CLINICAL TRIALS, INFORMED CONSENT, & EMERGENCY MEDICINE: A SYSTEMATIC LITERATURE REVIEW

by

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DEDICATION

To The Memory of My Parents, Betty & David

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by

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Background: In the United States, the Food and Drug Administration (FDA) regulates clinical trials. These regulations address good clinical practices as well as human subject protection (FDA, 2012). One of the most important legal and ethical concerns in clinical trials is informed consent. 21 CFR 50 governs human subjects research. Part 50.24 provides an emergency research exception to the informed consent requirement. Research was conducted to determine the appropriateness of this exception, whether the benefit justifies the exception, and its public health significance.

Methods: A systematic literature review was conducted and articles were identified from peer-reviewed journals.

Results: There is some variance in opinions regarding the appropriateness of the exception, but the literature reviewed found the study results of these trials justified the waiver.

Conclusion: The exception to the informed consent requirement is likely appropriate and justified in emergency research when implemented within the specified guidelines.

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BACKGROUND

The Rule

The regulation of clinical trials and informed consent is a frequently debated topic. Informed consent is a patient's willing acceptance of a medical intervention after sufficient disclosure has been made by the physician about the treatment, its alternatives, and associated risks and benefits (Jonsen, 55). There are plenty of articles and books that argue the merits of requiring or waiving informed consent. The ethical framework for human subjects research was first implemented in 1949 with the establishment of the Nuremberg Code (Halperin, 1855). The Code was followed by The Declaration of Helsinki in 1964 which states rules for clinical research allows certain patients to be enrolled without their consent via proxy or waiver of consent (Halperin, 1855). This exception was specifically directed at instances in which the research was "necessary to promote the health of the population represented [and could not] instead be performed on legally competent persons." (See Appendix D).

Because of informed consent concerns, the Food and Drug Administration (FDA) suspended emergency resuscitation research on humans in 1993 (Hiller, 1091). In 1996, the FDA implemented 21 CFR 50.24 allowing for an emergency research exception to the informed consent requirement for human subjects research. The exception is available when critically ill patients are admitted in an emergency clinical study (Parvizi, 654). The reasoning behind the rule is that a reasonable person would consent to treatment in an emergency event; if left untreated, the patient would suffer irreversible harm or perhaps death—which would then make further decision making unnecessary.

This literature review attempts to help fill the gap on whether providing an emergency research waiver of informed consent is actually justified by the results, and its public health implications.

Public Health Significance

This issue is significant because of the importance of clinical trial data to public health research, and the weight that is given to conclusions that are made. This U.S. spends approximately two trillion dollars a year on healthcare, with about 15-20% being used in acute care and emergency situations (Cofield, 2010). A search of ClinicalTrials.gov using the phrase "emergency department" yielded 1,373 studies[1]. The number of current studies could have wide-spread effects on the bioethics principle of patient autonomy. Some critics question whether it's practical to invoke rights involving autonomy, privacy, and bodily integrity when a patient is unconscious; by definition, the patient won't realize whether their previously expressed preferences are being honored and they won't sense any bodily invasion that accompanies continued medical treatment (Cantor, 1989). While it is acknowledged that supporting the autonomy of incompetent patients may be difficult for some to comprehend, it is important to remember that some patients are only temporarily incompetent (Berg, 94). Decisions made for these temporarily unconscious patients should protect their future autonomy (Berg, 94).

[1] This search was performed by Courtney Petty on October 25, 2012.

Hypothesis, Research Question, Specific Aims or Objectives

Title 21, part 50.24 of the Code of Federal Regulations provides an *emergency research* exception to the informed consent requirement for clinical trial participants (21 CFR 50.24). The exception allows the Institutional Review Board (IRB) governing the approval and continuing review of the clinical investigation to approve investigation without obtaining informed consent of all research subjects if the IRB finds and documents certain elements. The main elements to be met are: 1) the human subjects' lives are threatened; 2) currently available treatments are not satisfactory; 3) obtaining consent from the subject or their representative is not feasible; 4) the research holds a direct benefit for the subject; and 5) the clinical trial could not be carried out practically, without the waiver.

The questions presented here are: 1) Is it appropriate to leave the responsibility of opting out of the study on potential participants who are very likely unaware of the study, and often unable to consent at the time of enrollment; and 2) Does the benefit of the results obtained from such clinical trials justify waiving the requirement that informed consent be obtained before enrollment? 3) What effect does this have on public health research?

