Exception from Informed Consent Requirements for Human Subjects in Emergency Medicine Research

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It is late at night, far out on an isolated rural road. Emergency crews have been called to the scene of an accident. Upon arriving, they discover that the accident involves a motorcyclist, who is in critical condition. Whatever identification the motorcyclist was carrying can not be located. The motorcyclist himself is unconscious and bleeding out quickly.

The emergency team loads the accident victim into their rig. They then start a research emergency treatment, utilizing an experimental reagent which has shown great promise in reducing the mortality and morbidity rates associated with this sort of trauma.

Once they arrive at the nearest hospital, an hour away, the crew hands the still-unconscious motorcyclist over to the trauma team. The trauma team continues the experimental treatment.

Six hours later a police officer telephones in that they have found the motorcyclist’s wallet in dense underbrush. Upon learning the identity of the emergency John Doe, the hospital contacts the next-of-kin to inform them of the accident and the experimental efforts extended during treatment, both during transport and subsequently in the emergency room (ER) and the intensive care unit (ICU) where the motorcyclist has been stabilized. The next-of-kin arrives an hour later, distraught over the accident and gravely concerned about the odds of the motorcyclist

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surviving the injuries, and also concerned about what long-term consequences and therapies are going to result from the accident.

In the volume of information being conveyed to the next-of-kin, one of the emergency team physicians explains: “During treatment, we used an experimental technique.” The physician, who is the investigator conducting the research, then begins to convey a large amount of information about the research study, including all of the information required by federal regulations necessary to obtain informed consent from the next-of-kin on behalf of the subject.

The physician pauses and asks: “Do you wish to continue participating in this research?”

The next-of-kin has just been introduced to the world of emergency research.

**History of Informed Consent**

The history of medical research goes back to antiquity. Cleopatra, according to Plutarch’s perhaps apocryphal account, experimented before deciding on the bite of the asp as her method of suicide by subjecting slaves to various toxins and witnessing the characteristics of their deaths.⁴ Throughout history, non-informed non-consent has shadowed significant beneficial advances. Dr. Alfred Hess, for example, who assisted in the development of the pertussis

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⁴ Plutarch, *Antony*, The Lives of Noble Grecians and Romans, Vol. 3, John Dryden and Arthur H. Clough, translators and editors (Boston: Little, Brown and Co., 1902) available at [http://www.shsu.edu/~his_ncp/AntCleo.html](http://www.shsu.edu/~his_ncp/AntCleo.html) (last accessed October 29, 2008). (“But Cleopatra was busied in making a collection of all varieties of poisonous drugs, and, in order to see which of them were the least painful in the operation, she had them tried upon prisoners condemned to die. But, finding that the quick poisons always worked with sharp pains, and that the less painful were slow. She next tried venomous animals, and watching with her own eyes whilst they were applied, one creature to the body of another. This was her daily practice, and she pretty well satisfied herself that nothing was comparable to the bite of the asp, which, without convulsion or groaning, brought on a heavy drowsiness and lethargy, with a gentle sweat on the face, the senses being stupefied by degrees; the patient, in appearance, being sensible of no pain but rather troubled to be disturbed or awakened like those that are in a profound natural sleep.”)
vaccination, conducted other experiments in children; in experiments studying dietary diseases he induced rickets and scurvy by denying children necessary nutrients, such as vitamin C.\(^5\)

Medical research, until recently, was a side-bar of medical practice. Informal experiments and \textit{ad hoc} reporting of results were the norm. Two events changed this, one negative, and one positive. The revelation of the experiments conducted during the Nazi Holocaust inspired the Nuremburg Code, still the foundation document in clinical trial ethics. Additionally, the development of evidence-based medicine, requiring scientific rigor, also helped establish medical research as its own field of endeavor.\(^6\)

Throughout most of history, marginalized and vulnerable populations were often the research subjects of choice. The twentieth century chronicled the horrendous “experiments” conducted by the Nazis during the Holocaust,\(^7\) the Tuskegee syphilis study, 8 Humphrey’s “Teahouse Trade” study,\(^9\) the Jewish Chronic Disease Hospital study,\(^10\) and experiments

\(^7\) [http://www.auschwitz.dk/Auschwitz.htm](http://www.auschwitz.dk/Auschwitz.htm)
\(^8\) [http://www.cdc.gov/tuskegee/timeline.htm](http://www.cdc.gov/tuskegee/timeline.htm)
\(^9\) DR Gallant and A Bliss, “Chapter 10-3: Qualitative Social Science Research” in \textit{Institutional Review Board Management and Function}, eds. EA Bankert and RJ Amdur, Jones and Bartlett Publishers, Sudbury, MA 2006, page 398. (“In the mid-1960’s, Laud Humphreys, a sociology graduate student at Washington University, conducted a study of men who frequented “tearooms” (public restrooms where strangers met for impersonal sex). Most of his subjects had no idea that he was a researcher. Humphreys served as a “watchqueen” and would cough or otherwise signal to warn participants of the approach of police or others. He secretly noted the license plate numbers of many subjects and through the Registry of Motor Vehicles obtained their names and addresses. A year later he arranged for these subjects to be added to a city-wide health survey, and, in disguise, visited their homes to collect extensive personal data about them.” The study itself was published as Humphreys L. \textit{Tearoom Trade: Impersonal Sex in Public Places}. Chicago: Aldrin Publishing; 1970)
\(^10\) See Karen Stutzer-Treimel. \textit{Clinical Trials: Balancing Obligations.} 19 (2) AACN ADVANCED CRITICAL CARE 130, 130-133 (2008). (In the Jewish Chronic Disease Hospital study live cancerous liver cells were injected into patients without their full consent. The expectation was that the liver cells would be rejected. This study is germane to the present topic because the investigators argued that obtaining full consent would have frightened the subjects, and that the anticipated outcome was that the malignant cancer cells would be rejected. This scenario should be remembered when contemplated the arguments that distress and emotions cloud the judgment of potential subjects or their representatives, and that experimental procedures should be allowed without consent based on their likelihood of effecting no negative outcome. The regulations, as described in this paper, require a likelihood of \textit{benefit} to the subject, not merely an absence of potential harm. Likewise, the regulations require that informed
performed on institutionalized children.\textsuperscript{11} In addition, prisons were sometimes seen as a readily available source of human subjects.\textsuperscript{12}

In the latter part of the twentieth century, these and other atrocities led to the development of ethical principles guiding medical research and specific regulations regarding the protection of research subjects. The recognition of the exploitation of vulnerable populations supported the promulgation of additional regulatory safeguards designed to protect those who were at the most risk of abuses during the course of medical research.

The Nuremberg Code was the primary document formed in the wake of the evils conducted by the Nazis in the name of medical research. Nuremberg’s design provides the framework upon which much of the modern research subject protection zeitgeist has been formulated. First and foremost is Nuremberg’s opening statement that “\textit{t}he voluntary consent of the human subject is absolutely essential.”\textsuperscript{13}

Following the Nuremberg Code, the Belmont Report articulated the foundation principles of modern medical research utilizing human subjects. Belmont set forth an ethical paradigm that

\textsuperscript{11} Such as the Willowbrook State Institution experiment, in which children were infected with hepatitis, or the Fernald School experiment in which children were fed small quantities of radioactive cereal. (See “Chapter 5-2: Evaluating Study Design and Quality,” \textit{Institutional Review Board Management and Function}, eds. EA Bankert and RJ Amdur, Jones and Bartlett Publishers, Sudbury, MA 2006, at page 130.)

\textsuperscript{12} http://jama.ama-assn.org/cgi/content/full/280/17/1542-a

\textsuperscript{13} http://ohsr.od.nih.gov/guidelines/nuremberg.html (“The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.”) Last accessed November 7, 2008.
was composed of autonomy,\textsuperscript{14} beneficence, non-malfeasance, and justice, balancing\textsuperscript{15} both individual liberties and societal interests\textsuperscript{16} in an effort to allow beneficial research to proceed while minimizing the risks to human subjects.


Section 45 CFR 46.116,\textsuperscript{17} in particular, outlines the duties to the research subject regarding informed consent, and 45 C.F.R. 46.117\textsuperscript{18} specifies the requirements for documenting informed consent.

\textsuperscript{14} Kant’s discourse in “Groundwork for the Metaphysics of Morals” addresses autonomy in a sense germane to the topic of subjects unable to consent for themselves. Kant postulates that persons are not to be used for the ends of other’s. (“Now I say: man and generally any rational being exists as an end in himself, not merely as a means to be arbitrarily used by this or that will, but in all his actions, whether they concern himself or other rational beings, must be always regarded at the same time as an end. All objects of the inclinations have only a conditional worth, for if the inclinations and the wants founded on them did not exist, then their object would be without value. But the inclinations, themselves being sources of want, are so far from having an absolute worth for which they should be desired that on the contrary it must be the universal wish of every rational being to be wholly free from them. Thus the worth of any object which is to be acquired by our action is always conditional. Beings whose existence depends not on our will but on nature’s, have nevertheless, if they are irrational beings, only a relative value as means, and are therefore called things; rational beings, on the contrary, are called persons, because their very nature points them out as ends in themselves, that is as something which must not be used merely as means, and so far therefore restricts freedom of action (and is an object of respect). These, therefore, are not merely subjective ends whose existence has a worth for us as an effect of our action, but objective ends, that is, things whose existence is an end in itself; an end moreover for which no other can be substituted, which they should subserve merely as means, for otherwise nothing whatever would possess absolute worth; but if all worth were conditioned and therefore contingent, then there would be no supreme practical principle of reason whatever.”) (Emphasis added.) Translation by Thomas Kingsmill Abbott, available at: \url{http://www.class.uidaho.edu/nickelsen/texts/Kant\%20-Fundamentals\%20\%20\%20.txt} \url{http://www.class.uidaho.edu/nickelsen/texts/Kant\%20-Fundamentals\%20\%20\%20.txt} The concept that a person may not be used as a means to the ends of another was also articulated in \textit{Bonner v Moran}, 126 F.2d 121 (D.C. Cir. 1941) in which the issue of parental consent for pediatric participation in research was addressed. (“[H]ere we have a case of a surgical operation not for the benefit of the person operated on but for another. . . . We are constrained, therefore, to feel . . . that the consent of the parent was necessary.”)


\textsuperscript{16} \url{http://ohsr.od.nih.gov/guidelines/belmont.html} (last accessed November 24, 2008)
The Declaration of Helsinki is considered to be the third primary document supporting the modern framework of protection for human research subjects. The 59th World Medical Association General Assembly, Seoul, October 2008, included statements regarding participation in medical research by those individuals who might be unable to give their own informed consent.

17 45 C.F.R. §46.116 General requirements for informed consent. “Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.” (The regulation then specifies the information that needs to be given, such as risks and benefits of the research, the nature and duration of the research intervention or treatment, alternative treatments available to the subject, what protections may be in place to protect confidentiality of records, compensation and payments (if any), and contact information. The subject should also be reminded that participation in research is voluntary, and that as a subject he/she has the right to withdraw from the research at any time without fearing the loss of benefits to which they would otherwise be entitled. In keeping with allowing emergency medical standard-of-care (and in some cases emergency use of test drugs or articles based on the physician’s medical judgment, in a non-research setting), the regulations further specifies: “(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.”) (Approved by the Office of Management and Budget under Control Number 0990-0260.) [56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

18 45 C.F.R. §46.117 Documentation of informed consent. “(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:(1) A written consent document that embodies the elements of informed consent required by §46.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or(2) A short form written consent document stating that the elements of informed consent required by §46.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form. (c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.” (Approved by the Office of Management and Budget under Control Number 0990-0260.) [56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]"
consent. First, those “who cannot give or refuse consent for themselves” were recognized as a vulnerable population. 19 In contemplating medical research involving vulnerable populations, Helsinki stipulates that the research should include a likelihood of benefit to the individuals in the vulnerable population.20

Helsinki at first seems to preclude any sort of waiver of informed consent21, but Article 29 the document adds: “If no such [surrogate] representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee.”22

The fundamental concepts of modern human subjects research hinge upon the obtaining the voluntary informed consent from the subject before enrolling that subject23 in any research.

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19 59th WMA General Assembly, Declaration of Helsinki 2008. Available at: http://www.wma.net/e/policy/b3.htm Last accessed October 28, 2008. (“9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.”)

20 Id at Article 17. (“Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.”)

21 Id at article 22. (“Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.”)

22 59th WMA General Assembly, Declaration of Helsinki 2008. Available at: http://www.wma.net/e/policy/b3.htm (last accessed October 28, 2008). (“Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.”)

23 “Subject” is used to describe a person participating in research, as opposed to the word “patient” which applies in a clinical care setting. While there is debate over the proper terminology that should be used to describe the research participant, the word “subject” will suffice for this article.
Informed consent rests on three required criteria: (1) that the subject has volunteered to participate in the study, (2) that the subject has been provided all the necessary information required to make the decision to participate, and that the information was presented in a comprehensible fashion (i.e. that the subject was “informed”), and (3) that given that information, the subject has agreed to participate (i.e. has “consented”).

