PROTECTING HUMAN PARTICIPANTS IN RESEARCH
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WHAT YOU SHOULD KNOW AFTER THIS PRESENTATION:

Protecting Human Volunteers in Medical Research

1. Know why IRBs/HSCs exist and what they do.
2. Be familiar with the eight essential elements and six additional elements for an Informed Consent Form.
3. Know the difference between an Informed Consent and HIPAA Authorization.
4. Know what constitutes a Conflict of Interest for an investigator.
5. Know the difference between an Expedited Review and Exempt Research.
6. Who can help you with the IRB process?
## Protecting Human Participants in Research

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Helpful IRB Websites

Wichita Medical Research and Education Foundation
http://www.wichitamedicalresearch.org

KUMC HSC Forms
http://wichita.kumc.edu/afs/compliance/index.html

The Belmont Report
http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm

Declaration of Helsinki
http://www.wma.net/e/policy/b3.htm

OHRP Decision Charts
http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm

Federal Regulations and Policies
http://cflegacy.research.umn.edu/irb/regs.cfm

FDA Information Sheets
http://www.fda.gov/oc/ohrt/irbs/default.htm

OHRP – IRB Guidebook
http://www.hhs.gov/ohrp/irb/irb_guidebook.htm

Good Clinical Practice Guidelines
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090259.htm

NIH – Bioethics Websites
http://www.nih.gov/sigs/bioethics/

IRB Forum Links
http://www.irbforum.org/links/

Human Subject Protection Tutorial - KUMC
http://wichita.kumc.edu/compliance/training.html

Informed Consent Tutorial – U of Minnesota
http://www.research.umn.edu/consent/orientation.html

Research Categories – Expedited
http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm

Medical Terms
http://www.medterms.com/Script/Main/hp.asp
Protecting Humans in Research

Protecting Human Participants
In Medical Research
Ginger French, Pharm.D., CIM, CIP
(Certified IRB Manager and Certified IRB Professional)
Institutional Review Board Director
Wichita Medical Research
& Education Foundation (WMREF)

Phocomelia

“The IRB is a Granter of Privilege rather than a Restrictor of Right…”
---Dale Hammerschmidt, M.D.

Why are We Here?
(What are Our Objectives?)
• Need for protection of human participants in medical research.
• Rights of a human subject in a research study.
• What an Institutional Review Board is
  – make up of such a Board
  – responsibilities and general workings of an IRB
• Concept of Informed Consent
  – basic components
  – use in human subject protection.

Objectives II
• Concepts of
  – Exemption and
  – Expedited review by the IRB/HSC
• Identify the basic research requirements of HIPAA, including what a Privacy Board (PB) is
Objectives …

• History leading to:
  • Federal requirement of IRBs.
  • Recent events impacting
    – investigators,
    – IRBs, and
    – the people they protect.

Definitions
  – Human Subject

“Human Subject” is an individual about whom an investigator…conducting research obtains data through intervention or interaction with the individual, or identifiable private information.

“Research” defined

Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

Historical Perspective

• Nuremberg Doctors Trial of 1946
  --16 physicians and 7 others – 16 guilty, 7 hung
  Code in 1947

• The Thalidomide Tragedy
  --First US law requiring researchers to inform subject of drug’s experimental nature and to receive their informed consent before starting the research.

• The Study of Untreated Syphilis in the Negro Male

World and Federal Ethical Regulations

• Nuremberg Code
• Declaration of Helsinki
• The Belmont Report
• The Common Rule

Declaration of Helsinki

• World Medical Assembly
• Post Thalidomide
• Ethical as opposed to legalistic doctrine
• First version in 1964
The Belmont Report

- 1979 by The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- Boundaries between Practice and Research
- Respect for persons
- Beneficence
- Justice

Respect for Persons

- Treat Individuals as autonomous agents
- Fundamental right to be left alone
- Don’t use people as a means to an end
- Extra protections for those with diminished autonomy – vulnerable populations

Beneficence

- Maximize benefits & minimize risk of harm
- Practical applications: Study design, risk:benefit, competent investigators

Justice

- Burdens and benefits of research should be distributed equitably
- Treat people fairly
- International, not just in the U.S.

