules for the protection of human subjects that were identical to the human subjects guidance set forth in the HHS regulations [4]. Known as the “Common Rule,” this uniform set of regulations is the defining federal policy for the protection of human subjects.

The Common Rule is the standard of ethics to which nearly all academic institutions hold their researchers regardless of funding source. The US Food and Drug Administration (FDA) also has regulations for protection of human subjects which conform in large part to the HHS regulations; however, research involving drugs or devices may be subject to additional FDA regulations [5].

**The role of the institutional review board**

All research involving human subjects must be reviewed by an IRB. The main purpose of the IRB review is to assure that the rights of human subjects are protected and that research is conducted ethically. Although human subject protections are a shared responsibility of the IRB, investigators, and personnel involved in the research, the IRB is the primary mechanism responsible for carrying out the DHHS and FDA regulations.

There are defined categories of research with correspondingly rigorous levels of regulation. While some studies may not require IRB approval, investigators cannot self-exempt their human participant research projects. Determining if a project is exempt from IRB review is an administrative review process handled by the IRB staff. Likewise, a protocol may be deemed to be of minimal risk, and may qualify for an expedited review process; again this is determined by the IRB based on the qualities of the study. By design, each IRB is charged with establishing its own local processes for complying with federal regulations delineated in the Common Rule. Local IRBs generally offer good guidance to researchers to take them through the processes required.

**Issues affecting prehospital research**

Research conducted in the prehospital setting can be a challenge both for the researcher to design and for IRBs to review and understand. Many IRBs may be most familiar with research that occurs within the confines of the institution, and may not have had experience with prehospital studies. They may not fully understand the limitations placed on research that occurs in the field. Additionally, special provisions for research into emergency conditions for which consent is not feasible have not been widely used and therefore may not be fully understood by many IRBs across the country.

Only a modest evidence base exists to support many prehospital treatments, and often the lack of evidence for some practices currently in place makes defining a standard of care difficult for many conditions. This is sometimes accompanied by practitioner bias for existing therapies or new unproven devices, which further affects the goal of achieving clinical equipoise in research.

**Public perceptions of prehospital care**

The public has an “illusion of efficacy” regarding the availability of current and future medical treatments for emergency conditions such as sudden cardiac arrest, trauma, and stroke [1]. The fact that there is very little scientific evidence supporting much of what is done in resuscitation and trauma care is generally unrecognized. Similarly, the public is unaware that many emergency therapies currently in use have not been rigorously tested. Public awareness exists mainly to the extent that the media sensationalize accounts of research misconduct. There is little public understanding about the need for scientific evidence upon which to base new therapies or about the barriers facing researchers as they attempt to develop and test new emergency treatments. Acquiring knowledge about treatment efficacy, while assuring that reasonable ethical actions are in place, remains a complicated task. In spite of obstacles facing prehospital researchers, the progress in prehospital research methodology and knowledge in the last decade has been impressive [6].

**Informed consent**

Informed consent for research participation is one of the most sensitive issues in prehospital research because these patients are considered vulnerable, due to their reliance on EMS professionals for emergency treatment, and therefore may feel coerced when asked to consent to participate in research. More difficult still is the issue of conducting emergency research when subjects may not be able to consent to participate due to the nature of their illness or injury.

Human subjects research carried out in the prehospital setting for emergency conditions where a patient is unable to provide informed consent (e.g. during cardiac arrest) is possible, but a series of additional regulations designed to provide extra protection to these vulnerable subjects must be followed. This process is called the exception from informed consent in emergency research (EICER).

**History of the exception from informed consent for emergency research**

During the mid 1970s, articles began to appear in the medical literature debating the issues fundamental to informed consent. These articles proposed a spectrum of ideological issues ranging from questions of whether consent during emergencies is necessary at all, to introspective treatises on the ethics and morality invoked when researching treatments for subjects who cannot give permission [7,8].

For emergency medicine researchers, this debate was largely an interesting philosophical issue that did not affect research to a great degree. Little emergency medicine research was being conducted for conditions that today present the greatest challenge in this arena, such as resuscitation from sudden cardiac arrest, preservation of life and organ function in major trauma, and salvage of the brain during stroke. Even fewer studies were under way in the prehospital setting [9]. Research pioneers in these fields generally obtained consent for participation in their studies retrospectively from the subjects’ family members following the administration of emergency treatment, typically after families had been located or presented to the hospital.