It is beyond the scope of this article to fully address the requirements of informed consent. Additionally, this paper will not focus on a deontological evaluation of the informed consent process itself. The focus of this article is to examine the rationale behind enacting the current waiver of informed consent for emergency research regulations, and to consider how those regulations (a) came into being, and (b) issues related to their application.

**Surrogate Consent**

In those cases where the subject can not provide legally informed consent for him/herself, such as childhood or mental incapacitation, legally authorized representatives (LAR) may provide legal informed consent for the subject to participate in research activities.

This is a distinct duty from providing informed consent for clinical care, as research studies involve research questions and unknown endpoints. Research may also involve the blinding of participants as to the drug and/or intervention arm of the study they are involved in, or may even involve the subject being on a placebo arm, where no drug and/or invention is actually being administered.

In those circumstances where legal informed consent can not be obtained from the subject there is often an assent process which involves the actual subject in the decision making process. Refusal to assent, for example, is often regarded as refusal to participate in the research
and will frequently result in that subject not being enrolled in the research even where a LAR has consented on behalf of the potential subject.\textsuperscript{24}

The voluntary, knowing agreement to participate in a medical research study is the bedrock\textsuperscript{25} principle of informed consent. Performance of standard medical care, and certainly most research interventions, is predicated upon the informed consent of the patient (or subject, in the case of research) being obtained prior to beginning treatment.

However, certain circumstances may occur in which the ideal of informed consent may not be obtainable.\textsuperscript{26} These sometimes involve emergency care, where the unexpected trauma and urgency of medical care can preclude proper obtaining of informed consent. In these cases, proceeding without obtaining informed consent may be indicated. For standard of care, this is not necessarily problematic – the dire consequences of the medical event may recommend performing life-saving interventions even without informed consent.\textsuperscript{27}

Medical research is another matter. Research, by definition, is designed to answer a question. The outcome of the intervention is unknown, even where preliminary evidence may suggest that the intervention will produce beneficial outcomes.

Researching emergency medical interventions provides a unique challenge. The prevailing standard of care may be unsatisfactory, or even inadequate, to the circumstances of unexpected illness or trauma. There is a need to develop procedures, assessments, and interventions that will improve mortality and reduce morbidity in the emergency care setting.\textsuperscript{28}

\begin{itemize}
\item \textsuperscript{24} [http://www.onlineethics.org/cms/9070.aspx?printfriendly=true]
\item \textsuperscript{25} Acknowledgment to Paula Knudson for this language. (See also [http://books.nap.edu/openbook.php?record_id=10638&page=81])
\item \textsuperscript{26} DJ Mazur. Why the goals of informed consent are not realized: Treatise on informed consent for the primary care physician. 3 J GENERAL INTERNAL MEDICINE 370, 370-380 (1988).
\item \textsuperscript{27} This will be discussed in a subsequent section of this paper.
\item \textsuperscript{28} Protection of Human Subjects; Informed Consent; Proposed Rule, Department of Health and Human Services, Docket No. 95N-0158, 60(183) Fed. Reg.: 49085-49103 (September 21, 1995), available at [http://www.fda.gov/OHRMS/DOCKETS/98fr/092195.txt] (“By permitting certain adequate and well-controlled..."}
\end{itemize}
These new interventions are needed to improve treatment for emergency patients, the very population unable to provide adequate consent in many severe emergencies as they may be unconscious or in severe shock.

Robert Burt wrote in *The Suppressed Legacy of Nuremberg*:

“[T]he confident assertion of the self-determination right leaves unacknowledged and unanswered a crucial background question: who can be trusted to care for me when I am too vulnerable and fearful to care for myself?”

Much of the literature on the topic of waiver of informed consent for emergency research focuses on who can be trusted to make decisions for potential emergency research subjects. But obtaining informed consent is only one aspect of this research, and eventually the waiver question involves considering all three Belmont principles in an effort to sustain the legacy of the Nuremberg Code and enable necessary research.

**Waiver of Informed Consent in Medical Emergencies – Standard of Care**

The Food and Drug Administration (FDA) promulgated regulations designed to assist in conducting clinical trials in emergency medicine research, addressing those studies where the subject could not provide adequate informed consent and the narrow therapeutic window of the research intervention precluded obtaining proper surrogate consent. This paper seeks to evaluate how this regulation was developed and articulate some of the issues that have arisen as the regulations have begun to find application. It is beneficial to first reference how standard of care operates where the patient is incapable of providing informed consent.

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In non-research medical emergency settings, standard of care may be given without first obtaining the consent of the patient. In Texas, for example, if the patient is unable to provide consent, and in a life-threatening condition, emergency care may be provided. As long as the treatment rendered is consistent with standard of care, there is a limitation on civil liability for providing the emergency care.

The rationale behind this codification is that it makes common sense to allow physicians to provide emergency care to persons unable to immediately consent to that care. The life-threatening emergency itself demands rapid response; it is highly unlikely to be a prudent course of action to wait until the patient is capable of providing informed consent before initiating life-saving treatment. The patient might, for example, die prior to regaining consciousness, or contacting an appropriate surrogate decision maker.

Irrespective of if the intervention is standard of care or research, the quality of informed consent obtained from emergency room patients may be of questionable quality. In a study evaluating the effects of sedation and delirium in subjects presenting with acute lung injury, it was reported that the ability to adequately provide consent was compromised in approximately

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30 TEXAS HEALTH & SAFETY CODE, §773.008 (“Consent for emergency care of an individual is not required if: (1) the individual is: (A) unable to communicate because of an injury, accident, or illness or is unconscious; and (2) suffering from what reasonably appears to be a life-threatening injury or illness; (2) a court of record orders the treatment of an individual who is in an imminent emergency to prevent the individual’s serious bodily injury or loss of life; or (3) the individual is a minor who is suffering from what reasonably appears to be a life-threatening injury or illness and whose parents, managing or possessory conservator, or guardian is not present.”)

31 TEXAS HEALTH & SAFETY CODE, §773.009 (“A person who authorizes, sponsors, supports, finances, or supervises the functions of emergency room personnel and emergency medical services personnel is not liable for civil damages for an act or omission connected with training emergency medical services personnel or with services of treatment given to a patient or potential patient by emergency medical services personnel if the training, services, or treatment is performed in accordance with that standard of ordinary care.”)

32 Susan S. Ellenberg. Informed Consent: Protection or Obstacle? Some Emerging Issues. 18 CONTROLLED CLINICAL TRIALS 628-636, 632 (1997). (“Physicians are empowered to deliver emergency treatment in such situations, even with experimental agents, but the status of research protocols studying the treatment of these patients was not so clear.”)
75% of potential subjects. This suggests that even a conscious patient (or potential research subject) may be compromised by their condition, or other factors, to the extent that they are incapable of providing truly valid informed consent. Given that observation, the propriety of obtaining consent from a patient in an emergency, life-threatening situation may be logistically impracticable in certain cases.

Indeed, the distinction of informed consent in the provision of emergency care dates back to one of the foundation informed consent cases, Schloendorff v. The Society of the New York Hospital, in which Justice Cardozo wrote:

“Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient’s consent, commits an assault, for which he is liable in damages. (Pratt v. Davis, 224 Ill. 300; Mohr v. Williams, 95 Minn. 261) This is true except in cases of emergency where the patient is unconscious and where it is necessary to operate before consent can be obtained.” (Emphasis added)

The inherent possibility of conflict between obtaining informed consent and providing the best care was also addressed as part of Salgo vs. Leland Stanford etc. Bd. Trustees, 154 Cal.App.2d 560 (1957). In Salgo, the court recognized that a physician might exercise discretion regarding the disclosure of risks and the necessity of providing sufficient information to the patient to

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34 Eddy Fan, Shabana Shahid, Praveen Kondreddi, O. Joseph Bienvenu, Pedro A. Mendex-Tellez, Peter J. Pronovost, and Dale M. Needham. Informed consent in the critically ill: A two-step approach incorporating delirium screening. 36 (1) CRIT CARE MED 94-99, 97 (2008). (“By mistakenly obtaining what is thought to be informed consent from patients who lack decisional capacity, we risk violating patients’ rights to appropriate care, leading to the potential for causing harm in these vulnerable patients … An unanticipated benefit observed with large-scale implementation of these instruments [assessing sedation-agitation and delirium] was the identification of alert, but delirious, patients who were inappropriate for consent…Although not directly assessed in our study, other potential barriers to intact decisional capacity in patients who were not delirious include neurocognitive or neuropsychiatric issues that may be comorbid conditions preceding critical illness or direct complications of critical illness.”)

35 Schloendorff v. The Society of New York Hospital, 211 N.Y. 125, 105 N.E. 92 (1914). (In Schloedorff the plaintiff was operated upon without her consent. Subsequently, she developed gangrene and required amputation of some of her fingers, among other complaints. She sued, and the case has become a seminal citation in the legal history of the doctrine of clinical informed consent.)
facilitate actual acquisition of informed consent.\textsuperscript{36}

Additionally, it may be added that current Health Insurance Portability and Accountability Act of 1996 (HIPAA) guidance allows a physician to communicate with a family member regarding emergency care if the patient is unconscious, with certain limitations and conditions.\textsuperscript{37}

\textbf{21 C.F.R. 50.24}

It was recognized that the detailed regulations found at the “Common Rule”\textsuperscript{38} and the FDA regulations\textsuperscript{39} might negatively impact the conduct of research where adequate informed consent could not be obtained, particularly in the area of emergency research, where patients

\textsuperscript{36} \textit{Salgo v. Leland Stanford etc. Bd. Trustees}, 154 Cal.App.2d 560 (1957.) (“The court gave a rather broad instruction on the duty of a physician to disclose to the patient ‘all the facts which mutually affect his rights and interests and of the surgical risk, hazard, and danger, if any’ A physician violates his duty to his patient and subjects himself to liability if he withholds any facts which are necessary to form the basis of an intelligent consent by the patient to the proposed treatment. Likewise the physician may not minimize the known dangers of a procedure or operation in order to induce his patient’s consent. At the same time, the physician must place the welfare of his patient above all else and this very fact places him in a position in which he must choose between two alternative courses of action. One is to explain every risk attendant upon any surgical procedure or operation, no matter how remote; this may well result in alarming a patient who is already unduly apprehensive and who may as a result refuse to undertake surgery in which there is in fact minimal risk; it may also result in actually increasing the risks by reason of the physiological results of the apprehension itself. The other is to recognize that each patient presents a separate problem, that the patient’s mental and emotional condition is important and in certain cases may be crucial, and that in discussing the element of risk a certain amount of discretion must be employed consistent with the full disclosure of facts necessary to an informed consent.”)

\textsuperscript{37} “The Patient’s Guide to the HIPAA Privacy Rule: When health care providers may communicate about you with your family, friends, or others involved in your care.” September 16, 2008. “If I am unconscious or not around, can my health care provider still share or discuss my health information with my family, friends, or others involved in my care or payment for my care? Yes. If you are not around or cannot give permission, your health care provider may share or discuss your health information with family, friends, or others involved in your care or payment for your care if he or she believes, in his or her professional judgment, that it is in your best interest. When someone other than a friend or family member is asking about you, your health care provider may share or discuss your health information with family, friends, or others involved in your care or payment for your care if he or she believes, in his or her professional judgment, that it is in your best interest. When someone other than a friend or family member is asking about you, your health care provider must be reasonably sure that you asked the person to be involved in your care or payment for your care. Your health care provider may share your information face to face, over the phone, or in writing, but may only share the information that the family member, friend, or other person needs to know about your care or payment for your care. Here are some examples: • A surgeon who did emergency surgery on you may tell your spouse about your condition, either in person or by phone, while you are unconscious. • A pharmacist may give your prescription to a friend you send to pick it up. • A doctor may discuss your drugs with your caregiver who calls your doctor with a question about the right dosage. BUT: • A nurse may not tell your friend about a past medical problem that is unrelated to your current condition.” Available at: \url{http://www.hhs.gov/ocr/hipaa/consumer_ffg.pdf} (last accessed on December 4, 2008)

\textsuperscript{38} 45 C.F.R. Part 46.

\textsuperscript{39} 21 C.F.R. parts 50, 56, 312, 314, 601, 812, and 814.
were most likely to be experiencing life-threatening or serious conditions.\textsuperscript{40} In response, the

The regulation embodies seven basic concepts relevant to conducting emergency research
without first obtaining informed consent from the subject:

1. The research addresses a life threatening condition\textsuperscript{41}
2. Obtaining prospective consent is not feasible\textsuperscript{42}
3. Previous experience supports the potential benefit of the proposed research\textsuperscript{43}
4. The therapeutic window, and therefore the window for enrollment into the study, is
   narrow\textsuperscript{44}
5. Adequate Institutional Review Board (IRB) oversight exists to evaluate and review the

\textsuperscript{40} Protection of Human Subjects; Informed Consent; Proposed Rule, Department of Health and Human Services, Docket No. 95N-0158, 60(183) Fed. Reg.: 49085-49103, 49094 (September 21, 1995); Available at http://www.fda.gov/OHRMS/DOCKETS/98fr/092195.txt (“FDA believes that evidence submitted at the Public Forum on the chilling effect of current regulations on the care and medical management of such persons in life-threatening situations, including impairing their access to potentially life-saving therapy, justifies the prompt issuance of regulations governing research on such subjects.”)