DHHS and FDA Regulations

-1981 – The Common Rule
- Based on Belmont Principles
- IRBs with people of diverse backgrounds
- Community attitudes
- Informed consent required
  - Specific elements listed

Institutional Review Boards (IRBs aka HSCs)
Federally Mandated
Committee Make Up

- Number
- Gender
- Ethnic
- Scientific
- Non-scientific*
- Unaffiliated – including family member
- Conflict of Interest
- Diverse
- Consultants with competence in special areas

IRB Duties and Responsibilities

- The IRB, under authority of the federal regulations, shall review and have authority to
  - Approve
  - Require modifications in (to secure approval)
  - Disapprove research
- Review of changes required by the IRB for proposal acceptance

Duties and Responsibilities II

- Always, the participant is #1
- Scientific Merit
- Initial review of
  - Protocols
  - Investigator Brochures*
  - Informed Consent Document
  - Advertising
- Emergency Review
- Continuing Review
- Investigator Qualifications

Duties and Responsibilities - III

- Ongoing Oversight (monitoring) of the research (including the consent process)
- Serious Adverse Events
- Elements required for research approval

Informed Consent

- Process
- Document
- Functions
Process

- Environment
- Timing
- Opportunity for reflection
- Opportunity for consultation
- Person Obtaining Consent
- Ongoing nature
  - Questions and answers
  - Ability to Change Mind at any Time

Document

- Eight Essential Elements
- Six additional elements when applicable
- Elements specific to the IRB or Institution
- Checklist
  - May be combined with HIPAA Authorization

Informed Consent, a Process that Includes:

- Subject recruitment materials
- Verbal instructions
- Written materials
- Question/answer sessions
- Agreement documented by signature and date
- Follow up questions
- Functions

Other Types of IRB Review

- Expedited Review
  - Nine Categories – Designate Category
  - All other regulations of Common Rule still apply – Consent, Rules for Approval, etc.
  - Only the meeting of the fully convened IRB is not required – Chair or designee(s)
- Exempt Research
  - Six Categories – Designate Category
  - Only IRB Oversight is if research changes – PI not decide if exempt

Agreement between IRBs/HSCs -- MOU

- Signed in early 2009
- Allows cooperation and use of commonly developed forms for local research
- Minimal risk research only
- User-friendly way to designate exempt and expedited categories
- Between:
  - UKSM-W and WMC and WMREF
  - UKSM-W and Via Christi

Investigator Responsibilities
Statement of Investigator (FDA Form 1572)

Nine statements of agreement of responsibility

Statement 8

- I will ensure that an IRB that complies with the federal regulations
  --Does initial and continuing review and approval of the clinical investigation.

- Promptly report to the IRB
  --all changes in research activity and
  --all unanticipated problems involving risks to human subjects or others.

- Not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Health Insurance Portability & Accountability Act - HIPAA

● Privacy Board Duties (HIPAA)

  Caveat:
  ● The Common Rule remains THE RULE for research issues.
  ● The Privacy Rule was not written with research in mind – so not a perfect fit
  ● If the Common Rule and the Privacy Rule do not agree – do whatever has the higher protection
  ● Stimulus package added HITECH 2009

Protected Health Information (PHI)

Individually identifiable health information that a covered entity creates or receives

- Includes information about the past, present or future physical or mental health of a person, the provision of health care to a person and payment for care
- (Even chart reviews use PHI)
- Includes information in written, electronic and/or oral form

- VERY OFTEN MISUNDERSTOOD!

Recent Events in the IRB World

FEDERAL OVERSIGHT

DHHS
  Katherine Sebelius

HHS
  Jerry Nadoff, MD, JD

FDA
  Margaret A. Hamburg, MD

IRB

page 7
Shutdowns of Research

- 3/99 – Veterans Affairs – Greater Los Angeles Health Care Center
- 5/99 – Duke University Medical Center
- 8/99 – University of Illinois, Chicago
- 1/00 – Virginia Commonwealth University
- 6/01 - University of Oklahoma Health Sciences Center in Tulsa
- 7/01 – Johns Hopkins Medical Institutions
- 2003 – All VA Research
- 2009 – 24 OHRP Determination Letters by 06/24
- 2009 – GAO “Sting” Operation – closed Coastal IRB
- And on...