METHODS

Study Design

The inquiries addressed in this review are: 1) Whether it is appropriate to place the responsibility of opting out of emergency research clinical trials on potential participants who are likely unaware of the study, and often unable to consent at the time of enrollment; 2) Does the benefit of the results obtained from such clinical trials justify waiving the requirement that informed consent be obtained before enrollment? and 3) What effect does this have on public health research?

To effectively answer these questions, publications related to "informed consent and clinical trials" as well as "informed consent and emergency research" were targeted. Publications that described a variation of this theme were also considered for review.

Study Setting

Because clinical trials are federally regulated, the study setting included all 50 U.S. states. Although international studies were not included, they were reviewed to provide additional guidance in completing this research.

Data Collection

Literature Search Strategy

Search terms were generated to discover literature relevant to the exception to the informed consent requirement for clinical trial participants. The keywords used in the search of the databases are listed in the table below:

Table 1: Search Terms
• Clinical Trials • Emergency Research • Emergency Medicine • Emergency Department • Informed Consent • Deferred Consent • Surrogate Consent • Proxy Consent • Waiver of Informed Consent • Clinical Research • Exception from Informed Consent

The searches were limited to literature published in English after 1996, which is the year 21 CFR 50.24 went into effect.

Article Selection

The search results located in PubMed, MEDLINE (OVID), EBSCO (Academic Search Complete), and LexisNexis were exported into Refworks. Once completed, the results were screened to exclude any duplicate articles or studies.

Titles and abstracts of search results were used to determine initial eligibility. Each abstract was then reviewed to determine its relevancy, and saved into one of three folders:

no, *maybe*, or *background only*. Abstracts placed into the *no* folder were those that did not meet any of the inclusion criteria, and did not provide relevant background information. These abstracts were assigned an exclusion code, such as "wrong publication year." The *maybe* folder included abstracts for which inclusion is was not readily ascertainable. The *background folder* was for abstracts that met some, but not all of the inclusion criteria, and were considered for background or descriptive information.

Next, full text articles were reviewed and moved into additional folders: *yes*, *no*, and *background only*. Articles were only placed into the *yes* folder if they met all of the inclusion criteria listed in **Table 2**. Articles were placed into the *no* folder if they did not meet the inclusion criteria. The excluded texts were coded just as the excluded abstracts were. Articles that were placed into the *background only* folder met some, but not all of the inclusion criteria and provided useful background or descriptive information.

After the full review was completed a PRISMA Flowchart was developed and included in this research to demonstrate the article screening process, **See Figure 1**.