\textsuperscript{41} 21 C.F.R. 50.24 (a), (1): “The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.”

\textsuperscript{42} See 21 CFR 50.24 (a), (2). (The subject is not capable of consenting for him/herself, it is unlikely than a LAR could be contacted before the research intervention must begin, there is no way of pre-identifying subjects to prospectively obtain consent, and there is a potential that the research intervention will directly benefit the individual subject.)

\textsuperscript{43} 21 CFR 50.24 (a), (3), (ii-iii). (Prior animal or other studies support that the proposed research holds out the prospect of benefit to the individual subject, and that the risks anticipated in the research are reasonable, as compared to the existing standard (non-research) of care.)

\textsuperscript{44} 21 C.F.R. 50.24 (a), (4-5). (The therapeutic window is the time period in which the research intervention must be initiated/administered in order to benefit the subject. Short therapeutic windows – in the order of four hours of less, risk being too short to enable contacting LARs or any other surrogate decision maker. Therapeutic window duration is based on scientific evidence, and the defined time period should be reviewed by the IRB as a prerequisite to approving the waiver of informed consent for emergency research. In addition to the limitations of the therapeutic window, the IRB should consider the likelihood that a LAR cannot be contacted in time to approve enrollment into the study during the therapeutic window, and the subject will likely be unable to consent for him/herself during this time frame. In the end analysis, the IRB should determine if the study could or could not be carried out without the waiver of informed consent. If it is unlikely that the study could be conducted without the waiver, then the IRB may consider that the study is an appropriate candidate for the waiver.)
6. Appropriate community consultations and public disclosures are afforded by the research plan.

7. Methods for obtaining consent, where applicable, from the subject or a legally authorized representative (LAR), are in place.

Additional procedural requirements for an exception of informed consent for emergency research include the maintenance of records for three years, and their availability to the FDA for inspection. If an Investigational New Drug (IND) or Investigational Device Exemption (IDE) is to be used in the research intervention, the application(s) for the IND/IDE must “clearly identify such protocols as protocols that may include subjects who are unable to consent.” If the IRB determines that the exception to informed consent cannot be granted, or that other ethical concerns exist, the IRB is directed to inform the PI and the sponsor; the sponsor in turn

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45 21 C.F.R. 50.24 (a), (6). (IRB approval constitutes an important oversight component for the emergency research study at all phases, including: before the study begins, during the study, and after the study has closed. The IRB will properly review the protocol, discuss the qualifications of the waiver of informed consent, and communicate concerns with the Principal Investigator (PI) as directed by 45 C.F.R. 46.109, or other applicable regulations, policies, and procedures in order to approve, require modifications to (in order to secure approval), or disapprove the research. An IRB approved informed consent document will still be required, and require IRB approval prior to implementation, for use in the unlikely circumstance that subject or LAR consent can be feasibly obtained prior to commencing the research. In addition, procedures should be defined and in place to allow for a family member, once contacted about the subject’s participation in the research, to object to the participation and withdraw the subject without any loss of benefits to which the subject would otherwise be entitled. Per 21 C.F.R. 50.24 (a) (7) (v), the PI is committed to attempting to contact a family member “who is not a legally authorized representative, and asking whether he or she objects to the subject’s participation in the clinical investigation.” The PI’s ongoing efforts to contact family members should be documented, and this information should be submitted to the IRB during the continuing review of the protocol.)

46 21 C.F.R. 50.24 (a) (7) (i-iii). (As individual potential subjects cannot be identified, and the nature of the waiver envisions that actual subjects, their family members, and LARs will not be available for consenting, the regulation has built in attempts to communicate the study to the community as almost a quasi-proxy. This communication process involves consultations with the community about the proposed research, public disclosure to the community about the study before the study begins – including standard informed consent information as risks and benefits, and public disclosure after the study is closed, including both demographic data regarding the subjects and the results of the study. The effectiveness and character of these consultations and disclosures is the topic of many excellent papers on the topic, and is beyond the scope of this paper to fully address.)

47 21 C.F.R. 50.24 (a) (7) (b).

48 21 C.F.R. 50.24 (7) (c).

49 21 C.F.R. 50.24 (7) (d).
communicates this negative determination to the FDA and other investigators involved in the study or studies like it.\textsuperscript{50}

In addition, if the subject can consent at a later date for him/herself, then informed consent should be obtained from the subject at that time. This reflects the practice in traditional (with prospective informed consent) research, where research subjects may have been entered on to the trial using a proxy’s consent, and have now gained the legal competence to consent for themselves (e.g., reached age of majority if a child, or entered a lucid phase if cognitively impaired when enrolled).

The subject should also be afforded the opportunity to withdraw from the research, either upon gaining consciousness/competence, or upon the decision of an LAR. Logistically speaking, the use of data obtained prior to the subject’s withdrawal may be a matter of debate.\textsuperscript{51}

When the regulation was proposed, the foundation principles of the Belmont report (respect, beneficence, and justice) were considered:

“\textbf{In emergent situations, protection is provided and the principle of respect for persons is satisfied if, in circumstances of clinical equipoise, either the test therapy or its historical alternative is provided, even without specific consent.} When the relative benefits and risks of the proposed intervention, as compared to standard therapy, are unknown, or thought to be equivalent or better, \textbf{there is clinical equipoise between the historical intervention and the proposed test intervention}. Clinical equipoise would exist, according to the testimony presented at the January 1995 FDA/NIH Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances, whenever at least a reasonable minority of medical professionals believe the experimental treatment would be as good as, or better than, the standard treatment.

This proposed rule is also consistent with the principle of beneficence. The principle of beneficence maximizes possible benefits and minimizes possible harms. In order to avoid harm, one must know what is harmful. In emergency medicine, the standard of care may

\textsuperscript{50} 21 C.F.R. 50.24 (7) (e).
\textsuperscript{51} Henry J. Silverman and Francois Lemaire. Ethics and research in critical care. 32 INTENSIVE CARE MED 1697, 1700 (2006) (“An emerging issue is whether subjects should be given the right to withdraw the data obtained from them when they were unconscious if they believe they would have refused participation at that time. This is a sound proposal, ethically speaking, but from a methodological point of view it is arguable since it could ruin the comparability of the study groups.”)
not have been validated – it may be beneficial or it may be harmful. The principle of beneficence dictates that knowledge be gathered when there is clinical equipoise between established and proposed interventions, through the conduct of research. Beneficence can be assured by the collection of valid scientific evidence, including evidence derived from randomized controlled clinical trials, in order to determine whether the particular intervention is beneficial. Harms are minimized, in part, by careful monitoring of the study by an independent data and safety monitoring board that regularly compares study data with pre-established 'stopping rules' designed to terminate the study before any serious harm occurs.

The principle of justice is also pertinent to this proposed rule. Systematically excluding persons who are unable to give informed consent and who have no surrogate to consent for them from research may be discriminatory, as noted above. An inability to consent, or lack of an authorized representative, should not in itself be a reason for excluding persons from participating in potentially beneficial and scientifically well-designed, controlled, studies."  

One of the tangential concerns regarding access to emergency medical research was that patients from lower socioeconomic groups might be denied access to potentially beneficial research interventions because those patients might be less likely to have an LAR arrive during the crucial therapeutic window. The right to access research interventions, and the right to decline participation in clinical trials, have each impacted ethical discussions regarding research enrollment for some time. Dr. Susan Ellenberg, of the Division of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, Food and Drug Administration, writing in 1997, noted:

“There is an irreconcilable conflict between such an individual’s [patient’s] right to be protected from interventions he or she would not want, and the right to have access to interventions he or she would want.”

As self-determination is denied when the participant is entered into research using a

waiver of informed consent, the protocol itself should have very defined endpoints and adequate oversight by a safety and data monitoring board to ensure that the rights of the subject are being safeguarded.\textsuperscript{55}

\textbf{Controversy}

The public’s perception of medical research is generally limited. Public understanding of informed consent (or the implications of waiving it) may be even more limited.

The concept of the medical research subject as a “guinea pig” still pervades even modern culture.\textsuperscript{56} Advertisements for clinical trials can be frequently found in the back pages of college newspapers and free publications, where “guinea-pigging”\textsuperscript{57} appears targeted to those most susceptible to financial coercion.\textsuperscript{58} The medical experiments conducted by the Nazis in World War II, images of \textit{Frankenstein}, and improbable experiments and results sketched out in comic books comprise more readily recognizable images of medical research to the general public than the Belmont Report, 45 C.F.R. 46, or the Office of Human Research Protections (OHRP). How many people, stopped at random on a city street, will be familiar with the protections granted to them as potential research subjects by Declaration of Helsinki?

\textsuperscript{55} This concept was presented by Bambi Grilley, RPh, RAC, CIP, CCRC, CCRP, Director of Clinical Protocol Research and Regulatory Affairs, Texas Children’s Cancer Center, Center for Cell and Gene Therapy, in a talk on clinical protocol research in pediatric populations, where consent is obtained from parents/guardians, and pediatric subjects may be asked to assent to participation in research. Given that the safeguards of data/safety monitoring and well-designed protocols are so important where the subject was at least informed of the research and their participation, the extension of the concept to emergency research, wherein adult subjects are enrolled without being informed, seems appropriate.

\textsuperscript{56} Wilets I, O’Rourke M, Nassis D. \textit{How patients and visitors to an urban emergency department view clinical research}. 10(10) ACAD EMERG MED 1081-5 (2003). (With regards to even “consented” medical research, the authors interviewed individuals in an adult emergency room setting. Within this study, the authors noted: “Although the majority [of respondents to the interview] (96%) endorsed a statement about the potential benefit of research for themselves or their loved ones, a sizeable proportion of respondents (49%) equated research subjects to “human guinea pigs.””)

\textsuperscript{57} The practice of enrolling in medical studies as a method of making money.

Against this backdrop, suggestions that medical experiments will be conducted without first obtaining the permission of the subject can garner less than positive press. In 2007 a WIRED blog contained the following entry:

“You’re unconscious, suffering from cardiac arrest on the floor of a shopping mall. The paramedics rush to the scene and promptly being … to enroll you in a randomized trial to determine if a new type of CPR-based treatment is better than the traditional one.

The only way you can get out of this involuntary research project is to wear a wristband saying you’ve opted out. And the only way you’d have a wristband was if you happened to know about the project in the first place.

Otherwise, you may get randomized to the new, untested way of doing things – and it could kill you. (Or you might get randomized to the old, tested way of doing things – and it could kill you too, since it doesn’t appear to work very well.)

If you live in one of about a dozen regions around the U.S and Canada, this scenario could happen to you. It’s all thanks to a waiver of “informed consent” regulations, which require people to give an OK before research is done on them.

The upcoming cardiac arrest project appears to be the first of its kind to be launched since a study drew intense criticism – and a federal rethink in the U.S. – by forcing unknowing trauma patients to get transfusions of fake blood.

While the blog represented a variety of viewpoints in its discussion thread, the article reflected public objections to waiving informed consent for emergency research. The flavor of the blog could also be found in an article in *Nature Medicine.*

To avoid negative images regarding emergency research, care should be taken to educate the public about research in general, emergency research in particular, informed consent, and conducting worthwhile emergency research.

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60 Andrea Anderson. *Emergency trials of blood substitutes skirt ethical questions.* 13(6) *NATURE MEDICINE* 652 (June 2007). (“Did you wear a thick, blue bracelet with the words “I decline the Northfield PolyHeme study” splashed across it in bold black writing during the years 2004 to 2006? If not, and had you been in a serious accident during that time, you could have been unwittingly enrolled in a phase 3 clinical trial for the blood substitute PolyHeme.”)
A brief history of the legislation\textsuperscript{61}

The call for waiver of informed consent gained momentum during the execution of the National Acute Brain Injury Study: Hypothermia (NABISH).\textsuperscript{62} The emergency intervention in this study had a six-hour therapeutic window. At the inception of the study, subjects were enrolled utilizing traditional informed consent. Later on in the study, the waiver of informed consent option became available. Using both methods, in addition to facilitating the research itself, allowed for the identification of various factors contingent upon the consent mechanism used.

Part and parcel of the NABISH trial was the achievement of hypothermia (33°C) within a brief therapeutic window (6 hours); the hypothermia was to be sustained for 48 hours.\textsuperscript{63} When limited to enrolling only those subjects from whom informed consent had been obtained (either from the subject or an appropriate relative), the study experienced two significant problems: first, subject accrual was low, and second, the target hypothermic temperature was attained later than desired. While the accrual problem might have been alleviated by adding additional investigative sites (and/or extending protocol duration), the time period to attaining target temperature could not be remedied by adding more sites.\textsuperscript{64} The trial was halted, due in part to these problems, until the waiver of informed consent could be implemented.

One of the interesting observations in this study was that minority and unskilled worker enrollment was enhanced by using the waiver of informed consent. “The NIH requires efforts to ensure that minorities are represented in research and have equal access to enrollment in

\textsuperscript{61} The author thanks Ms. Paula Knudson for insight into the history of this legislation and its history.
\textsuperscript{63} Id at 1122.
\textsuperscript{64} Id at 1125.
research,” and increasing representation of these populations was a side benefit of the waiver of informed consent. It was concluded that without employing the waiver of informed consent, minorities would have been 30% underrepresented in this study.