Several different consent strategies, all retrospective, were in use including deferred or implied consent and a two-tiered strategy [10,11]. These methods were used for several more years, particularly in resuscitation research that was sometimes conducted in the prehospital setting [12,13]. In 1993, a series of incidents raised concerns about research misconduct and prompted a presidential directive to investigate these offenses which resulted in the Office of Protection from Research Risks (now the Office for Human Research Protection) issuing a call for IRBs to stop all federally funded studies that did not involve obtaining prospective informed consent. An excellent review of the issues that led up to this action and the research implicated is detailed in Michelle Biros’ article “Research without consent: current status, 2003” [14].

The FDA also halted all resuscitation research in the United States for almost 4 years. Some researchers believe that this significantly affected the progress of resuscitation research, which was just beginning to gain momentum in the United States, and outcries were heard from the researchers [15]. This was accompanied by a flurry of communication between the FDA, HHS, emergency researchers, and professional societies with research missions [16].

Released in 1996, the Final Rule provides a mechanism by which prospective research can occur in emergency situations that meet certain conditions. Some researchers argued that the requirements added excessive regulatory burden and were overly restrictive to the conduct of research in areas where scientific evidence was sorely needed in order to establish effective new therapies, particularly in emergency and trauma care [17]. Others believed that the regulations provided appropriate safeguards to human subjects but that further refinement and standardization of the process were necessary to adequately facilitate resuscitation research [18].

The Final Rule was criticized for being too vague in sections to adequately advise IRBs on how to proceed, and for adding regulatory requirements without evidence as to their efficacy [19]. Part of the imprecision inherent in the Final Rule is purposeful, with the intent of leaving many decisions to the authority of the local IRB; however, when an IRB has little or no experience using the concepts of the EICER, this latitude can be viewed as more problematic than helpful.

**EMS research during the 1990s**

Although there was an increase in the number of prehospital publications evident during the 1990s, the majority of these were retrospective reviews. In an analysis of the literature published between 1985 and 1994, Brice et al. found that only 15% of the studies (42 in total) were clinical trials and 53% were retrospective in design [20]. Overall, the scientific rigor of the prehospital studies during that period was limited, and it was suggested that a strengthening of study designs would benefit EMS research progress.

Following the release of the Final Rule in 1996, there have been several successful examples of prehospital studies successfully negotiating the EICER rules. The first was the study of diaspirin cross-linked hemoglobin in severe traumatic hemorrhagic shock [21,22]. Others, including the large, multicenter study of public access defibrillation [23], soon followed, with varying experiences in the time invested in the process, expense, and perceived success of the exception of the process [24].

The specific conditions that must be met to allow research to proceed under the EICER are listed in [Box 45.1](https://jigsaw.vitalsource.com/books/9781118990827/epub/OPS/Vol2/c45.xhtml#c45-fea-0001). These were developed to help balance the need for advanced treatments in sudden cardiac arrest, trauma, and stroke with the assurance of adequate protections to research subjects who are not able to provide informed prospective consent. Detailed information about how these conditions are to be interpreted can be found in the FDA Information Sheets: “Guidance for Institutional Review Boards” and “Clinical Investigators 1998 Update: Exception from Informed Consent for Studies Conducted in Emergency Settings” ([www.fda.gov/oc/ohrt/irbs/except.html](http://www.fda.gov/oc/ohrt/irbs/except.html)) [22].

**Box 45.1 Conditions under which the exception from informed consent for emergency research may be used**

* A life-threatening situation exists
* Available treatments are unproven or unsatisfactory and scientific evidence is necessary to determine safety and effectiveness of the intervention
* Consent is not feasible due to the subject’s medical condition
* Treatment must be given before it is possible to obtain consent from a legally authorized representative (LAR)
* There is no reasonable way to identify prospectively those likely to become eligible subjects
* Risks and benefits must be considered to be reasonable
* Participation holds some prospect of direct benefit to the subjects
* The investigation could not practicably be carried out without the waiver of prospective consent
* The proposal defines the therapeutic window. The investigator will attempt to contact the LAR, if feasible, during the therapeutic window and will document these efforts for the IRB
* The IRB reviews and approves the consent procedures and documents to be used
* Additional protections of community consultation and public disclosure of risks and expected benefits be made to the communities from which the subjects may be expected. Community consultation and public disclosure will be conducted prior to study enrollment, and disclosure of demographic information and results will be made to the community and other researchers following completion of the study
* An independent data monitoring committee will be established to oversee risks and benefits
* IRBs must ensure that the earliest feasible attempts are made to inform the subject or his or her LAR of the subjects inclusion in the investigation as well as the other information contained in the informed consent document
* Protocols involving an exception to the informed consent requirement must be performed under a separate investigational new drug application or investigational device exemption that identifies them as including subjects who are unable to consent. The FDA must approve the application before the study may proceed
* If an IRB determines it cannot approve a clinical investigation because it does not meet criteria or because of ethical concerns, the IRB must provide this information in writing to the investigator and the study sponsor. The study sponsor must disclose this information to the FDA and other investigators participating in an equivalent investigation as well as to other IRBs that have been asked to review this or an equivalent protocol