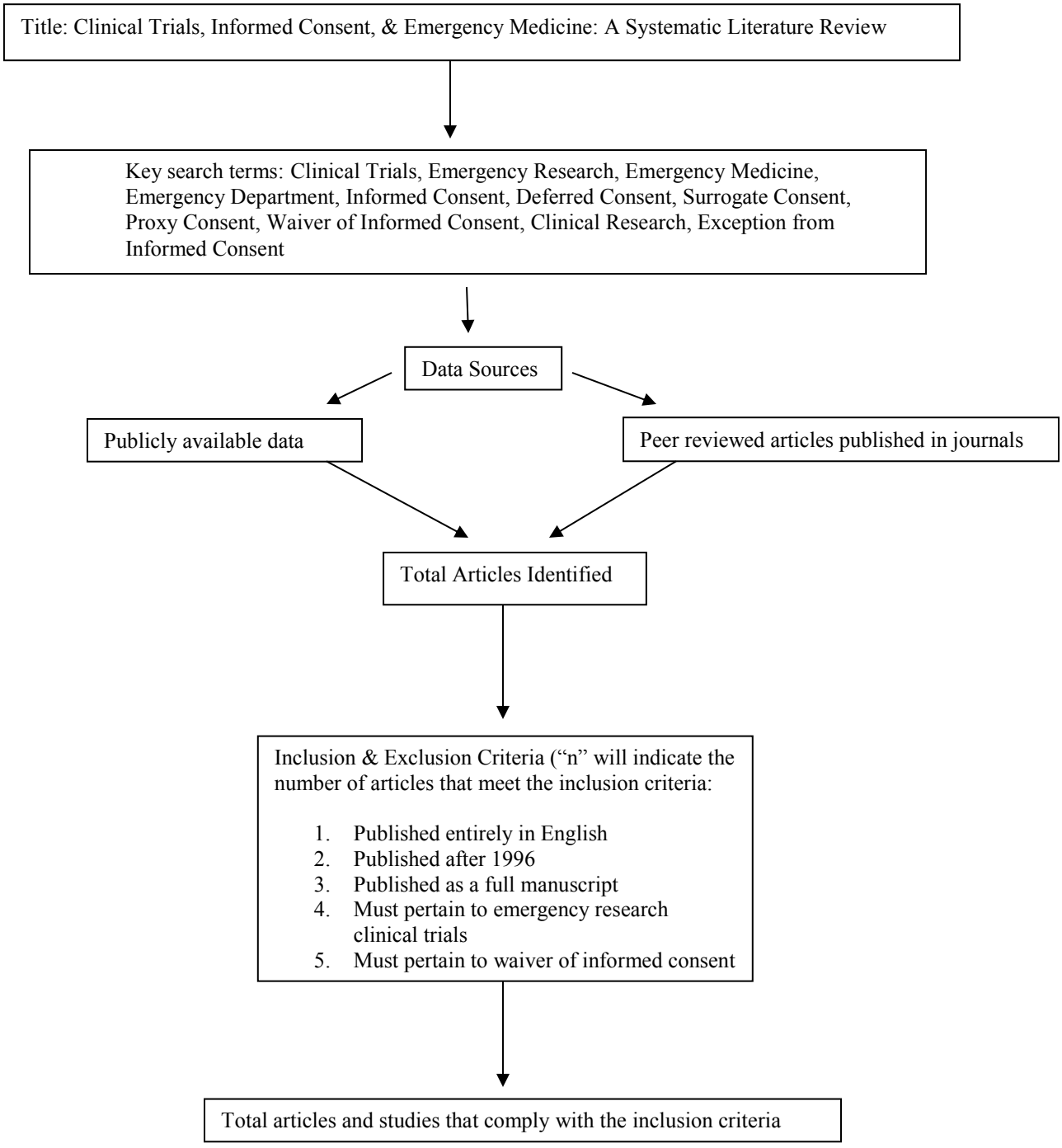
Inclusion and Exclusion Criteria

Literature included in the systematic review had to meet all of the eligibility criteria, which are listed below:

Table 2: Eligibility Criteria for Inclusion in the Review
• Published entirely in English • Published during or after 1996 • Published as a full manuscript • Must pertain to emergency research clinical trials • Must pertain to waiver of informed consent • Must be published in peer reviewed journal

The following data were excluded: studies and articles not published entirely in English, studies and articles not published as full manuscripts, studies and articles not published in peer reviewed journals, and studies and articles published prior to 1996.

Figure 1: Methodology Flowchart



RESULTS

The search identified 1,021 potential journal articles after searching the databases previously listed. The results of the article screening are outlined below in **Table 3:**

Table 3: Reasons for Article Exclusion	
Folder	Number of Articles Placed into the Folder
No After Abstract Review	409
Maybe	172
Background	21
No After Full Text Review	128
Yes	10

After the initial screening of the articles, 1021 were excluded. The reasons for exclusion are listed in the table below:

Table 4: Reasons for Excluding Articles After Screening		
Exclusion Code	Code Explanation	Number of Articles excluded
Exception	Article did not relate to 21 CFR 50.24 or waiver of consent	276
Year	Article was written prior to 1996	6

Lang or country	Article did not include study conducted in U.S. or article was not written entirely in English	218
PR	Not Peer Reviewed: editorial, opinion, commentary	19
FM	Full manuscript not available	19
ST	Article pertains to non-emergency study and/or	483

Overall, a total of 10 articles were included in this systematic review. These included articles that met all of the inclusion criteria. All of the articles were about emergency research and the informed consent exception. They were all published after 1996, in English, and any studies referenced were conducted in the United States.

Results of the Articles Reviewed

Appropriateness

The first question is whether it is appropriate that the likely unconscious participant bear the burden of opting out of the trial? A study was conducted from 1997-1998 involving patients with severe, uncompensated traumatic hemorrhagic shock (Sloan, 1203). The 21 CFR 50.24 exception was used when consent was not able to be obtained from either the

patient or their proxy. The study tested the use of Diaspirin cross-linked hemoglobin in patients as opposed to the traditional use of oxygen-carrying resuscitation fluid (Sloan, 1203-04). Requests to continue were submitted for 83% of the patients who were still enrolled about a month after initial enrollment. Consent was granted by 98% of those patients.