Prior to 1995, emergency research was sometimes approached using a “deferred consent” mechanism. In 1992, Dr. Guy Clifton (working in the area of preventing or limiting traumatic brain injury by applying hypothermia), initiated a study using deferred consent. This “deferred consent” notion was used to allow research for 48 hours. The Office of Protection from Research Risks (OPRR) then issued a statement in 1993 that it did not recognize “deferred consent.” When the request to obtain consent via telephone was made, OPRR also declined to recognize that method as a valid means to obtain informed consent.

Frustrated that the emergency medicine discipline was limited in its ability to acquire evidence-based medicine data and implement randomization in meaningful clinical trials,

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65 Id at 1122.
66 Id at 1125.
67 Protection of Human Subjects; Informed Consent; Proposed Rule. Department of Health and Human Services, Docket No. 95N-0158, 60(183) Fed. Reg.: 49085-49103 (September 21, 1995); Available at http://www.fda.gov/OHRMS/Dockets/98fr/092195.txt. (“[Deferred consent] was used to describe a procedure whereby subjects or representatives of subjects are informed, after the fact, that the subject participated, unknowingly, in a clinical investigation of an experimental product, and was administered a test article in the course of the investigation. Subjects or their representatives were then asked to ratify that participation retroactively, and to agree to continuing participation. As described, “deferred consent” is nothing other than post-hoc ratification. Post-hoc ratification is not genuine consent because the subject or representative has no opportunity to prevent the administration of the test article, and cannot, therefore, meaningfully be said to have consented to its use.”)
68 Nancy C. Molter. Exemption of Informed Consent (Final Rule): Procedures for Clinical Trauma Studies. 62 J TRAUMA S78-79, 78. (“Research could be conducted in ICUs for 48 hours while seeking surrogate consent.”)
69 The Office of Human Research Protections (OHRP) now fulfills this role.
70 Office for Protection from Research Risks. “Informed Consent – Legally Effective and Prospectively Obtained.” 1993. Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/hsrc93-03.htm. Accessed on November 26, 2008. (“Recently, we have become aware of the use of a consent procedure referred to as “deferred consent” or “ratification.” Informed consent procedures which provide for other than legally effective and prospectively obtained consent, fail to constitute informed consent under the HHS regulations for the protection of human research subjects.” Gary B. Ellis, Ph.D., Director, Office of Protection from Research Risks, August 12, 1993).
71 In which clinical practice incorporates current research to enhance the medical delivered. (See William Rosenberg and Anna Donald. Evidence based medicine: an approach to clinical problem solving. 310 BMJ 1122-1126 (1995). “Evidence based medicine is the process of systematically finding, appraising, and using contemporaneous research findings as the basis for clinical decisions. For decades people have been aware of the gaps between research evidence and clinical practice, and the consequences in terms of expensive, ineffective, or even harmful decision-making.”)
efforts were spurred to create an exception to informed consent for emergency research.

The evaluation of emergency medicine techniques, particularly with regards to identifying ineffective or potentially harmful interventions, and promoting improved methods of intervention, support, and care, were hindered by the logistical difficulties in formulating clinical trials that could work within the emergency’s therapeutic window and facilitate informed consent requirements. It was time for changes to be made that would allow emergency research to proceed according to both the medical demands of the disease and remain within the scope of regulatory compliance.

Dr. Clifton, accompanied by Paula Knudson of the University of Texas Medical School Health Science Center in Houston, Texas, petitioned the United States Congress for an exception to the informed consent requirements, in order to allow emergency research studies to proceed. Dr. Clifton and Ms. Knudson, along with others, gave testimony before a mixed Federal Drug Administration (FDA)/ National Institutes of Health (NIH)/legislative panel. The ongoing brain trauma studies were discussed, along with the difficulties of subject accrual and obtaining results

making.”) See also McCullough LB. Toward ethical best practices in community consultation for research conducted with waiver of informed consent. Crit. Care Med. 2008; 36(3): 993-4. (“The ethical imperative to improve medical care especially applies in such areas as critical care medicine, which is not unique in having developed without the evidence base that it requires.”)

A similar dilemma occurred in Europe, when European Clinical Trial Directive 2001/20/EC was published; this directive required prospective, written informed consent. In response, the European critical care and emergency research communities pointed out the threat to developing evidence-based care, particularly in the area of pharmacological medicine, in their areas. For a report on the European experience, see E. J. O. Kompanje. ‘No Time to be Lost!’ Ethical Considerations on Consent for Inclusion in Emergency Pharmacological Research in Severe Traumatic Brain Injury in the European Union. 13 SCI ENG ETHICS 371-381 (2007). (In arguing for waiver of informed consent, Dr. Kompanje states: “As two of us have said before: ‘treat first, ask later’ seems ethically defendable in acute care research [citing Kompanje EJO and AIR Maas. ‘Treat first, ask later?’ Emergency research in acute neurology and neurotraumatology in the European Union. 30 INTENSIVE CARE MED 168-9 (2004).]

The phrasing of the question, ‘treat first?’, embodies many of the underlying ethical issues involved when assessing what is hoped to be a superior research intervention over a less satisfactory standard-of-care. On one hand there is the concept of providing the best medical care and improving patient outcome, but on the other hand the specter of therapeutic misconception arises, as the research intervention is not yet an established ‘treatment’ and but is still an intervention or interaction undergoing scientific evaluation. In waiving the rights of the patient/subject to self-determination regarding participation in research, this ethical dilemma is highlighted.

Who graciously provided insight into the history of the regulation.

Including Senators Kennedy and Waxman.
that could translate into evidence-based emergency practice and potentially benefit patients.

On July 19, 1995, Philip R. Lee, the Assistant Secretary for Health, published a notice in the Federal Register\textsuperscript{75} allowing a waiver specifically for the NABISH study (recounted above). This waiver applied only to this study and was accompanied by a number of limitations:

“(i) The opportunity for the subjects to participate in the research is in the health interest of the subjects;

(ii) The waiver of consent will not adversely affect the rights and welfare of the subjects;

(iii) Additional appropriate protections of the rights and welfare of the subjects will be provided, including, but not limited to, consultation (which may include consultation carried out by the IRB itself) with representatives of the communities from which the subjects will be drawn;

(iv) The research could not practicably be carried out without the waiver; and

(v) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.”\textsuperscript{76}

Actual practical guidance regarding how to achieve these goals was not defined, but the NABISH study was continued using the waiver of informed consent. With this waiver, an option for conducting emergency medical research was created, and energy was injected into securing regulations that would permit the waiver of informed consent for emergency research.

\textsuperscript{75} 60(143) Fed. Reg. 38353-4 (July 26, 1995).
\textsuperscript{76} Id.
Involvement of the Community

Public involvement in waiver of informed consent for emergency research trials is enhanced, as compared to public involvement in reviewing and approving tradition research studies.

Federal regulations, as stated in 21 C.F.R. 50.24 (a)(7)(i & ii), direct the Principal Investigator (PI) and the IRB to conduct adequate community consultation before approving an emergency research waiver of consent study, and also direct for public disclosure before beginning the trial. Community consultation bears some contemplation, because it provides an opportunity for the community to “have opportunity for input into the IRB’s decision-making process before initiation of the study.” While this is in some ways similar to mandating community representation on an IRB when considering traditional research studies, this provision goes farther, incorporating explanation of the research, its risks, and benefits in a presentation (or series of presentations) to the public. This has two potential effects – one, the community almost stands in place of the subject, and receives the core information provided in an informed consent, and two, the community provides for an “expanded” community

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77 21 C.F.R. 50.24 (a)(7)(i-ii).
79 45 C.F.R. 46.107 (a) (“The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration if race, gender, and cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.”) and 45 C.F.R. 46.107(d) (“Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.”)
80 Exception from informed consent requirements for emergency research. Draft Guidance. http://www.fda.gov/ora/compliance_ref/bimo/default.htm#emer (Accessed November 20, 2008) (“Thus there needs to be an opportunity for the community(ies) to understand the proposed clinical investigation and its risks and benefits, and to discuss the investigation. The IRB should consider this community discussion when reviewing the investigational plans.”
81 45 C.F.R. 46.116 (a). (“Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of
representation with the IRB.

It is important to note that community consultation is just that – a consultation. The community does not “approve” of the study, although the IRB is directed to consider the results of the community consultation.\(^{82}\) One of the goals of the consultation is to provide a forum for feedback, in which the community can provide input regarding the study, but in practice this usually does not occur.\(^{83}\)

The primary goals of a community consultation should include fundamental education points, such as:

1. What is research?
2. The name of the institution where the research will occur.
3. Describing the function of the IRB.
4. Communicating that regulatory and ethical protections are in place for those participating as human subjects, and what those protections are.

In the wake of the NABISH study, the “Houston Model” was developed to establish guidance for community consultation and public disclosure methods and standards. This model establishes a

\(^{82}\) Exception from informed consent requirements for emergency research. Draft Guidance.  

\(^{83}\) Public disclosure at the end of the trial is also a component of the regulations.
high standard of community outreach and education for communicating the trial to the area from which subjects will be drawn.

The best methods for community consultation are still being developed. Draft guidance itself suggests that “[t]here is no single, set way to accomplish this requirement.” Research in establishing norms of conducting and evaluating community consultation remain notoriously difficult to conduct and interpret. Some studies of community consultation choose to focus on the goals of community consultation, some reports address how to properly consult the community (through random outreach or targeted meetings), and others attempt to identify the factors that underlie the community’s response to the proposed research.

Another facet of community consultation, and public disclosure, may be publicizing “opt out” mechanisms for the study. “Opt out” is peculiar to emergency research with waiver of informed consent studies, as it necessitates expressing an attitude about a trial that the person may never actually be an eligible candidate for. In a way, opting out is informed non-consent. This mechanism is frequently exercised by supplying the person who wishes to opt out of the

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84 Id. At page 16.
85 Janice N. Longfield, Michael J. Morris, Kimberly A. Moran, John F. Kraugh, Jr., Rick Wolf, and Toney W. Baskin. Community meetings for emergency research community consultation. 36(3) CRIT CARE MED 731-736 (2008). (Examining factors that may influence the “ethical goals of enhanced protection, benefit, legitimacy, and shared responsibility for research in the emergency setting.”); Laurence B. McCullough. Toward ethical best practices in community consultation for research conducted with waiver of informed consent. 36(3) CRIT CARE MED 993-4 (2008). (Suggesting critical thinking tools that may assist the IRB when considering the results of community consultations.)
86 Roger J. Lewis. Community Consultation by Randomly Reaching Out to the Community. ANN EMERG MED November 3, 2008 [ePub ahead of print, PMID: 18986733]. (The use of random telephone calls, among other methods, to elicit community response, as well as avoiding therapeutic misconception in the phrasing of questions asked of the community.)
87 Raina M. Merchant, Jonathan D. Rubright, John P. Pryor and Jason H.T. Karlawish. Who can speak for the emergently ill? Testing a method to identify communities and their leaders. 15 ACAD EMERG MED 581-583 (2008). (Suggesting that consulting on geographic communities and faith-based organizations and leaders might assist in improving the effectiveness of the community consultation.)
88 J.M. Baren, J.P. Anicetti, S. Ledesma, M.H. Biros, M. Mahabee-Gittens and R.J. Lewis. An approach to community consultation prior to initiating an emergency research study incorporating a waiver of informed consent. 6 (12) ACAD EMERG MED 1210-5 (1999). (Looking at potential reasons for consenting to, or not consenting to, emergency research, as well as deriving that data in a population pre-exposed to minor trauma circumstances, such as patients and patient families in an emergency department waiting room.)
study with a bracelet that expresses a desire not to be enrolled into the ongoing emergency research. While feasible, the bracelet opt-out method presents with obvious flaws: the potential subject would need to be aware of the emergency research being conducted; the potential subject would have to be aware of the opt-out provision and go about obtaining the opt-out bracelet; and the potential subject would have to be committed to wearing the bracelet throughout the duration of the study.

In a study designed to characterize the experience of the Resuscitation Outcomes Consortium (ROC) with an opt-out bracelet strategy, the investigators reported receiving 395 telephone requests for 718 opt-out bracelets. Interestingly, the majority of these requests (90%) were received within the first two months of bracelet distribution, and by six months, there were about 2 requests a month. Another factor noted in this study is that distribution of the requests from the subject pool community revealed some insight into who was more likely to request an opt-out bracelet. Graduate school level education and higher household incomes were related to opt-out bracelet requests – the authors suggest that this may reflect an increased likelihood of receiving information about the study, as these populations might have better access to home computers or other media sources as a means of learning about the trial.

21 C.F.R. 50.24 was adopted in 1996, along with the Announcement of the HHS

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Secretarial Emergency Research Consent Waiver; the draft regulation was issued in 2000 and updated in 2006. The first study conducted using the rule was approved on November 21, 1996, and involved studying the effects of diaspirin cross-linked hemoglobin (DCLHb), in addition to standard therapy, in critically injured adults. This trial is discussed later in this article.