Source: Data from Food and Drug Administration, Department of Health and Human Services. Exception from Informed Consent Requirements for Emergency Research: Guidance for Institutional Review Boards and Clinical Investigators. Available at: [www.fda.gov/oc/ohrt/irbs/except.html](http://www.fda.gov/oc/ohrt/irbs/except.html)

**Additional protections required when using the exception from informed consent for emergency research**

**Community consultation**

The most debated portion of the Final Rule is the requirement for community consultation and public disclosure. Community consultation refers to discourse between investigators and a wide variety of community members and representatives and addresses multiple issues, including an opportunity for input from the community, ensuring transparency in the research process, and engendering trust in the research process and the proposed study. Community consultation also provides a mechanism by which community members may opt out of enrollment [25].

Community consultation must occur prior to the enrollment of any subjects. Local IRBs assess the adequacy of plans for community consultation prior to study implementation and consider the results of the community consultation before making a decision about whether the research may proceed. Researchers are advised to work closely with their IRBs to determine an appropriate community consultation plan. The specific requirements for the scope of this activity were purposely left vague in the Final Rule so that local IRBs could ensure that community consultation activities were appropriate, based on their knowledge of their own communities.

In the past, many researchers have chosen to conduct community consultation by holding town hall meetings. At these meetings, the investigator presents information about the study and exception from informed consent. These presentations are typically scripted, with the IRB approving the script prior to the first presentation. Sometimes an IRB representative will also be monitor the consultation process and occasionally to provide additional information about the protection of human subjects to the attendees. Attendees are then given an opportunity to ask questions, and surveys are sometimes used to formally report the demographics of the attendees and their support or lack of support for the study.

Other strategies used to conduct community consultation prior to implementation of an EICER study include population-based telephone surveys and social media [26,27].

**Public disclosure**

Public disclosure is a one-way transfer of information to the community. It generally includes a notice that the study is planned, describes the nature and purpose of the research including the fact that consent will not be prospectively obtained, and presents the possible risks and expected benefits that might result. Public disclosure must be performed prior to the start of the study and after the study is complete. The intended purpose of public disclosure before the study is to inform the community, the public and other researchers about the details of the upcoming study. This should include the following elements.

* The intent to conduct the research without prospective informed consent
* A description of the treatment under study as well as its risks and benefits
* A synopsis of the protocol and study design
* Information about how subjects will be identified
* A list of sites participating in the research
* A description of the attempts that will be made to contact each subject’s legally authorized representative

Public disclosure to the community and to other researchers following completion of the study should include the following.

* Aggregate demographic information (age, sex, and race) about the population that participated
* Results of the study

Many researchers have found that submitting press releases to local media outlets is an effective way of initiating public disclosure. These typically also result in newspaper and radio interviews that allow study information to be relayed to the public. Further, the placement of classified ads and the release of public service announcements have also been used for public disclosure. These announcements also include references to websites and the researcher’s phone number so that those who are interested can obtain more information. These announcements are typically approved by the local IRB prior to their release. Some institutions will allow or even require researchers to work with their public relations office to produce high-quality press releases. Disclosures to other researchers can be accomplished through the publication of the study in a scientific journal.

**Meeting the requirements**

Most researchers agree that regulatory guidance such as the Final Rule is necessary and helpful to ensure that research maintains an ethical standard. However, the complexity of the rules, combined with inexperience of both researchers and IRBs in applying the guidelines, continues to impose financial and time costs which are considered barriers to conducting resuscitation research in the United States [24,28]. For example, among the 24 sites and 101 IRBs participating in the multicenter Public Access Defibrillation Trial, there were nearly 12,000 activities conducted to achieve community consultation and public disclosure [24]. Clearly, investigators must consider the time and cost of these activities in both planning and budgeting an EICER study [24].

The researcher who needs to apply these guidelines should become familiar with the rules, seek guidance from colleagues who have participated in this process, and establish early and regular communication with the IRB. This will help the parties to work through the regulations together and to design and conduct emergency research in an ethical manner and with every opportunity for success.

**Conclusion**

It is often said that EMS research is challenging to carry out. Conducting any research study requires meticulous planning to ensure that methodological issues are considered and also that ethical treatment of the human subjects who make research possible is adequately addressed. When conducting EICER research, it is helpful to become familiar with the regulations, to communicate early and often with your IRB, and to seek input from other researchers who have had experience with the process.

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