A 2001 article published in the *Journal of Emergency Medicine* looked at the problem of informed consent in emergency research (Foex, 2001). The article discussed the 1999 CRASH Trial (Corticosteroid Randomisation After Significant Head injury) in which it was determined that consent was unnecessary because all eligible patients would have reduced levels of consciousness (Foex, 2001).

In 2005 the ASPIRE trial began at multiple sites California, comparing manual CPR with AutoPulse CPR (Paradis, 391). All participants were enrolled under 21 CFR 50.24. The trial was terminated by the data safety monitoring board for safety concerns. One of the four sites participating in the trial made a significant protocol change mid-study. The survival rate for AutoPulse at this site was dramatically lower than those at the other sites.

A survey was administered in 2005 to survivors of sudden cardiac death (Dickert, 183). At the time it was the first study to enroll patients from a group that were likely to need the intervention (Dickert, 184). Most of the participants supported stroke research. They were less concerned with consent issues than they were with the risks and benefits of the intervention. However, condition related prognosis and adequacy of existing treatment were expressed as substantial additional factors (Dickert, 187).

Justification

The second question addressed in this review, and perhaps the most important, is whether the *Final Rule* waiving the informed consent requirement is actually justified in emergency research.

Between 2002 and 2004 a randomized, double-blind, clinical trial was conducted at Atlanta's Grady Hospital to test the potential benefit and safety of administering progesterone to patients with acute traumatic brain injury (Wright, 391). There were 100 participants, all of which were enrolled via proxy consent. Seventy-seven patients received the drug and twenty-three were given the placebo. There was no harm observed from the progesterone and participants that received the drug had a lower 30-day mortality rate (Wright, 392). Researchers found that obtaining proxy consent delayed the beginning of treatment by hours. They concluded that using 21 CFR 50.24 would maximize potential benefits of the treatment, given that promising effects of administering progesterone can be seen up to twenty-four hours post-injury (Wright, 400).

In 2006 the Shock Trauma Center at the University of Maryland Medical System was visited by 7,335 patients, 5,102 of which had arrived directly from the scene of an injury. (Dutton, 1106). From March to October of that same year, the trauma center screened 2,011 patients for their potential to give consent within one hour of admission. This was a hypothetical research trial. The study projected that consent would be unobtainable for 20% of the center's admissions. (Dutton, 1106). The researchers also noted, from a patient's viewpoint, informed consent is an intrinsically coercive process. (Dutton 1111). Some of the

barriers to obtaining consent that were mentioned include patient incompetence and delayed arrival of surrogate decision-makers.

A study was conducted in Seattle to assess the effectiveness of magnesium, diazepam or both, when given right after resuscitation of a patient experiencing out-of-hospital cardiac arrest (Longstreth, 506). While this study concluded that the intervention seemed harmless, its efficacy was not determined (Longstreth, 512). The group that received magnesium sulfate showed slightly higher rates in awakening and following commands or having intelligible speech, than the group to which the placebo was administered. On the other hand the diazepam group demonstrated slightly less frequent awakenings than the placebo group.

From 2008-2009, a pediatric study was conducted in Texas. The goal was to assess the feasibility of a large trial comparing the use of a combination of epinephrine-arginine vasopressin and initial epinephrine in pediatric ICU patients with cardiopulmonary arrest that called for chest compressions and epinephrine (Carroll, 265). Arginine vasopressin had been accepted as a viable alternative or supplementary vasopressor in adults with cardiopulmonary arrest. This study found that any specific determinations about arginine vasopressin and improved survival and neurologic outcomes in children, would need to be answered in a future trial (Carroll, 270). This particular sample size was too small to draw significant inferences. While the preliminary results showed a higher 24 hour survival rate in the intervention group there were no differences in neurologic status, survival to discharge, or return of spontaneous resuscitation.

Implications

The last question asked about implications of the waiver. A multi-center study begun in 2007 is testing surface-induced moderate hypothermia in patients with acute traumatic brain injury (Clifton, 393). All of the patients in the trial were randomized by waiver of consent except in cases when family members were readily available. The goal is to assess whether hypothermia can be used effectively as a neuroprotectant. The researchers note the treatment window for hypothermia with this specific patient population is unknown, and difficulty lies in preventing patients from being cooled below thirty-five degrees (Clifton, 397).