Failure to Report Adverse Events (UPs)

- University of Rochester – Nicole Wan
- University of Pennsylvania Institute for Human Gene Therapy – Jesse Gelsinger
- University of Oklahoma (Tulsa) Melanoma Vaccine Study
- Johns Hopkins University – Ellen Roche
- MOST Occur in locally developed studies

Unexpected Study Deaths

- University of Rochester – Nicole Wan
- University of Pennsylvania Institute for Human Gene Therapy – Jesse Gelsinger
- University of Oklahoma (Tulsa) Melanoma Vaccine Study
- Johns Hopkins University – Ellen Roche
- MOST Occur in locally developed studies

Education of IRBs, Investigators, & Staff

Then add…
...more:
- Registration of IRBs – Mandatory as of July 2009
- Federal Wide Assurances (FWA)
- Accreditation of Human Protection Programs  
  – Not just IRBs
- Conflict of Interest
- Certification of IRB Professionals
- Certification of Investigators
- (HHS) Secretary’s Advisory Committee on Human Research Protection (SACHRP)
- Clinical Trial Registration
- Ongoing Issuing of New Guidances – 2 on 10/27/08
- Latest July 2009 on IRB Registration Mandates

Additional Information Sources
- This handout and members of this research community
- Newsletters  
  – “Human Research Reports”  
  – The Hastings Center “IRB: Ethics & Human Research”  
  – “IRB Advisor”
- Books and journals on clinical ethics and human subject research protection
- Websites

Summary
- Walk through Table of Contents
- What have you learned?
- Apply what you have learned…

THANK YOU!
- WMREF IRB 686-7172
- KUSM-W HSC 293-2600
- Via Christi IRB 268-5114
Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review

Applicability

(A) Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

(B) The categories in this list apply regardless of the age of subjects, except as noted.

(C) The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

(D) The expedited review procedure may not be used for classified research involving human subjects.

(E) IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.

(F) Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Research Categories

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
(b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(3) Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) unannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject’s privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

(8) Continuing review of research previously approved by the convened IRB as follows:

(a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
(b) where no subjects have been enrolled and no additional risks have been identified; or

(c) where the remaining research activities are limited to data analysis.

(9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

1 An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements set forth in 45 CFR 46.110.

2 Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." 45 CFR 46.402(a).

Source: 63 FR 60364-60367, November 9, 1998
Further Regulations on Expedited Review:

An IRB may use the expedited review procedure to review either or both of the following:

(1) some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

(FDA) 21 CFR §56.104  Exemptions from IRB requirement.

The following categories of clinical investigations are exempt from the requirements of this part for IRB review:

(a) Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.

(b) Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.

(c) Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.

(d) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28028, June 18, 1991]
Human subjects term indicating six research categories exempt from human subjects regulations:

1. Research conducted in educational settings involving normal educational practices, such as research on instructional strategies, techniques, curricula, or classroom management methods.

2. Research using cognitive, diagnostic, aptitude, and educational achievement tests, or surveys, interviews, or observations of public behavior, unless human subjects are identifiable, and disclosure of responses could put them at risk of liability, or damage to their reputations or financial standing.

3. Research using cognitive, diagnostic, aptitude, and educational achievement tests, or surveys, interviews, or observations of public behavior, unless subjects are public officials or candidates for public office, or federal statutes require that the confidentiality of identifiable information will be maintained.

4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if the sources are publicly available, or the information is recorded so subjects cannot be identified.

5. Research and demonstration projects conducted or approved by [Federal] Department or Agency heads to study public benefit or service programs, procedures for obtaining benefits or services, or other changes to those programs.

