



# Human Subjects Protection 101

**The Basics,  
Common Issues, and  
Hot Topics**



# The Basics

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- The Nuremberg Code
  - Impetus: Medical Experiments by Nazis in WWII
  - The result: Human Subject Experimentation requires
    - Voluntary consent; legal capacity; sufficient information to make "enlightened" decision; without duress or coercion; able to be withdrawn at any time
    - Study design based on current knowledge or animal modeling
    - Conducted to avoid unnecessary physical or mental suffering
    - If death or disability likely, physician should also be study subject



# The Basics

## ■ Helsinki Declaration

- Impetus: The Nuremberg Code, and the desire of the medical community to self-police research
- The result: Biomedical Research for Human Subjects must:
  - Be based on scientific knowledge, with prior analysis of risks, and address only subjects of importance
  - Be reviewed by a specially appointed committee (the IRB)
  - Respect the privacy and integrity of research subjects
  - Have informed consent, with ability to withdraw at any time; particular caution if dependency relationship exists
  - Consent from guardian or "responsible relative" if minor; "consent" from minor as well if capable; research in non-consent must be justified by importance to group



# The Basics

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## The Belmont Report

- Impetus: The Tuskegee Syphilis Study, which led to the National Research Act (1974)
  - Created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
  - Charged with identification of the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human participants and development of guidelines to be followed to assure that such research is conducted in accordance with those principles
- The Result: The basic document which underlies ethical issues in human subject research in the United States
  - An attempt to distinguish between treatment, innovative



# The Basics

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- The Belmont Report: Basic Ethical Principles
  - Respect for Persons / Self Determination
    - As autonomous agents
    - If diminished autonomy, entitled to protection
  - Beneficence
    - An obligation to not harm, and to maximize benefits and reduce risk
  - Justice
    - Fairness in distribution of risks and benefits
    - Not overburdening a population at risk of exploitation
    - Research supported by public funds which results in therapeutic interventions should benefit all, not just those who can afford the intervention



# The Basics

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## ■ The Belmont Report: Application

### ■ Informed Consent: Primarily Respect for Persons

#### ■ Issues:

- Information
- Comprehension
- Voluntariness

### ■ Assessment of Risks and Benefits: Primarily Beneficence

- Nature and Scope of Risks and Benefits
- Systematic Assessment of Risks and Benefits



# The Basics

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- The Belmont Report: Application
  - Selection of Subjects: Primarily Justice
    - Social Justice
      - Requires consideration of population that should / should not participate in a particular research activity, based on ability of members of that class to bear burden and appropriateness of adding burdens to that class
      - Consider racial, social, gender, cultural biases
      - Special care for vulnerable populations
      - Who carries the risk? Who stands to benefit?
    - Individual Justice
      - Fairness in selection of subjects: for example, no disproportionate selection of "undesirable" for risky research



# The Basics

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## The Common Rule

- Title 45, Part 46
  - Subpart A: Basic HHS Policy for Protection of Human Research Subjects
    - 45 C.F.R. 46.101 – 46.124
  - Subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
    - 45 C.F.R. 46.201 – 46.207
  - Subpart C: Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
    - 45 C.F.R. 46.301 – 46.306
  - Subpart D: Additional Protections for Children Involved as Subjects in Research
    - 45 C.F.R. 46.401 – 46.409
- Covers all research funded by HHS and other federal agencies



# The Basics

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## ■ FDA Regulations

- Title 21, Part 50: Protection of Human Subjects
  - 21 C.F.R. § 50.1 – 50.56
- Title 21, Part 54: Financial Disclosure by Clinical Investigators
  - 21 C.F.R. § 54.1 – 54.6
- Title 21, Part 56: Institutional Review Boards
  - 21 C.F.R. § 56.101 – 56.124
- Title 21 Part 312: Investigational New Drug Application
  - 21 C.F.R. § 312.1 – 312.160
- Title 21 Part 812 (Subpart H): Investigational Device Exemptions

# The Basics



- International Research Regulation
  - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
  - International Compilation of Human Subject Research Protections
  - EU, country-specific laws, regulations and rules regarding
    - Conduct of clinical trials/human subject research
    - Issues related to privacy