From 2006-2007, a survey was conducted by researchers at Yale University. The researchers sent over 100 surveys to academic emergency medicine residency training programs (Monico, 573). Half of those selected to participate responded. The survey study found that the people in charge of obtaining consent are most often emergency residents, followed by medical students, other medical residents and emergency department nurses. 41.4% of the programs that responded did not require documentation of an individual resident's understanding of the specific research protocol and consent before they were allowed to obtain consent from the potential participant (Monico, 576).

DISCUSSION

In 1979, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research published the Belmont Report (Pretz, 1443), considered to be the foundation of ethical principles regarding federal U.S. regulations for the protection of human subjects (Halperin, 1855). The report advocates three main beliefs: respect for persons (autonomy), beneficence, and justice (See Appendix C). The real arguments against allowing for the exception relate back to whether the research can be conducted while still keeping in place the assurances that are provided by informed consent —primarily, autonomy and beneficence. (Largent, 668). The Belmont Report has three requirements when it comes to informed consent (Getz, 71):

1. Research subjects are told everything about the study, including risks.
2. The information must be easy to understand.
3. Research subjects who agree to participate must do so voluntarily (without coercion or persuasion).

Given that this research is concerned with emergency research, it is easy to understand that not all of these requirements can be met under the time constraints typical of emergency situations. During life-threatening emergencies, patients may not be able to consent because they are either unconscious or in shock (Jonsen, 87). Largent, et. al recommends the use of a *consent substitute model*. The model has five conditions that must be met before enrollment. 1) Responsiveness: the proposed intervention has to respond to an urgent medical need of the patient; 2) At most, the risk-benefit ratio of the intervention must be deemed favorable toward the patient, and at least as favorable as any established standard of care; 3) there

cannot be any known compelling reason that the trial would conflict with the patients interests; 4) when taken all together, necessary non-beneficial procedures should not pose more than the minimal risk; 5) consent should be obtained as soon as possible after enrollment.

While the consent substitute model provides what may be considered a sufficient alternative to consent, the question of public disclosure is still left unaddressed. 21 CFR 50.24 requires an IRB to document public disclosure to the community of the trial before it begins. However, there are no specifics as to how that public disclosure should be made. An editorial written by Iowa Senator Chuck Grassley expresses concern about a trial that was conducted using a blood substitute (Grassley, 9). Community members that did not want to participate in the trial were to wear "hospital-like bracelets, 24 hours a day" to inform medical professionals of their decision (Grassley, 9). The commentary goes on to mention that the community meetings meant to address the trial had poor community attendance, and some residents were unaware of the meetings. The Senator expresses deep concern about citizens bearing the burden of alerting medical staff of their wishes to opt-out of an emergency research trial—whether conscious or not. Given that there are no direct instructions about how the public disclosure should be completed, this is an area that warrants further study. Here, the IRB could conceivably advertise community meetings in a weekly newsletter that is only distributed in discreet locations within a community. The IRB would then be able to argue that it followed the regulation and gave notice of the study. While this might be construed as constructive knowledge; it does not seem too much for the government to require an IRB to fully attempt actual knowledge of the trial. Of course this

would take up more of the study institution's resources, but providing more knowledge could result in a more complete study sample. If the entire community is likely to be aware, then it is possible that members may express interest in the study. Then, if a community member happens to be considered for enrollment and a proxy is available, the proxy may be more likely to consent- if they are already aware of the patient's desire to participate.

CONCLUSION

In conclusion, the advancement of emergency research is very important to the creation and development of better medical interventions. These are studies that have the potential to dramatically impact the face of medicine. The fact that most eligible participants for such trials are often unable to consent does present an ethical dilemma. However, as this review sets forth, there are standards and rules to help guide these research trials. If the trials are implemented within these guidelines, then they are likely to be ethically appropriate even when the participant does not have sufficient, advance knowledge of the study. Because these trials are restricted to enrolling participants who are facing death, and for whom there is no proven treatment, it is likely to be justified as well. One issue that came up during this research that was not frequently addressed is whether it is ethically appropriate to enroll vulnerable populations in these studies (prisoners, children, pregnant women, the elderly and the mentally ill). A few articles mentioned elderly individuals and obtaining prior consent for various medical conditions. There were also a few that addressed emergent treatments for children, though children are not able to waive consent because minors are not able to

consent in the first place. Posing these research questions in terms of vulnerable populations is a potential area of further inquiry.