6. Taste and food quality evaluation and consumer acceptance studies in a) wholesome foods without additives or b) food containing a food ingredient at or below a level and use found to be safe, or an agricultural chemical or environmental contaminant at or below a level deemed safe by the following agencies: the Food and Drug Administration, Environmental Protection Agency, and U.S. Department of Agriculture Web sites.
**GENERAL GUIDELINES**

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1. Is the consent form written in “lay language”? Such as is there a randomization of subjects? Is this process explained (i.e., by chance, like a flip of a coin)? If a placebo is used, is this explained?

2. Is the title of the study specified?

3. If an investigational drug is to be used, does it have an IND#? (protocol submission requirement)

4. If an investigational device is to be used, does it have an IDE#? (protocol submission requirement)

5. If children are to be included as subjects, is provision made for securing the assent of the child and the permission of the parent(s) or guardian(s)?

6. Are the pages numbered accurately and the date of revision included?

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7. Is a statement included which states the study involves research?

8. Is the principal investigator identified?

9. Are all physician investigators identified?

10. If an investigational drug is used, is it identified as experimental/investigational?

11. If an investigational device is used, is it identified as experimental/investigational?

12. *Is the number of study participants stated (local and all sites)?

13. Is the expected length of the subject’s participation stated?

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14. Is the purpose of the research adequately explained?

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15. Is a description of study procedures provided?

16. Are experimental procedures identified and distinguished from normal medical care?

17. Are activities, which the subject must complete, adequately explained (e.g., diaries, questionnaires, visit times)?

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18. Is there a description of any benefits to the subject or to others which may reasonably be expected from the research? (Compensation, if any, should not be in this section.)

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19. *Is a statement included which describes any reasonably foreseeable risks or discomforts to the subject (*or to the embryo or fetus, if the subject is or may become pregnant) from this particular treatment or procedure described?*

20. *Is a statement regarding unforeseeable risk to subject (or to the embryo or fetus) included?*

21. If women of childbearing potential are in the study, is information concerning birth regulation/sterilization/lactation (if applicable) included?

### Alternate Treatments

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- Is disclosure of appropriate alternative procedures or courses of treatments provided, if any, that might be advantageous to the subject? If there are no approved treatments available, describe common intervention being used.

### Confidentiality

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- Is a statement describing the extent to which medical records will be kept confidential including a list of whom may have access to records which identify the subject, i.e., persons involved in their care, WMREF’s Institutional Review Board?

- Is information included that the FDA, study sponsor, and/or their designees may inspect records that identify subjects in the case of research involving Food and Drug Administration regulated products?

### Financial Cost of Research

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- Is there a statement covering each of the following items:
  a. *Are there any study costs to the subject? If yes, are these costs outlined?*
  b. *Who pays for study related costs?*

### Compensation

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- *Is subject compensation, if any, outlined? If none, is this explained?*

- For research involving more than minimal risk, is an explanation included to explain if compensation or medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained?

- Are payment of costs related to injury described?

- If the consent form or the protocol offers research related medical treatment or compensation for medical treatment, does it state in the consent form the sponsor and not the institution will provide payment for research-related medical care?

- Is it free of language in which the subject waives any legal rights, including release of the investigator, the sponsor, the institution/state or its agents from liability for negligence?

### INVESTIGATOR COMPENSATION

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- Is there a statement which states how the investigator is being financially compensated?
  Examples:
  - The Investigator is not being compensated.
  - The Investigator is being reimbursed for his/her time and costs.
  - The investigator is being compensated by the sponsor beyond his/her time and costs.
  - The investigator has financial interest in the company that is sponsoring this study.

### INDEMNITY CLAUSE

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- Are the appropriate indemnity clause/s included?

### NON-PARTICIPATION/Right to Withdraw

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- Is there a statement of the right of the subject to refuse participation?

- Is there a statement which states they may withdraw their consent at any time without penalty or loss of benefits?

- *Is there a statement that the investigator or sponsor has the right to withdraw*
36. "Is there a statement which states consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by the subject?"

37. "Is there a statement that the subject will be informed of any significant new findings?"