## Common Issues and Hot Topics

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- What are some of the most common issues in implementing the various federal human subject research requirements?
- The following examples are based on OHRP Determination Letters, FDA Warning Letters, and personal experience
- Case studies are based on published research controversies, OHRP Determination Letters, and FDA Warning Letters



# IRB Membership/ Governance

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## ■ Membership

- Lack of Diversity
- Failure to include community perspective
- Special representatives for vulnerable populations
- “Ad hoc” Alternates

## ■ Governance

- Lack/loss of quorum
- Absence of non-scientific member
- Participation of interested member in discussion/  
voting
- “Proxy” voting



## Initial and Continuing Review

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Not obtaining IRB approval for:

- Use of excess tissue collected for clinical purposes.
- Concurrent record reviews, even if merely looking for trends
- Deviations from the protocol without prior IRB approval, unless the deviation is necessary to avoid apparent imminent harm
- Enrolling subjects who do not meet inclusion criteria
- Adding normal controls to the protocol



# Initial and Continuing Review

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■ Not obtaining IRB approval for:

- Adding/revising interventions
- Retrospective studies
- Social and behavioral research
- Grant applications
- Research that would be exempt, but it involves prisoners
- Privately funded research, when an FWA is in place

# Initial and Continuing Review

- Failing to recognize activity as research
  - Where some interventions are standard of care, and some are experimental, but information about both are included in protocol/research
  - Innovative care versus research
  - Where two different regimens, both of which are acceptable standard of care, are compared
  - Is it a wolf ...  
in sheep's clothing?





## Initial and Continuing Review

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### Inadequate substantive review

- Failure to provide sufficient information for substantive review
- Information provided, but no evidence IRB considered substance of study carefully
- Inappropriate or unclear endpoints, inclusion or exclusion criteria, procedures for monitoring safety, etc.
- Unclear toxicity criteria
- Unclear study objectives
- Does the scientific method, as described in the protocol, appear reasonably likely to result in an answer to the question?

# Initial and Continuing Review: Special Concerns

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## Adequate Substantive Review:

- Does the protocol describe prior knowledge/literature search of the topic?
- Does the information in the protocol reflect information in the investigator's brochure, etc.
- Does the protocol discuss rationale for inclusion criteria?
- Does the scientific design make sense?
- If possible, avoid placebos. If a placebo is used, is there standard therapy? Why is placebo necessary and appropriate given the study? Is there another approach?
- If a cross-over design is used, what happens if a patient's condition worsens on the second arm?

# Initial and Continuing Review: Special Concerns

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- Consideration of Risks and Benefits
  - If there is significant risk, is the research addressing important issues?
  - Minimize risk by using standard diagnostic/therapeutic procedures to extent possible
  - Benefits are those experienced by the subject, not including those offered by standard therapeutic components
  - Appropriate study design given risks
    - TeGenero monoclonal antibody trial – concurrent administration of first-in-human drug to healthy volunteers



# Initial and Continuing Review

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■ Failure to consider, or failure of the documentation to reflect IRB consideration of, mandated topics:

- Risk-Benefit Analysis
- Informed Consent
- Selection of Subjects
- Privacy and Confidentiality
- Monitoring and Observation
- Additional Safeguards
- Incentives for Participation
- Continuing Review



# Initial and Continuing Review

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- Using expedited review for:

- An amendment of a protocol which expands inclusion criteria, even if it is claimed to be “clarifying” a class of similar disorders
- A review of new consent forms
- IRB-required modifications to a study or consent document, except when the IRB dictates specific revisions
- Continuing review of projects which are not minimal risk, or are not in the listed categories
- Modifications in study design



# Initial and Continuing Review

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## ■ Expedited Review (con't)

- Protocol changes which increase the duration of the study, or which may cause shifts in the risk-benefit analysis
- "Emergency approval" of changes in inclusion criteria
- Using expedited review for "more than minimal risk" FDA studies
- Using expedited review for studies in which an IND or an IDE is required

# Initial and Continuing Review: Special Concerns

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## Equitable Selection of Subjects