**Additional duties for the Institutional Review Board (IRB)**

IRBs may be uncertain regarding how to interpret and/or apply federal regulations. Emergency medical research studies may include multiple institutions. This may result in discrepancies between the boards as to the requirements of the waiver and/or the research. Cooperative efforts between OHRP, the FDA, IRBs, and investigators to establish more defined guidance for interpreting and applying the regulations governing exception to informed consent for emergency research may help alleviate some of the uncertainties in evaluating when the exception can and should be applied. As the number of these studies increases, and familiarity with the specific demands of approving and conducting this sort of research becomes established, it is hoped that rational standards will evolve to guide investigators, IRBs, and federal agencies involved in this type of research.

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93 S.F. Goldkind and M. Carome. *Exception from informed consent for emergency research: brief highlights.* Available at: [http://www.fda.gov/ohrms/Dockets/dockets/06d0331/06d-0331-ts00002-vol2.pdf](http://www.fda.gov/ohrms/Dockets/dockets/06d0331/06d-0331-ts00002-vol2.pdf) (last accessed November 21, 2008)


96 G. Nichol, E. Huszti, J. Rokosh, A. Dumbrell, J. McGowan and L. Becker. *Impact of informed consent requirements on cardiac arrest research in the United States: exception from consent or from research?* 62 RESUSCITATION 2-23, 9 (2004). (“Also, the FDA should work with members of the resuscitation research community to clarify criteria for exception from informed consent by educating members of Institutional Review Boards.”)
The waiver of informed consent for emergency research protocols differ in their logistics, as well as their execution, from more traditional (prospective consent obtained) research. In standard medical research studies the IRB will review the full protocol, the informed consent documents, proposed study advertising, and any other pertinent information in order to reach a decision regarding approval of the research study.\(^{97}\) In an emergency research waiver of informed consent study the process is more complex. The IRB reviews the overall protocol, including the adequacy of the proposed outreach to the community in the form of public disclosure and community consultation. The IRB is often involved in community consultation meetings, frequently attending them alongside the investigator.

Once the community survey as been completed, the IRB again reviews the protocol while referencing the community response. There is varying opinion on what exactly a satisfactory community response is \(^{98}\) with some sources suggesting that 90%+ approval should be the standard.\(^{99}\) The actual standard thresholds, and what should be done with information gleaned

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\(^{97}\) 45 C.F.R. § 46.109 IRB Review of Research. “(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy. (b) An IRB shall require that information given to subjects as part of informed consent is in accordance with §46.116. The IRB may require that information, in addition to that specifically mentioned in §46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects. (c) An IRB shall require documentation of informed consent or may waive documentation in accordance with §46.117. (d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. (e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.” (Approved by the Office of Management and Budget under Control Number 0990-0260.) [56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

\(^{98}\) Charles Contant, Laurence B. McCullough, Lorna Mangus, Claudia Robertson, Alex Valadka and Baruch Brody. Community consultation in emergency research. 34(8) CRIT CARE MED 2049-2052 (2006).

\(^{99}\) Personal communication, Paula Knudson to Laura Sanger-Kelly.
during community consultations, are currently undefined\textsuperscript{100} and can frustrate an IRB attempting to discern if a threshold acceptance of the research has been obtained in the community from which subjects will be drawn.

The Data and Safety Monitoring Board\textsuperscript{101} Charter and proposed membership should also be established and this information supplied to the IRB during the approval process. The possibility of FDA oversight, where the research intervention involves an investigational drug or device, must be addressed with the FDA, including notification to the FDA that the IND or IDE is in connection to a protocol involving emergency waiver of informed consent. The appropriate IND and/or IDE numbers should be provided to the IRB.

The PI, in addition to providing traditional research protocol information, must also justify the waiver of informed consent to the IRB’s satisfaction. This may include going through 21 C.F.R. 50.24 item by item to establish the rationale for why the waiver of informed consent should be granted. Survey instruments used in the community consultations, informed consent documents (in the event that a subject can be consented prospectively), and letters to patients and family members/LARs regarding the subject’s enrollment in the study all must be reviewed and approved by the IRB prior to use. Supplying and amending\textsuperscript{102} these documents, if necessary, is part of the approval criteria for the study.

In addition to medical and scientific co-investigators, the protocol may also include ethicists and statisticians as protocol personnel. Ethicists, for example, could assist in study design and provide insight into issues such as community consultation. Statisticians may be

\textsuperscript{100} Charles Contant, Laurence B. McCullough, Lorna Mangus, Claudia Robertson, Alex Valadka and Baruch Brody. \textit{Community consultation in emergency research}. 34(8) CRIT CARE MED 2049-2052 (2006).

\textsuperscript{101} Required under 21 C.F.R. 50.24 (a) (7) (iv).

\textsuperscript{102} It would not be unexpected that the protocol would go through multiple “approval with modifications” determinations, in which the information needed by the IRB is requested, and the PI provides that information back, in order to obtain approval in accordance with 45 C.F.R. 46.109.
instrumental in evaluating sample sizes and assisting with interim analyses.

The underlying science forming the foundation of the study, and parameters such as inclusion/exclusion criteria for prospective subjects, may require extra vigilant review, as these factors will influence if the waiver is appropriate or not. For example, it will need to be established that the therapeutic window for the proposed research intervention does indeed constitute so short a time interval as to preclude reasonable expectations of being able to contact family members/LARs and obtain prospective consent. Likewise the proposed benefit of the research intervention over current standard-of-care options must be established, along with supporting documentation of animal studies, preclinical data, and data from trials conducted elsewhere utilizing similar techniques.

In cases where the research does not involve an IND/IDE – and therefore does not fall under FDA purview - the Office of Human Research Protections (OHRP) should be informed of the protocol, IRB determinations and approval regarding the protocol, and OHRP should be supplied with documentation that the required conditions were met for waiver of informed consent under 45 C.F.R. 46.101(i). These conditions will be predicated upon the IRB

103 21 C.F.R. 50.24 (2).
104 As required by 21 C.F.R. 50.24 (a) (1).
105 21 C.F.R. 50.24 (a) (3) (ii).
106 Where FDA oversight is indicated, OHRP notes: “(a) Research subject to FDA regulations. The IRB responsible for the review, approval, and continuing review of the research activity has approved both the activity and a waiver of informed consent and found and documented: (1) that the research activity is subject to regulations codified by the Food and Drug Administration (FDA) (see Federal Register, Vol. 61, pp. 51498-51531) at Title 21 CFR Part 50 and will be carried out under an FDA investigational new drug application (IND) or an FDA investigational device exemption (IDE), the application for which has clearly identified the protocols that would include subjects who are unable to consent, and (2) that the requirements for exception from informed consent for emergency research detailed in 21 CFR Section 50.24 have been met relative to those protocols …”(the next section outlines non-FDA regulated research) http://www.hhs.gov/ohrp/humansubjects/guidance/hsdic97-01.htm (Accessed December 4, 2008).

107 45 C.F.R. 46.101(i): “Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes or research activities otherwise
covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Human Research Protections, Department of Health and Human Services (HHS), or any successor office, and shall also publish them in the FEDERAL REGISTER or in such other manner as provided in department or agency procedures.108 Institutions with HHS-approved assurances on file will abide by provisions of Title 45 CFR part 46 subparts A-D. Some of the other departments and agencies have incorporated all provisions of Title 45 CFR part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, subpart C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.”) [56 FR 28012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991, as amended at 70 FR 36328, June 23, 2005]

108 http://www.hhs.gov/ohrp/humansubjects/guidance/hsdc97-01.htm (Accessed December 4, 2008). (Emergency Research Consent Waiver. “Pursuant to Section 46.101(i), the Secretary, HHS, has waived the general requirements for informed consent at 45 CFR 46.116(a) and (b) and 46.408, to be referred to as the “Emergency Research Consent Waiver” for a class of research consisting of activities, each of which have met the following strictly limited conditions detailed under either (a) or (b) below: (b) Research not subject to FDA regulations. The IRB responsible for the review, approval, and continuing review of the research has approved both the research and a waiver of informed consent and has (i) found and documented that the research is not subject to regulations codified by the FDA at 21 CFR Part 50, and (ii) found and documented and reported to the OPRR that the following conditions have been met relative to the research: (1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions. (2) Obtaining informed consent is not feasible because: (i) the subjects will not be able to give their informed consent as a result of their medical condition; (ii) the intervention involved in the research must be administered before consent from the subjects' legally authorized representatives is feasible; and (iii) there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research. (3) Participation in the research holds out the prospect of direct benefit to the subjects because: (i) subjects are facing a life-threatening situation that necessitates intervention; (ii) appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and (iii) risks associated with the research are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity. (4) The research could not practically be carried out without the waiver. (5) The proposed research protocol defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact representatives and make this information available to the IRB at the time of continuing review. (6) The IRB has reviewed and approved informed consent procedures and an informed consent document in accord with Sections 46.116 and 46.117 of 45 CFR Part 46. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the research consistent with paragraph (b)(7)(v) of this waiver. (7) Additional protections of the rights and welfare of the subjects will be provided, including, at least: (i) consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research will be conducted and from which the subjects will be drawn; (ii) public
Information supplied to OHRP will be shared with the FDA, a standard practice where the study relies upon the waiver of informed consent for emergency research. In addition, as special regulatory protections are conferred upon subjects where the research involves fetuses, pregnant women, human *in vitro* fertilization (Subpart B of 45 C.F.R. 46), or prisoners (Subpart C of 45 C.F.R. 46) the waiver of informed consent stipulated in 45 C.F.R. 46.101(i) is

disclosure to the communities in which the research will be conducted and from which the subjects will be drawn, prior to initiation of the research, of plans for the research and its risks and expected benefits; (iii) public disclosure of sufficient information following completion of the research to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results; (iv) establishment of an independent data monitoring committee to exercise oversight of the research; and (v) if obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the research. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review. In addition, the IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the research, the details of the research and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the research and the subject dies before a legally authorized representative or family member can be contacted, information about the research is to be provided to the subject's legally authorized representative or family member, if feasible.

For the purposes of this waiver "family member" means any one of the following legally competent persons: spouses; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

61 Fed. Reg. 51498-51531 (October 2, 1996). The FDA published a final rule which amends FDA regulations to authorize a waiver of informed consent in research which is regulated by FDA. The joint publication of these actions permit harmonization of the HHS and FDA regulations regarding research in emergency circumstances. The HHS waiver, just as the FDA regulatory change, provides a narrow exception to the requirement for obtaining and documenting informed consent from each human subject or his or her legally authorized representative prior to initiation of research if the waiver of informed consent is approved by an IRB. The waiver authorization applies to a limited class of research activities involving human subjects who are in need of emergency medical intervention but who cannot give informed consent because of their life-threatening medical condition, and who do not have available a legally authorized person to represent them. The Secretary, HHS, is authorizing this waiver in response to growing concerns that current regulations, absent this waiver, are making high quality research in emergency circumstances difficult or impossible to carry out at a time when the need for such research is increasingly recognized."
inapplicable to these categories. Accordingly, populations such as pregnant women and prisoners are not within the scope the 45 C.F.R. 46.101(i) waiver.\textsuperscript{109} These circumstances may involve additional steps for the research team to assure that Subpart B and Subpart C subjects are not enrolled in the research, such as evaluating potential female subjects for pregnancy (by use of a urine pregnancy test, for example) or establishing if a potential subject is a prisoner (for instance, was the potential subject in the custody of a law enforcement officer when brought into the emergency department). In those cases where the subject is covered by Subpart C or Subpart D, and identified after enrollment,\textsuperscript{110} the subject should be immediately withdrawn from the study upon Subpart C or D status being identified. It is unlikely that any data collected regarding that subject (who should never have been enrolled to begin with) can be used.\textsuperscript{111}

In addition to IRB and regulatory agency oversight, emergency research waiver of informed consent studies are under the purview of a Data and Safety Monitoring Committee (DSMC),\textsuperscript{112} which is responsible for reviewing adverse events, the current findings of similar trials, and other data that may impact the study’s safety or progress.

This mechanism resulted in halting of the first study conducted under 21 C.F.R. 50.24, after it was noted that those subjects enrolled in the study were experiencing a higher mortality rate (46%) than those enrolled in the control arm of the study (17%).\textsuperscript{113} While the Data

\textsuperscript{109} \url{http://www.hhs.gov/ohrp/humansubjects/guidance/hsdc97-01.htm}
\textsuperscript{110} It is conceivable that this could inadvertently happen. Imagine, for instance, a woman early in her pregnancy being involved in an automobile accident, and the research intervention being one of those initiated immediately in the field.
\textsuperscript{111} IRBs should have mechanisms in place regarding how these events should be handled, such as through a protocol deviation reporting process.
\textsuperscript{112} 21 C.F.R. 50.24 (a)(7)(iv): “Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation;”
\textsuperscript{113} Roger J. Lewis, Donald A. Berry, Henry Cryer III, Norman Fost, Ronald Krome, Geraldine R. Washington, Jaime Houghton, John W. Blue, Robin Bechhofer, Thomas Cook and Marian Fisher. Monitoring a clinical trial conducted under the Food and Drug Administration regulations allowing a waiver of prospective informed consent:
Monitoring Committee (DMC) in this study did not conclude that the research intervention was the cause of the increased mortality, the DMC recommended that the trial be terminated based on “futility considerations.”114 Baxter Healthcare Corporation, which sponsored the trial, terminated the trial and eventually “ended all clinical development and testing of DCLHb,”115 the research intervention being evaluated.