### Questions

<table>
<thead>
<tr>
<th>Yes</th>
<th>NO</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>38. Is an explanation included as to whom and how to contact appropriate persons for answers to pertinent questions involving the research and in the event of a research-related injury? Phone number for injury contact should include a number during regular business hours and a 24-hour number and person’s name.</td>
<td></td>
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<tr>
<td>39. Is an explanation included as to whom and how to contact the appropriate persons or organizations for answers to questions regarding research subject’s rights? Phone number for injury contact should include a number during regular business hours and a 24-hour number and person’s name.</td>
<td></td>
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</tr>
</tbody>
</table>

### Voluntary Consent

<table>
<thead>
<tr>
<th>Yes</th>
<th>NO</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>40. Is there a statement that participation is voluntary?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41. Is there a statement that the subject will receive a copy of the consent form?</td>
<td></td>
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<tr>
<td>42. Is there a Printed Name and Signature Line for the Study participant or Study subject?</td>
<td></td>
<td></td>
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<tr>
<td>43. &quot;Is there a Printed Name and Signature Line for the parent or legally-authorized representative, if applicable?</td>
<td></td>
<td></td>
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<tr>
<td>44. Is there a Printed Name and Signature Line for the investigator (not &quot;physician&quot;)?</td>
<td></td>
<td></td>
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<tr>
<td>45. Is a Printed Name and Signature Line for the Person Obtaining Consent included?</td>
<td></td>
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</tr>
<tr>
<td>46. &quot;If applicable, is there an Assent for a Child provided in the consent form?</td>
<td></td>
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</tr>
</tbody>
</table>

‘Institutional’ Indemnity Clause: “No guarantee has been made to you as to results that may be obtained. (Insert Institution Name Here), and other involved organizations do not provide free medical treatment or other forms of compensation for injuries incurred as a result of participating in this study.”

USKM-Wichita Indemnity Clause (Added Additionally, If Appropriate)

“Although the University Of Kansas Medical Center does not provide free medical treatment or other forms of compensation to persons injured as a result of participating in research, such compensation may be provided under the terms of the Kansas Tort Claims Act. If you believe you have been injured as a result of participating in research, you should contact the Office of Legal Counsel; University of Kansas Medical Center, Kansas City, Kansas 66160-7700.”
# WMREF Checklist for IRB Review of Pediatric Research

To be approved by an IRB, pediatric research must comply with all of the items in one of the following three categories:

## Research not involving greater than minimal risk (45 CFR 46.404) (21 CFR 50.51)

- The research is of no greater than minimal risk.  
  *(Indicate reasons why)*

- Adequate provisions are made for soliciting the permission of one or both parents/guardians.

- Adequate provisions are made for soliciting the assent of the children.

## Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (45 CFR 46.405) (21 CFR 50.52)

- The intervention or procedure holds out the prospect of direct benefit for the individual subject or the monitoring procedure is likely to contribute to the subject's well being.  
  *(Indicate reasons why)*

- The risk is justified by the anticipated benefit to the subjects.  
  *(Indicate reasons why)*

- The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.  
  *(Indicate reasons why)*

- Adequate provisions are made for soliciting the assent of the children.

- Adequate provisions are made for soliciting the permission of one or both parents/guardians.

## Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition (45 CFR 46.406) (21 CFR 50.53)

- The risk represents a minor increase over minimal risk.  
  *(Indicate reasons why)*

- The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations.  
  *(Indicate reasons why)*

- The intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition, which is of vital importance for the understanding or amelioration of disorder or condition.  
  *(Indicate reasons why)*

- Adequate provisions are made for soliciting the assent of the children.

- Adequate provisions are made for soliciting the permission of both parents/guardians.

---

When approving research with children OHRP strongly recommends that these findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding. *(OPRR Compliance Activities: Common Findings and Guidance, Item 64.) Please include this information on your review sheet.*
WMREF IRB Waiver of Consent Form Request

**Study Title:**_____________________________________________________________________

If you are requesting the waiver of participant consent, the following items must be addressed and deemed appropriate by the IRB.