APPENDICES

Appendix A: 21 CFR 50.25 Elements of Informed Consent

[Code of Federal Regulations]
[Title 21, Volume 1]
[Revised as of April 1, 2012]
[CITE: 21CFR50.25]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A--GENERAL

PART 50 -- PROTECTION OF HUMAN SUBJECTS[2]

Subpart B--Informed Consent of Human Subjects

Sec. 50.25 Elements of informed consent.

(a) *Basic elements of informed consent.* 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 the procedures to be followed, and identification of any procedures which are experimental.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

[2] Retrieved at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.25 (Last accessed 11/30/12).

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) *Additional elements of informed consent.* When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

(c) When seeking informed consent for applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), the following statement shall be provided to each clinical trial subject in informed consent documents and processes. This will notify the clinical trial subject that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank under paragraph (j) of section 402 of the Public Health Service Act. The statement is: "A description of this clinical trial will be available on*http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can

search this Web site at any time."

(d) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

(e) Nothing in these regulations 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.

[46 FR 8951, Jan. 27, 1981, as amended at 76 FR 270, Jan. 4, 2011]

[Code of Federal Regulations]
[Title 21, Volume 1]
[Revised as of April 1, 2012]
[CITE: 21CFR50.24]

Appendix B: 21 CFR 50.24 Exception from Informed Consent Requirements for Emergency Research

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A--GENERAL

PART 50 -- PROTECTION OF HUMAN SUBJECTS[3]

Subpart B--Informed Consent of Human Subjects

Sec. 50.24 Exception from informed consent requirements for emergency research.

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

(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 under investigation 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

[3] Retrieved at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.24 (Last accessed 11/ 30/12).

likely to become eligible for participation in the clinical investigation.

(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 investigation 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 clinical investigation could not practicably be carried out without the waiver.

(5) The proposed investigational plan 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 legally authorized 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 consistent with 50.25. 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 clinical investigation consistent with paragraph (a)(7)(v) of this section.

(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 clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical

investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation 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 clinical investigation; 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 clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) 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 clinical investigation, the details of the investigation 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 clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new

drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

[61 FR 51528, Oct. 2, 1996]

Appendix C: The Nuremberg Code

Nuremberg Code[4]

Directives for Human Experimentation

1. The voluntary consent of the human subject is absolutely essential.

2. The experiment should be such as to yield fruitful results for the good of society.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of thegood faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject. (Link)

[4] Retrieved at http://ori.dhhs.gov/education/products/RCRintro/c03/b1c3.html (Last accessed 12/10/12).

Appendix D: The Declaration of Helsinki

Initiated: 1964 17.C
Original: English

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI[5]
Ethical Principles
for
Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects**.** Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

[5] Retrieved at http://www.fda.gov/ohrms/dockets/dockets/06d0331/06D-0331-EC20-Attach-1.pdf (Last accessed 12/10/12).

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient’s information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. *(See footnote*)*

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

**FOOTNOTE:*

Note of Clarification on Paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebocontrolled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

The Belmont Report

Office of the Secretary

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Members of the Commission

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.
Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.
Robert E. Cooke, M.D., President, Medical College of Pennsylvania.
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Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes (1) intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

Part A: Boundaries Between Practice & Research

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. (2) By contrast, the term "research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project. (3)

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

Part B: Basic Ethical Principles

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant

to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons. -- Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. -- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: **(1)** do not harm and **(2)** maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek

certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. -- Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are **(1)** to each person an equal share, **(2)** to each person according to individual need, **(3)** to each person according to individual effort, **(4)** to each person according to societal contribution, and **(5)** to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply

because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

Part C: Applications

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. -- Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that **(1)** incomplete disclosure is truly necessary to accomplish the goals of the research, **(2)** there are no undisclosed risks to subjects that are more than minimal, and **(3)** there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given

to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitle.

2. Assessment of Risks and Benefits. -- The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: **(i)** Brutal or inhumane treatment of human subjects is never morally justified. **(ii)** Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. **(iii)** When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation). **(iv)** When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature

and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. **(v)** Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. -- Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

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(1) Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

(2) Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

(3) Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

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