**PolyHeme – a short synopsis**

The requirement for a DSMC appears in the regulations immediately after the requirements for community consultation, and public disclosure. This reflects a policy designed to provide extraordinary oversight and require substantial community outreach efforts in these types of studies. Given that enrolling a person into research without their consent is so controversial, the attention to communication of the study, and its evolving findings, is especially important. Negative press – just or unjust – can be generated when it appears that vital information is being withheld from the community or an oversight committee (IRB and/or DSMC).

The controversy over emergency research waiver of consent studies was recently highlighted by the PolyHeme trial, in which an oxygen-carrying blood substitute was used in the diaspirin cross-linked hemoglobin traumatic hemorrhagic shock efficacy trial. 38 ANN EMERG MED 397-404, 402 (2001).


place of banked blood in trauma victims, both in the field and after admission to an emergency
department. Without dwelling on the underlying scientific issues attendant with the PolyHeme
trial, the trial itself became a microcosm of the debate regarding waiver of informed consent.

Most of the debate in the PolyHeme trial centered on the in-hospital phase, where
standard of care (banked blood) was available; critics argued that enrollment in this phase should
require prospective informed consent, either from the subject or a LAR. In 2006, the
PolyHeme trial became the subject of further criticism, in part due to corporate practices of
Northfield Laboratories (the manufacturer of PolyHeme) and in part due to the appearance that
Northfield was less than forthcoming in releasing information regarding the incidence of heart
attacks in previous trial where aortic aneurysm patients received PolyHeme (Northfield
questioned the causality of the cardiac arrests in the aortic aneurysm trial, and expressed that it
felt that inexperienced doctors had pushed too much fluid into subjects).  

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116 The PolyHeme trial had two components. One phase involved administering PolyHeme, a product of Northfield Laboratories, to trauma victims in the field (before reaching a hospital). The theory behind this phase is that trauma victims in the field – or injured soldiers on a battlefield – do not always have access to blood products, and that development of an oxygen-carrying blood substitute, which could be maintained without refrigeration, and had a longer shelf life than blood, would be beneficial to these critically injured patient populations. The second phase involved continuation of the PolyHeme after reaching the hospital, when presumably real blood was available. This second phase was criticized, as it denied the unconsented research subject the current standard of care; the validity of this second phase was couched in terms of possible advantages of PolyHeme over banked blood. (Nancy C. Molter. Exemption of Informed Consent (Final Rule): Procedures for Clinical Trauma Studies. 62 J Trauma S78-79, 79. Banked blood transfusions “increase the incidence of multi-organ failure (MOF) and mortality if >6 units are given in the first 12 hours post injury. This is a result of the lipid mediators and cytokines released from red cell membranes that combine with traumatized tissue in a two step inflammatory response beginning with the priming of neutrophils and oxygen radical production.”)


118 Sameer S Apte. Blood substitutes – the polyheme trials 11(1) MCGILL J MED 59-65, 62 (2008). (Such as requiring non-disclosures from the FDA and IRBs, and not disclosing the study protocol at community meetings.)

119 Thomas M. Burton. Despite heart attack deaths, Polyheme still being tested on trauma patients. Wall Street Journal, Februray 22, 2006, At:
http://online.wsj.com/article/SB114057765651379801.html?mod=home_page_one_us, last accessed September 11, 2008. (An initial PolyHeme trial, in which prospective informed consent was obtained, compared administration of PolyHeme (research intervention) or blood (control group) to patients undergoing aortic aneurysm surgeries.)
Publicizing emergency research studies

As of October 2006, the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH), and the Center for Biologics Evaluation and Research (CBER) had received fifty-six requests to conduct studies using 21 C.F.R. 50.24, with twenty-one studies in some phase of being conducted.\textsuperscript{120}

As community consultation and public disclosure are considered additional sources of protection for potential research subjects, there is great interest in optimizing these communication strategies and evaluating how to optimize publicizing these studies. The community consultation is often comprised of a series of meetings throughout the community, designed to inform the public about the trial, elicit comments regarding the study from the community in which it will be conducted, and gauge approval of the study within the population from which potential research subjects will be derived. Meetings may take place in civic centers, churches, community club meetings – the objective is to reach small audiences where people may be informed about the trial and ask questions about the study. These audiences will also be those filling out survey questionnaires, providing feedback on the community’s awareness and attitudes about the proposed study.

Public disclosure, and information about upcoming community meetings, should go out to the envisioned subject population. This is often described by the geographic area in which the trial will take place. It is not uncommon to see print advertisements (in both English and foreign language publications, and sometimes “free” newspapers), radio spots, Internet ads, and even television announcements.\textsuperscript{121} The various forums come with their own advantages and

\textsuperscript{120} S.F. Goldkind and M. Carome. *Exception from informed consent for emergency research: brief highlights.* Available at: \url{http://www.fda.gov/ohrms/Dockets/dockets/06d0331/06d-0331-ts00002-vol2.pdf} (last accessed November 21, 2008)

\textsuperscript{121} All potential advertising material must be reviewed and approved by the IRB prior to distribution.
limitations, including scope of audience, cost, and accessibility.

While the Internet may provide a useful tool in maintaining information about a study, as well as linking to opt out mechanisms, not everybody has access to the Internet, and not everybody may be inclined to look up ongoing exception to informed consent trials. The use of traditional media – such as radio, newspapers, and community meetings – is certainly not to be discounted, even our electronic age.

One example of an emergency research waiver of informed consent trial and its publicity outreach efforts can be found in the “ResQPump” trial, occurring in Michigan. The “ResQPump” trial is designed to evaluate the effectiveness of a device designed to improve blood flow in cardiopulmonary resuscitation (CPR), thereby improving survival rates and enhancing blood flow to the brain.\(^{122}\) St. Joseph Mercy Hospital in Michigan is the lead institution in this study, which utilizes the emergency exception from informed consent. In addition to information on the hospital’s website, the study was publicized using newspaper advertisements, radio spots, and by contacting 136 community organizations.\(^{123}\)

An ongoing trial at Baylor College of Medicine, located in Houston, Texas, also utilizes a website to advertise a study in which lowered blood pressure is maintained in an effort to reduce mortality.\(^{124}\) This study includes trauma patients (e.g., gunshot wounds) presenting at the Level 1 trauma center at Ben Taub General Hospital. The study involved multiple community presentations prior to approval. Publicity was sent out to both English and Spanish speaking newspapers, as the Houston area includes people who speak Spanish as their primary (and

\(^{124}\) http://www.bcm.edu/clinicalstudies/?PMID=7205
sometimes only) language. Likewise, post-enrollment letters to subjects and/or family members were composed in English and Spanish to reflect this linguistic diversity.\textsuperscript{125}

Public disclosure, community consultation, and opt-out mechanisms can also be influenced by self-selection. For example, those who have the leisure time to surf the Web and become aware of - and respond to - notices of emergency research plans are more likely to have the free time to attend community meetings.

Telephone calling has served as a marketing tool for years, and utilization of telephone calls to inform the public about ongoing studies has followed suit. However, telephone canvassing presents with its own unique challenges and characteristics, especially as people can now pre-screen calls, or place themselves on “do-not-call” lists. Also, the information that an individual is likely to discuss with a stranger on the telephone is also usually very limited.

In a study by Simon, Mercy, and Barker\textsuperscript{126} that used random-dialing telephone surveys to study injury prevention, the authors noted challenges to collecting data when the data being collected involved “sensitive topics or from potentially vulnerable populations.” Random telephone dialing, it was noted, did not always lead to frank and open discussions about circumstances sometimes associated with injury, such as alcohol use or assault.\textsuperscript{127}

This study is interesting because it addresses the opposite end of the interventional spectrum from emergency research; injury prevention is designed to prevent the very traumatic

\textsuperscript{125} Translations customarily require certification to confirm that they are accurate and complete translations; the IRB will review translated documents, as well as English language versions.


\textsuperscript{127} Thomas R. Simon, James A. Mercy, and Lawrence Barker. \textit{Can we talk? Importance of Random-Digit-Dial Surveys for Injury Prevention Research}. 31(5) AM J PREV MED 406-410, 408 (2006). (“Also, given that many health-risk behaviors and outcomes – particularly injury-related behaviors and outcomes such as binge drinking, alcohol-impaired driving, and assault victimization – are more common among young people, if the samples [of random telephone calls] are not adequately adjusted for response bias they could result in erroneous prevalence estimates.”)
injuries that might result in an emergency admission, and the patient population demographics overlap to a certain degree. Discussing the issues associated with traumatic injury, and consequently the possibility of being in a position where emergency research may be necessitated, can lead to sensitive and personal areas where the public setting may not always be amenable to discussing the research options. Likewise, the potential subject population for emergency research may have an “it will never happen to me” attitude regarding accidents or other acts of violence, and be less inclined to consider or discuss emergency research issues.

This phenomenon was noted by Paula Knudson when conducting community outreach as part of the NABISH study. Identifying that vehicular accidents involving alcohol and young male adults figured largely into the potential subject demographic, attempts were made to discuss the NABISH study with fraternities associated with the University of Houston (Houston, Texas) and the University of Texas (Austin, Texas). The response was underwhelming, as the fraternities declined offers for presentations on the research. However, when parents of the fraternity brothers were contacted, the parents were interested in the research. This, in some ways, reflects that the surrogate decision-maker may be in a different frame of mind than the potential research subject, and more likely to consider the data regarding the research option. This, in turn, yields some credence to the suggestion that substituted decision making, including that of an emergency physician, may be an appropriate substitute for an unconscious patient facing the choice between an unproven, or ineffective, standard of care, and the research.

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128 Thomas R. Simon, James A. Mercy, and Lawrence Barker. *Can we talk? Importance of Random-Digit-Dial Surveys for Injury Prevention Research.* 31(5) AM J PREV MED 406-410, 407 (2006). (“Injuries due to motor vehicle crashes, homicide, and suicide are the leading cause of death for persons aged 1 through 44 years. Because of the relatively greater impact on adolescents and young adults, injury ranked as the leading cause of premature mortality in the United States in 2002, accounting for almost 30% of all years of potential life lost before the age 65. About one-third of injury-related mortality is linked to motor vehicles, one third is due to other unintentional injuries such as falls and drowning, and one third is due to homicide and suicide.”)
intervention (that by definition must hold out some prospect of direct benefit to the subject).\textsuperscript{129}

The suggestion that physicians\textsuperscript{130} may provide substitute decision-making is reminiscent of the theory of paternalism, a now antiquated medical practice view that espoused that physicians, as educated practitioners of both the art and science of medicine, should make decisions for their patients.\textsuperscript{131} Perhaps this almost side-bar observation best evokes the essence of the debate regarding waiver of informed consent. Emergency research with waiver of informed consent, by definition, involves another person making a decision on behalf of the subject.\textsuperscript{132}

Even when that decision is buttressed with the potential benefit to the subject, supported by underlying data, and satisfies “justice” concerns such as weeding out ineffective interventions and promoting effective ones for the good of society, the notion of enrolling someone in a clinical trial without their consent potentially offends our Kantian sensibilities regarding autonomy.

The underlying notion is that where subjects are not informed of the research prior to being enrolled, and/or have no way of refusing to participate, the autonomy principle should be dispositive in the weighing of the Belmont principles. In the waiving the requirement for prospective informed consent by the subject, two factors crucial to our fundamental understanding of participation in modern medical trials are challenged: one, the subject is not truly consenting for him/herself, no matter what surrogate decision maker is contacted, how

\textsuperscript{129} 21 C.F.R. 50.24 (a) (3).
\textsuperscript{130} In this aspect, the European and American models may differ.
\textsuperscript{132} The emotional circumstances of an emergency admission may also impact a family member’s ability to make a decision regarding care. See E.J.O. Kompanje, A.I.R. Maas, M. T.Hillhorst, F.J.A. Sliker, and GM Teasdale. Ethical considerations on consent procedures for emergency research in severe and moderate traumatic brain injury. 147 ACTA NEUROCHIR (WIEN) 633-640, 636 (2005). (In a European study surveying opinions in neuro-trauma centers, “48% of 78 respondents [ ] believe that relatives were not able to make a balanced decision under the emotional and stressful emergency decisions.”)
educated that decision-maker is, or how supportive the community is of the research; and two, the subject does not have the opportunity to refuse to participate, a concept that is abhorrent in modern medical research, just as it is in standard-of-medical care practice, where refusal to be treated has been well established as a foundation principle of autonomy.\textsuperscript{133}

**Implications for the research team**\textsuperscript{134}

There are also potential ramifications of conducting this sort of research on the research team performing the research that are not articulated in either regulations or ethical foundation documents. The research team, it should be noted, is primarily comprised of medical professionals engaged in the field of emergency medicine. Their mandate is to save lives and minimize morbidities. Those practitioners involved in research will have an additional dedication to upholding the ethical principles of performing clinical research.\textsuperscript{135} The peculiarities of performing research on severely injured or ill patients, without first obtaining consent, will not be lost on the research team. Indeed, they will likely be highly aware of, or even most troubled by, the waiver of informed consent granted to them in order to facilitate what they hope is beneficial research.