An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

_____1. The research involves no more than minimal risk to the subjects;
   Explain why:

_____2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
   Explain why:

_____3. The research could not practically* be carried out without the waiver or alteration, and
   Explain why:

_____4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
   Explain why, if applicable:

45 CFR 46.116(d)

Signature of Principal Investigator:________________________   Date:_____________

*"Practicable" is not an inconvenience or increase in time or expense to the investigator or investigation, rather it is for instances in which the additional cost would make the research prohibitively expensive or where the identification and contact of thousands of potential subjects, while not impossible, may not be feasible for the anticipated results of the study.
Authorization to Use and Disclose
Protected Health Information (PHI*) for Research Purposes

The privacy law, Health Insurance Portability & Accountability Act (HIPAA), protects my identifiable health information (protected health information). The privacy law requires me to sign an authorization (or agreement) in order for researchers to be able to use or disclose my protected health information for research purposes in the study entitled [Insert title of study.]

I authorize [name of researcher] and his/her research staff to use and disclose my protected health information for the purposes described below.

Holder(s) of my PHI who may make the requested use and disclosure include:

- [List the holder(s) of the PHI, including institutions, physicians’ offices, repositories, etc.]

My protected health information that may be used and disclosed includes only:

- [List all of the protected health information* to be collected for this protocol/study such as all demographic information - including name, address, birth date, etc, results of physical exams, laboratory tests, x-rays, and other diagnostic and medical procedures as well as medical history, questionnaires, diaries, information on health care costs.]

My protected health information will be used for:

- [Provide a brief description of the research project or paste information from purpose section in consent form; indicate that one reason to share the information is to be able to conduct the research, another reason is to ensure that the research meets legal, institutional, and/or accreditation requirements.]

The Researchers may use and share my health information with:

- Wichita Medical Research & Education Foundation’s Institutional Review Board (WMREF’s IRB)
- Government representatives, when required by law [FDA, OHRP, etc.]
- [Institution Name] representatives
- [List any collaborators, outside laboratories, etc.]
- List CRO/monitors, data coordinating centers, DSMBs
- [If applicable - list the sponsor’s name]
- [List any other groups with whom the information may be shared]

Once my health information has been disclosed to anyone outside of this study, the information may no longer be protected under this authorization.

The researchers [and list sponsor’s name if applicable] agree to protect my health information by using and disclosing it only as permitted by me in this Authorization and as directed by state and federal law.

* PHI includes individual health information relating to past, present or future physical or mental health or conditions of any individual. To be PHI, the individual health information must be linked to one or more of the identifiers listed below.
- Identifiers include: Name, Address, Dates Directly Related to an Individual, Telephone/Fax Number, E-mail/Internet Protocol or Web URL Address, Social Security Number, Medical Record or Health Plan Number, Account Number, Certificate of License Number, Photographic Images, Vehicle Identifiers, Device Identifiers, Biometric Identifiers, Any Other Unique Code.

I do not have to sign this Authorization. If I decide not to sign the Authorization:

- I cannot participate in the research study.
• If applicable: It will not affect my treatment, payment or enrollment in any health plans or affect my eligibility for benefits.

After signing the Authorization, I can change my mind and:

• Not let the researcher disclose or use my protected health information (revoke the Authorization).
• If I revoke the Authorization, I will send a written letter to: [name and contact information] to inform him/her of my decision.
• If I revoke this Authorization, researchers may only use and disclose the protected health information already collected from me for this research study.
• If I revoke this Authorization my protected health information may still be used and disclosed if certain events (such as an adverse event or bad effect) occur.
• If I change my mind and withdraw the authorization, I may not be allowed to continue to participate in the study.

[If appropriate:] I will not be allowed to review the information collected for the research until after the study is completed. When the study is over, I will have the right to access the information again.

This Authorization does not have an expiration date.

If I have any questions or concerns about my privacy rights, I should contact the [name of institution] Privacy Officer at Ph: (316)__________________.

I am the subject or am authorized to act on behalf of the subject. I have read this information and agree to the uses and disclosures of my health information. I will receive a copy of this form after it is signed.

Printed Name of Research Subject   Signature of Research Subject or *research subject’s legal representative   Date

Printed Name of *Legal Representative (if applicable)

*Please explain Representative’s Relationship to Participant and include a description of Representative’s Authority to act on behalf of Participant:

________________________________________________________________________________
________________________________________________________________________________
________________________________________________________________________________

[Examples include parent of a minor, legal guardian, or durable power of attorney for health care.]
WMREF IRB Checklist for Authorization to Use and Disclose Protected Health Information (PHI*) for Research Purposes

(All of these items must be study-specific.)

______1. Is the Principal Investigator identified?

______2. Is the Title of the Study included?

______3. Is there a detailed description of the information to be used or disclosed that identifies the information in a specific and meaningful fashion? 45 CFR 46 §164.508(c)(1)(i)

______4. Is there the name or other specific identification of the person(s), or class of persons, authorized to make the requested use or disclosure (such as Wesley Medical Center)? 45 CFR 46 §164.508(c)(1)(ii)

______5. Is there a listing of the name or other specific identification of the person(s), or class of persons to whom the holder of the PHI (such as WMC) may make the requested use or disclosure? 45 CFR 46 §164.508(c)(1)(iii)

______6. Is there a description of each purpose of the requested use or disclosure? 45 CFR 46 §164.508(c)(1)(iv)

______7. Is there an expiration date or expiration event or a statement that there is no expiration date?

45 CFR 46 §164.508(c)(1)(v)

______8. Is there a place for the printed name (optional) and signature of the subject and the date of signature? 45 CFR 46 §164.508(c)(1)(vi) and 45 CFR 46 §164.508(c)(2)(iii)

______9. Is there a place for the printed name (optional), signature and date of signing for a personal representative of the participant? 45 CFR 46 §164.508(c)(1)(vi)

______10. Is there a place for a description of a personal representative’s authority to act for the participant?

45 CFR 46 §164.508(c)(1)(vi)

______11. Is there information about the participant’s right to revoke the authorization in writing, including who to write and where to send the notice? 45 CFR 46 §164.508(c)(2)(i)

______12. Is there a statement that upon revoking the authorization, researchers may only use and disclose the PHI already collected from the participant for the research project? 45 CFR 46 §164.508(c)(2)(i)(A)

______13. Is there a statement that if certain events (such as an adverse drug reaction) occur some of the PHI will still be used/disclosed after revocation? 45 CFR 46 §164.508(b)(5)(ii) and p. 95 12/3/02 Guidance

______14. (If applicable) Is there a statement as to whether the participant will have access to their collected information during the course of the study? 45 CFR 46 §164.524(a)(2)(iii)

______15. Is there a statement of the consequences of not signing the authorization (such as not being allowed to participate in the study)? 45 CFR 46 §164.508(c)(2)(ii)

______16. Is there a statement about the potential for information disclosed as a result of this authorization to be subject to redisclosure by the recipient and no longer protected by the HIPAA/Privacy rules? 45 CFR 46 §164.508(c)(2)(iii)

______17. Is the authorization written in plain language? 45 CFR 46 §164.508(c)(4)

* PHI includes individual health information relating to past, present or future physical or mental health or conditions of any individual. To be PHI, the individual health information must be linked to one or more of the identifiers listed below.

- Identifiers include: Name, Address, Dates Directly Related to an Individual, Telephone/Fax Number, E-mail/Internet Protocol or Web URL Address, Social Security Number, Medical Record or Health Plan Number, Account Number, Certificate of License Number, Photographic Images, Vehicle Identifiers, Device Identifiers, Biometric Identifiers, Any Other Unique Code.

Rev. 4/04/03
1. The use or disclosure of Protected Health Information (PHI)* involves no more than a minimal risk to the privacy of individuals. **Explain why.** Include a detailed list of the PHI to be collected and a list of the source(s) of the PHI. (add lines, if needed) 45 CFR §164.512(i)(2)(i)(A)

2. Describe the plan to protect identifiers and indicate where PHI will be stored and who will have access. (Researchers must list all of the entities that might have access to the study’s PHI such as IRB, Institutional representatives, sponsors, FDA, DSMBs and any others given authority by law.) (add lines, if needed) 45 CFR §164.512(i)(2)(ii)(A)(1) and (3)

3. All identifiers collected during the study will be destroyed at the earliest opportunity consistent with the conduct of research, which is: (explain below).