These concerns and effects of the emergency research without waiver of consent process bear mentioning. First, in “traditional” research settings, where informed consent is obtained, the PI and research team have the opportunity to present all of the necessary information regarding

\textsuperscript{133} See *Cruzan v. Director, Missouri Department of Health*. 497 US 261 (1990). (“The Fourteenth Amendment provides that no State shall “deprive any person of life, liberty, or property, without due process of law.” The principle that a competent person has a constitutionally protected liberty interest in refusing unwanted medical treatment may be inferred from our prior decisions.”)

\textsuperscript{134} The author is indebted to the insight provided for this section by Dr. Matthew Carrick.

the study prospectively to the subject. This provides a foundation of emotional support to the research process, as the PI and research team can feel somewhat assured that they have provided all the necessary information about the study to the subject, and that the subject is therefore entering into the study knowledgeable of the research and the potential consequences of their decision to participate in that research. In a waiver of informed consent situation, particularly where an unconscious patient is enrolled into research, the PI and research team may experience a personal queasiness about the process, as a result of the subject not being asked ahead of time if they wish to participate. These concerns with subject rights and the informed consent process are a testament to the integrity and professionalism of most of the investigators entrusted to conduct these studies. However, it should also be recognized that there might be an intellectual and emotional toll to be paid by the research team.

As an extension of these procedural concerns, the research is still exactly that – research. The operative concept is that research, by definition, has an unknown endpoint and the prospect exists that the research intervention might not be beneficial to the subjects, despite the requirement of evidence supporting the potential benefit over standard interventions. This raises the possibility that the research could potentially disadvantage, or even harm, research subjects who were already in a precarious medical situation to begin with. The scenario of enrolling subjects, and then discovering that the experimental group was faring worse than their standard-of-care cohorts could have a devastating effect on the morale of the research team.136

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136For example, the study chronicled in Roger J. Lewis, Donald A. Berry, Henry Cryer III, Norman Fost, Ronald Krome, Geraldine R. Washington, Jaime Houghton, John W. Blue, Robin Bechhofer, Thomas Cook and Marian Fisher. Monitoring a clinical trial conducted under the Food and Drug Administration regulations allowing a waiver of prospective informed consent: the diaspirin cross-linked hemoglobin traumatic hemorrhagic shock efficacy trial. 38 ANN EMERG MED 397-404 (2001) describes a study in which the trial was stopped early because of increased mortality rates in the experimental group when compared to the control cohort. This source did not speak to the effects of that observation of the research team, even in circumstances where the research itself was not definitively linked to the increased mortality rates.
Emergency research can also place peculiar demands on the time of the research team. Even while acknowledging that investigators in this area are emergency medicine specialists, and therefore likely to be accustomed to the odd hours required by the disease process (emergencies happen when they happen), this unscheduled medical event is makes research in the area distinct from other types of traditional research, which may be scheduled during regular working hours and even coincide with normal clinical care appointments. Once a subject has been enrolled, the research process approximates that of other medical research studies, with the exception that continuing diligence for obtaining consent from either the LAR or subject must continue until fully executed informed consent has been obtained.\textsuperscript{137}

Withdrawal from these studies, once the subject has been enrolled, appears to be rare, which helps support the notion that the regulatory process is adequately designed to anticipate subject acquiescence, if not potential consent. In a study of spinal cord injury subjects, who were conscious and potentially capable of providing consent, seems to support that subjects have an interest in participating in potentially beneficial research.\textsuperscript{138}

\textbf{Consent by self and/or others in exigent circumstances}

\textsuperscript{137} 21 C.F.R. 50.24 (a) (5), (a) (7) (v); 21 C.F.R. 50.24 (b).
\textsuperscript{138} E.J.O. Kompanje, A.I.R. Maas, M. T.Hillhorst, F.J.A. Sliker, and GM Teasdale. \textit{Ethical considerations on consent procedures for emergency research in severe and moderate traumatic brain injury}. 147 ACTA NEUROCHIR (WIEN) 633-640, 637 (2005). (“No information is, or probably ever will become available whether individual patients with [traumatic brain injury (TBI)] would have given consent to participation in research if they had been a position to do so. Some analogy may exist between procedures utilized in patients with severe TBI and in patients with acute traumatic spinal cord injury. Both populations relate to serious emergency situations, and time windows for opportunity of treatment are short, but unlike patients with TBI those with spinal cord injury are not unconscious. Three randomized controlled studies of the national acute spinal cord injury study showed that out of a total of 1392 patients only 76 (5.45\%) refused consent.”)
The quality of informed consent, even where the subject was conscious is may be questionable, as the subject is presenting in an often frightening situation, very likely in some state of shock, and unlikely to have full reign over his/her mental and emotional capacities due to the trauma they are experiencing. The same notion may also be applied to family members, who may – or may not – be emotionally capable of providing adequate surrogate consent, or have misconceptions regarding critical elements of the informed consent process.

The informed consent process itself may present other barriers to facilitating participation in medical research. First, physicians may be concerned that by presenting an alternative to conventional care, they are inadvertently suggesting an insecurity regarding treatment strategy. By suggesting that the standard of care has not been substantially validated - or may be less than optimal - as may be the case in critical care or emergency care, faith in the emergency care being provided may be eroded. Such considerations may carry a potential to further distress the

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139 G. Nichol, E. Huszti, J. Rokosh, A. Dumbrell, J. McGowan and L. Becker. *Impact of informed consent requirements on cardiac arrest research in the United States: exception from consent or from research?* 62 RESUSCITATION 2-23, 8 (2004). (“Even when the consent process meets regulatory requirements, patient comprehension and competence to autonomously give consent may be suboptimal.”)

140 DJ Manning. *Presumed consent in emergency neonatal research.* 26 J MED ETHICS 249-253, 250 (2000). (“More than 40% of parents perceived the requirement of a signed consent form, far from protecting the research subjects, as a mechanism for protecting the investigators from litigation. The authors [citing Harth SC, Thong YH. *Parental perceptions and attitudes about informed consent in clinical research involving children. Social Science and Medicine* 1995; 40: 1573-7.] Concluded that careful adherence to consent procedures, even in non-emergency research, did not guarantee substantial comprehension by the parents. While more could possibly be done to improve the process of communication and obtaining consent in less fraught situations and when time permits, it is difficult to see how substantial understanding can be improved in emergency neonatal research.” This paper addressed pre-emptive obtaining antenatal informed consent for research, where emergency research studies might be an option in a neonatal setting. The parents had the advantages of being present and aware of the research prior to enrollment, yet the factors that influenced these parents are not dissimilar from that which might be encountered upon contacting the family member of a potential subject who has just been severely injured, such as in an automobile accident or an act of violence.)

141 Susan S. Ellenberg. *Informed Consent: Protection or Obstacle? Some Emerging Issues.* 18 CONTROLLED CLINICAL TRIALS 628-636, 630 (1997). (“Taylor et al. have documented the view of many surgeons that the consent process causes patient distress and may impact adversely on the medical outcome; this paper also makes clear that the requirement to obtain informed consent is seen as a major impediment to physician participation in clinical trials, because physicians are uncomfortable appearing unsure of the optimal choice of treatment for an individual patient.”) Citing Taylor KM, Margolese RG, Soskolne CL. *Physician’s reasons for not entering eligible patients in a randomized clinical trial of surgery for breast cancer.* 310 N ENGL J MED 1363-1367 (1984).
subject/LAR, prejudice the subject/LAR against potentially life-saving or morbidity reducing interventions, or even raise the specter of liability.

Secondly, informed consent documents themselves may be confusing. Even if a subject could be provided with an informed consent opportunity, an emergency trauma patient is unlikely to be in frame of mind to comprehend the distinction between standard of care and research, much less understand the research being described. Even in traditional research, informed consent documents may present more confusion than they clear up.

**An extension of emergency practice?**

The statutory scheme for exception from informed consent for emergency research interventions contains a myriad of procedural safeguards to protect a patient population identified as vulnerable due their lack of decisional capacity. These include rigorous IRB review, community involvement, and special reporting mechanisms where INDs or IDEs are involved in the research. In addition, a plethora of substantive requirements must be met before the research qualifies for the waiver, including that the potential subject must be in a life-threatening circumstance, the standard of care is either non-existent or non-satisfactory, that the risks associated with the research are in line with the risks associated with standard of care, and that

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142 Informed consent documents are difficult to compose. They should be written at a seventh grade language level, or even less, and express complex medical and scientific points in layman’s terms. In addition, all of the regulatory requirements of 45 C.F.R. 46.116 must be met. This bulk of information, being potentially presented alongside medical care information or insurance/payment documentation, may not be immediately comprehensible. In traditional medical research the potential subject is encouraged to take study information and the informed document and consider the contents as needed. This may include conversations with others involved in care taking, and should involve asking questions and entering into a dialogue with the study PI or designee. In emergency care the disease may drive the timeline, and urgent treatment is likely to be demanded by the subject’s condition.

143 Susan S. Ellenberg. Informed Consent: Protection or Obstacle? Some Emerging Issues. 18 CONTROLLED CLINICAL TRIALS 628-636, 630 (1997). (“A different sort of concern is whether we have required so much detail in informed consent documents that we have defeated ourselves because most patients are unable to comprehend the detailed document that is being presented to them. Several studies have shown that patients may absorb little of the information provided in the consent documents.”)
scientific evidence supports the likelihood of potential benefit for the particular subject. Given this framework, the exception appears to serve more as an extension of the concepts embodied in the waiver of informed consent for standard medical care, than necessarily as a striking departure from research study procedures.

Often, for example, the standard of care itself has not been borne out by evidence as an effective treatment.\textsuperscript{144} The utilization of promising interventions, despite being characterized as “research,” appears appropriate where the promise of benefit is supported by scientifically gathered evidence, as required by 21 C.F.R. 50.24 (a) (3) (ii-iii).\textsuperscript{145} The ability to gather data for developing evidence-based medicine in emergency and critical care should be encouraged, as it will hopefully result in the improvement of interventions in this often understudied disease.\textsuperscript{146}

Additionally, the concept of informed consent is not stifled by the exception. Efforts must be put forth throughout the protocol’s progress to either obtain consent from the subject, or contact an appropriate surrogate and obtain consent during the study. \textit{It is the brevity of the therapeutic window that demands the exception, not a desire to circumvent the informed consent process.} The obtaining of informed consent is not obviated by the exception; it is postponed by the short therapeutic window in which the research intervention must be administered in order to

\textsuperscript{144} See Protection of Human Subjects; Informed Consent; Proposed Rule, Department of Health and Human Services, Docket No. 95N-0158, 60(183) Fed. Reg.: 49085-49103 (September 21, 1995); Available at \url{http://www.fda.gov/OHRMS/DOCKETS/98fr/092195.txt}. (II. Informed Consent Regulations. “Much of what has become standard, accepted, medical therapies for use in acute or resuscitation clinical care has not been evaluated by adequate trials that demonstrate either safety or effectiveness. Controlled clinical trials have demonstrated that some therapies that have become standard medical practice are ineffective or even harmful. Other standard therapies, although shown to be effective in clinical trials, have significant limitations, in that, for example, they only work in a small percentage of those individuals who receive the therapies, so the testing of improved or additional therapies remains critically important.”)

\textsuperscript{145} 21 C.F.R. 50.24 (a)(3)(ii-iii):

\textsuperscript{146} The distinction is that emergency research is an organized study designed to evaluate a research intervention. In standard of care, there is an option for use of research measures, such as using an investigational device under an Emergency Exception Treatment Use of an Investigation Device, in which 21 C.F.R. § 812.36 controls. These exceptions are just that – exceptions that allow for the use of a research article or drug where no appropriate alternative is available in a life-threatening situation. Repeated invocation of an exception would alert the FDA to the possibility that research was being conducted without proper IRB approval, or FDA oversight.
be of maximum benefit to the subject. Seeking informed consent from the subject/LAR during the intervention, and after the intervention has been initiated, are important requirements of the regulation.

In addition, the participant may be withdrawn from the study by a surrogate once the surrogate decision maker is identified. The subject, if and when they regain decisional capacity, can withdraw themselves from the study. Where it is reasonable to anticipate that consent can be feasibly obtained, research protocols are directed to the regulatory schema articulated in the Common Rule.\(^{148}\)\(^{149}\)

**Weighing Belmont**

At least one author has suggested that the Belmont principle of autonomy now overshadows the principle of beneficence,\(^{150}\) and this suggestion may bear further

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\(^{147}\) Claudia S. Robertson, Laurence B. McCollough, and Baruch Brody. *Finding family for prospective consent in emergency research*. 4 CLIN TRIALS 631-637, 636 (2007). (“Still another factor to assess is the meaning of the time period for assessment. A therapeutic window is usually not an all-or-nothing phenomenon. Usually, the earlier a neuroprotective drug is given, the more effective it is. A clinical study designed to test the drug will therefore be scientifically more rigorous if the drug is given as soon as possible. The more reason there is to believe that these generalizations are true in connection with a given research project, the more reason there is to obtain the emergency consent exception so that more subjects can be enrolled sooner, to increase the clinical value of the research.”)