   Please describe the procedure used to destroy all the data collected during the study (electronically, paper, audio/video, photography, other). OR

   Alternatively, the identifiers collected during the study will not be destroyed because: (explain below).

   45 CFR §164.512(i)(2)(ii)(A)(2)

4. The research could not practicably be conducted without the waiver because (explain below). 45 CFR §164.512(i)(2)(ii)(B)

5. The research could not practicably be conducted without access to and use of the PHI because (explain below). 45 CFR §164.512(i)(2)(ii)(C)

6. The HIPAA regulation requires reasonable efforts to limit protected health information to the minimum necessary to accomplish the intended purpose of the use, disclosure or request. Please note that researchers are accountable for PHI released under a waiver. **Explain why PHI obtained for this study is/are the minimum information needed to meet the research objectives.** 45 CFR §164.512(i)(2)(iii) & §164.502(b)(1)

The information listed in the waiver application is accurate and all research staff** will comply with the HIPAA regulations and the waiver criteria. I assure that the information I obtain as part of this research (including protected health information) will not be reused or disclosed to any other person or entity other than those listed on this form, except as required by law. If at any time I want to reuse this information for other purposes or disclose the information to other individuals or entity I will seek approval by the IRB.

Principal Investigator Name Typed or Printed __________________________ Date ______________

Principal Investigator Signature ______________________________

*PHI: Individually identifiable health information transmitted or maintained in any form (electronic means, on paper, or through oral communication) that relates to the past, present or future physical or mental health or conditions of an individual.

**Note: Research staff is defined as ALL study personnel (including PI) that is involved in the research.

***HIPAA Regulations allow IRBs to waive use of authorization form if all of the criteria listed above are met.

030603
Research which involves the use of "de-identified" protected health information (PHI)* is exempt from HIPAA requirements. To be exempt from HIPAA, none of the following subject identifiers can be reviewed or recorded by the research team.

CHECK OFF EACH ITEM:

___Names (individual, employer, relatives, etc.)
___Address (street, city, county, zip code - initial 3 digits if geographic unit contains less than 20,000 people, or any other geographical codes)
___Telephone/Fax Numbers
___Social Security Numbers
___Date (except for years):
  ___Birth Date
  ___Admission Date
  ___Discharge Date
  ___Date of Death
  ___Ages >89 and all elements of dates indicative of such age (except that such age and elements may be aggregated into a category "Age>89")
___E-mail Addresses/URLs
___Medical Record Numbers
___Health Plan Beneficiary Numbers
___Account Numbers
___Certificate/License Numbers
___Vehicle Identifiers and Serial Numbers (e.g. VINs, License Plate Numbers)
___Device Identifiers and Serial Numbers
___Biometric Identifiers (e.g. finger or voice prints or full face photographic images)
___Any other unique identifying number, characteristic, or code

I certify the protected health information (PHI)* received or reviewed by research personnel for the research project referenced above does not include any of the 18 identifiers listed above.

Principal Investigator Signature: _____________________________ Date: __________________

Research Coordinator Signature: _____________________________ Date: __________________

Printed Name of Principal Investigator: _____________________________

Printed Name of Research Coordinator: _____________________________

*PHI: individually identifiable health information transmitted or maintained in any form (electronic means, on paper, or through oral communication) that relates to the past, present or future physical or mental health or conditions of an individual.

Revised 3/4/03
Box 9 of FDA Form 1572

**COMMITMENTS** [CODE LETTER for “SMALL PRINT”]

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects. [A]

I agree to personally conduct or supervise the described investigation(s). [S]

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met. [I]

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.84. [P]

I have read and understand the information in the investigative brochure, including the potential risks and side effects of the drug. [L]

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments. [T]

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68. [M], [L], and [R]

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects. [N]

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.
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, thereby 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.
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.
Dorothy I. Height, President, National Council of Negro Women, Inc.
Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.
Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.
Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.
David W. Louisell, J.D., Professor of Law, University of California at Berkeley.
Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.
Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.

*** Deceased.

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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.

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**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.

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**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 entitled.

**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.
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.

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.

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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