\(^{148}\) *Id* at 635. (“For disorders like stroke or traumatic brain injury, where the therapeutic window for interventions may only be several hours, a percentage of the patients will still have family available who can be asked to give prospective consent for enrollment. For example, with a 6 h time window in the multicenter hypothermia trial for traumatic brain injury, 38% of patients were enrolled by prospective consent. [Citing Guy L. Clifton, Paula Knudson, Marilyn McDonald. *Waiver of consent in studies of acute brain injury*. 19(10) J NEUROTRAUMA 1121-1126 (2002).] … In addition, the percentage of available family members might increase when the emergency occurs more often at home or in a clinical setting.” It should be noted, however, that emergency exception to informed consent is designed to envision those circumstances in which family members will likely not be readily available, such as automobile accidents, acts of violence, or other unexpected trauma.)

\(^{149}\) The emergency research waiver of informed consent should not be confused with the waiver of informed consent documentation provided for under 45 C.F.R. 116(d). By definition, the research encompassed by 45 C.F.R. 116(d) involves “no more than minimal risk to subjects.” (45 C.F.R. 46.116(d)(1)) The research typically approved under 45 C.F.R. 116(d) is research in which the informed consent document *itself* is likely to be the only item linking the subject to the research, and the primary risk is the risk to personal information. An example of this sort of research is a pre-research feasibility study, wherein medical records may be checked to determine the likelihood of successfully enrolling subjects in a trial, or determining how many years it may take to accrue sufficient subjects presenting with a certain condition. In this example, requiring an informed consent document creates additional documentation that may expose the subject to information loss. Even in these cases, the IRB may require that subjects be notified that their information has been referenced.

\(^{150}\) The Belmont Report acknowledges that application of the principles of autonomy, beneficence, non-malfeasance, and justice might result in conflict and require the making of difficult decisions. (See
examination.\textsuperscript{152} The concept of informed consent itself relies heavily on autonomy, dating back to core principles embodied in \textit{Schloendorff} and the Nuremberg Code.

The concept of \textit{waiver} of informed consent in emergency research may, in actuality, derive more from the principle of beneficence. Research conducted in this area may benefit individual subjects where standard of care is inadequate, the research may validate existing interventions or may provide scientific foundation for the development of new interventions, and society would conceivably by the provision of such knowledge and/or new techniques developed by the research.

Another author has suggested that autonomy as a controlling principle may come at the expense of the principle of justice.\textsuperscript{153} The waiver of informed consent for conducting emergency research may be necessary to enable access to clinical trials that hold out the possibility of benefit for the subject population.\textsuperscript{154} This concept of justice – access to beneficial care - recommends that the waiver of informed consent, if necessary to enable access to that care, may be justified. The Belmont principles of justice and beneficence, in addition to the underlying

\begin{itemize}
  \item \texttt{http://ohsr.od.nih.gov/guidelines/belmont.html}, “Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.” And “Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.”
  \item DJ Manning. \textit{Presumed consent in emergency neonatal research}. 26 J MED ETHICS 249-253, 249 (2000). (“In the past 30 years, respect for autonomy has overtaken beneficence as the most important ethical consideration governing medical research.”)
  \item S.F. Goldkind and M. Carome. \textit{Exception from informed consent for emergency research: brief highlights}. Available at: \texttt{http://www.fda.gov/ohrms/DOCKETS/dockets/06d0331/06d-0331-ts00002-vol2.pdf} (last accessed November 21, 2008) (With regards to public input concerning 21 C.F.R. 50.24, it has been suggested that “[m]any participants expressed concern that the current regulations value individual autonomy and the right to informed consent at the expense of the principles or beneficence and justice.”)
  \item Jan Lecouturier, Helen Rodgers, Gary A. Ford, Tim Rapley, Lynne Stobbart, Stephen J. Louw and Madeleine J. Murtagh. \textit{Clinical research without consent in adults in the emergency setting: a review of patients and public views}. 9 BMC MEDICAL ETHICS (2008). [epub ahead of print, available at \texttt{http://www.biomedcentral.com/1472-6939/9/9}. (Also suggesting that there may be an ethic issue with excluding patients from potentially beneficial research where the barrier to access to that participation is a lack of traditional research informed consent.)
\end{itemize}
potential benefit to the subject, favor the allowing the waiver of informed consent in the area of emergency research where indicated. 155

Finally, the autonomy argument may not entirely militate against enrollment without prior informed consent in the case of emergency research. Proxy consent, which is allowable in numerous circumstances where obtaining individual subject consent is not feasible, may or may not represent the subject’s intent regarding research.

Surrogate consent, for example, is mandated in pediatric research, where minors may be assented, 156 but legal informed consent is obtained from parents, guardians, or other LARs. 157 Substituted consent may also be obtained in lieu of the adult subject’s where the potential adult subject may be unconscious, mentally disabled, or cognitively impaired. 158

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156 45 C.F.R. §46.408 Requirements for permission by parents or guardians and for assent by children. “(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with §46.116 of Subpart A.” (Note that assent is not automatically extended to all pediatric research participants. The IRB carefully considers the appropriateness of soliciting assent.)

157 45 C.F.R. 46.408 “(b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by §46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 or §46.405. Where research is covered by §§46.406 and 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.”

158 Article 29, Declaration of Helsinki: “Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the
Yet, does allowing for proxy consent reflect truly substituted consent? Does the surrogate consenting party accurately stand in loco of the subject, and provide consent according to an understanding of the subject’s directives regarding research, or is the surrogate consent more likely to be a reflection of the surrogate’s desires regarding the research, even in cases where the surrogate may be designing their decision with the best interests of the subject in mind.

It has been suggested that a certain percentage of patients would not want family members or spouses to act as surrogate decision makers, even in the standard-of-care medical decision making setting. Approximately 29% of a cohort of French patients stated that they “would not want family members as surrogates if they should become incapacitated.” The same study reported that 59% of patients would not want a spouse representing them in making

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159 E.J.O. Kompanje, A.I.R. Maas, M. T. Hillhorst, F.J.A. Sliker, and GM Teasdale. Ethical considerations on consent procedures for emergency research in severe and moderate traumatic brain injury. 147 ACTA NEUROCHIR (Wien) 633-640, 635 (2005). (“Most proxies seem to make decisions in emergency and life-threatening situation [sic] based on what they hope will happen (survival of their loved one), rather than what is likely to happen (facing possible death or disability); this will bias decision making towards possible therapeutic benefit, however small that chance may be.”) This observation is interesting, because of the requirement under 21 CFR 50.24 (a) (3) (ii) that requires that previously conducted animal and preclinical studies support the “potential for the intervention to provide a direct benefit to the individual subjects.” This requirement, while providing an ethical comfort supporting the regulation, could indirectly influence the decision to continue in the research once an LAR has been located, as that surrogate may become focused on the likelihood of direct benefit from the research intervention.

160 This conundrum applies to circumstances other than emergency research waiver of informed consent. In cases of consenting to standard medical care, or non-emergency research, this discrepancy may influence the decision making process. It also bears mentioning that because someone holds a medical power of attorney for health care, they may not automatically be enabled to make decisions regarding participation in medical research. If there are questions regarding the surrogate’s ability to enroll a subject in research, it is often advisable to communicate with the IRB of record for the study. Most IRBs will have procedures in place that reflect the Common Rule and governing state law.

medical decisions; interestingly, “29% reported that they preferred to be represented by the physician in charge of their care rather than by a surrogate family member.”\textsuperscript{162}

The concept of independent physician consent, while in part evoking the aversion to medical paternalism, has the countervailing advantages of incorporating the physician’s professional training and improved comprehension of the disease as well as the possible consequences of choosing between different courses of action. The independent physician model, wherein the physician making the decision is not involved in the research, however, may face other challenges.

In patients with myocardial infarction there was a tendency to favor (84\%) independent physicians making intervention decisions where the patient was unable to consent; in contrast, parents in a neonatology setting were considerably less in favorable (11\%) regarding the medical staff making such decisions.\textsuperscript{163} This reflects the milieu of factors that may influence a subject’s, or a surrogate’s, decision making process. Does the age of the potential subject matter? Is it easier to make decisions for one’s own child, rather than one’s own parent? Do factors such as quality of life balance against quantity of life? Does the identity of the underlying condition matter?


At least one study examined the distinction between patients presenting with cardiac arrest versus patients presenting with atrial fibrillation.\textsuperscript{164} In the case of cardiac arrest, patients were considered unable to provide informed consent, whereas those presenting with atrial fibrillation were considered competent to consent.\textsuperscript{165} This supports that the disease itself may influence the informed consent decision capacity of the subject, suggesting that urgency of the condition, pathology of the disease/event, onset of the condition, duration of the illness, and options regarding intervention may enter into the equation when balancing standard of care and research interventions.

Finally, one’s own attitudes about what one would consider doing for oneself may differ from the efforts one would put forth on behalf of another. A person may consider a spectrum of interventions appropriate for him/herself, but when faced with making a decision for their children, spouse, parent, or even a friend who has listed them a decision maker for research, the surrogate’s attitudes may shift, depending on the condition and the alternatives presented to them. Very few individuals probably have detailed discussions with loved ones about if they want to be enrolled in potentially beneficial research interventions in the case of an emergency.\textsuperscript{166} Eventually, most surrogate decisions regarding emergency care will be made on sympathetic, rather than empathetic, grounds.


\textsuperscript{166}E.J.O. Kompanje, A.I.R. Maas, M. T.Hillhorst, F.J.A. Sliker, and GM Teasdale. Ethical considerations on consent procedures for emergency research in severe and moderate traumatic brain injury. 147 ACTA NEUROCHIR (Wien) 633-640, 635 (2005). (\textsuperscript{\ldots}Coppolino & Ackerson (2001) [citation] concluded that surrogate decision makers for critical care research resulted in false-positive consent rates in up to 20% Sulmasy et al (1994) [citation] studied the wishes of 50 patients and their proxies for treatment in 3 scenario’s [sic] of coma and brain death, and found that agreement between patients and their proxies varied between 57% and 81%, depending on whether previous discussions had taken place on similar situations. It is unlikely that such existential discussions...
Summary

In summary, there are three considerations that support the validity of allowing emergency research with a waiver of informed consent.

First, the ethical principles of autonomy, beneficence, and justice may be served by allowing the research. The Belmont principles do not exist in discreet vacuums, isolated from one another. They should be weighed and considered relative to their own, and each others, merits and limitations. Beneficence and justice are supported by allowing access to potentially beneficial interventions; autonomy may be in some part be paid tribute by making sure that continuous efforts are made to obtain consent at the earliest feasible moment, and that the potential subject’s rights are kept in mind by both the IRB approving the research and the research team designing and conducting the research.

Second, the nature of emergency practice has been to date based on empirical observation, with the result that some interventions have not been subjected to scientific scrutiny. This gives the pallor of research to the practice area as a whole. Allowing more stringent observation and evaluation of emergency techniques could benefit individual patients/subjects, society (in the form of improving care and outcomes), and the medical community (by providing assurance of interventions and validating parameters of care). Adequate research efforts are needed to ensure the development and validation of optimal treatment strategies for those finding themselves in need of emergency interventions; regulatory strategy should allow for this research to proceed, both for the benefit of individuals and society.\"167\"

\textsuperscript{167} See G. Nichol, E. Huszti, J. Rokosh, A. Dumbrell, J. McGowan and L. Becker. \textit{Impact of informed consent requirments on cardiac arrest research in the United States: exception from consent or from research?} 62
Third, a regulatory schema itself should not defeat the underlying principles of its enactment.\textsuperscript{168} The ethical principle, as well as the embodiment of that principle via a regulation, should be consulted when weighing ethical decisions. The right of access to medical research, and the ability to avail oneself of potentially beneficial medical outcome, are proper considerations when thinking about allowing emergency research protocols to proceed.

The Belmont principles serve to remind the research community of the value of human dignity; by encouraging informed decision making that dignity is assisted. Belmont also teaches that extra vigilance is warranted whenever the core principals of autonomy, beneficence, and justice appear at odds, and that the IRB should be on heightened awareness of the protection of human subjects in those circumstances. However, application of the Belmont principles supports that waiver of informed consent for emergency research, as directed by regulations such 21 C.F.R. 50.24 and 45 C.F.R. 46.101(i), should be allowed for the potential benefit of subjects and society, as society –and its individual members (including potential subjects) – have an interest in obtaining optimized emergency care, as well an interest in not being subjected to care that might not benefit them. Within the careful scrutiny of the IRB, and the sensitive conduct of these trial by medical professions, it is hoped that emergency care will be enhanced for the benefit of individuals and the society those individuals eventually define. Thus, the waiver of informed consent for emergency research where the parameters of that research can not be met without the waiver should be supported.

\textsuperscript{168} In fact, it should be noted that regulations \textit{qua} regulations do not guarantee ethical conduct of research; many of the atrocities cited at the beginning of this paper were not contrary to the regulatory schemes of their time and place. It requires moral, as well as legal and ethical, vigilance to do the right thing.