- Escalating payments for participation
- Senior/subordinate position between investigator and subject
- Vulnerable populations
- Disadvantaged populations – is targeting scientifically valid?
- Students, when participation may appear to impact grades/graduation
- Payment of Incentives
- Charges to participant (devices)



# Initial and Continuing Review: Special Concerns

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## Vulnerable Populations

- Vulnerable populations including
  - Pregnant women, fetuses and neonates (Subpart B)
  - Prisoners (Subpart C)
  - Children (Subpart D)
- Require special considerations by the IRB
  - Specific consideration of the components of the applicable subpart should be reflected in the minutes
- May require OHRP approval, published in Federal Register

# Initial and Continuing Review: Special Concerns

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## Vulnerable Populations:

### Children

- Special rules for IRB consideration of studies involving children, especially wards
- Assent versus permission
- If frequent, have child advocate as IRB member

### Prisoners:

- If a study subject becomes incarcerated during the study, and the study was not reviewed under the Subpart C criteria, research interventions and interactions with that individual must be suspended until the study is re-reviewed, using Subpart C criteria, unless continuation is in the subject's best interest

# Initial and Continuing Review: Special Concerns

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## ■ Informed Consent:

- Factually adequate and reflects the protocol
- Accurately discloses possible costs to the patient or the patient's insurer in the consent
- No exculpatory language
- Appropriate language level
- Available in languages common in the community
- Informed consent obtained early enough in the investigator/subject interaction
- Informed consent as a process, not a document
- Updated if initial data reveals additional risks
- Explains why the study is being conducted
- "Waiver" in FDA studies??

# Initial and Continuing Review: Special Concerns

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## ■ Privacy and Confidentiality:

- Intersection of HIPAA, the Common Rule, FDA, and state law
- Realistic disclosure of confidentiality and risks of disclosure
- In some studies, the greatest risk may be that of breach of confidentiality and consequences of improper disclosure
- Proper storage – by the principal investigator/ research staff and by the IRB
- Mismatch between confidentiality measures described in informed consent and confidentiality measures implemented
- “Review preparatory to research”
- “Certificate of Confidentiality” option



# Initial and Continuing Review: Special Concerns

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## Monitoring and Observation:

- Adequate monitoring is important to ensure the safety of subjects.
  - Require reports to IRB based on risk (continuing review)
  - Require use of Data Monitoring Board or oversight committee
  - Ensuring monitoring of data includes reports of both experimental intervention and, when applicable, standard of care intervention
  - Require observation of informed consent process to ensure no coercion

# Initial and Continuing Review: Special Concerns

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## Monitoring and Observation

- Add safeguards based on early data from the trial
  - Consistent with FDA Critical Path plan to permit flex in study based on early results
  - Approach in manner that avoids bias
- Other outcomes of monitoring and observation: may find problems in management of study
  - Mandate closer supervision of research staff
  - External validation of compliance/no change since prior review
  - Supervision/observation of informed consent

Monitor results/data from all sites, not just your own. The fact that it is a multi-site study does not absolve the IRB from responsibility to monitor and act.

# Initial and Continuing Review: Special Concerns

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## Continuing Review:

- Defaulting to “annual review” without consideration of potential need for more frequent review
- Failure to adequately review information during continuing review.
- Permitting research to continue after expiration of IRB approval
- Incorrect calculation of due date for continuing review
- Failure to set forth in policies criteria for determining proper frequency of review



# Initial and Continuing Review: Special Concerns

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## ■ Continuing Review:

- “Block” protocol review/approval
- Failure of minutes to reflect substantive consideration of issues
- Minimal review of multi-site studies
- Treating a new protocol as an “amendment” of a previously approved study
- “Retroactive reapproval”



# Reporting Obligations

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## ■ What must be reported to IRB?

- Unanticipated problems involving risks to subjects or others
- Serious or continuing non-compliance with government regulations or IRB requirements/ policies
- Suspension or termination of IRB approval at another site

## ■ What must be reported to OHRP/FDA?

- All of the above, plus suspension or termination of IRB approval at your site
- FDA: Study data. The fact that data cannot be used to support a marketing application does not permit withholding of the data.



# Reporting Obligations

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- Must report serious or continuing non-compliance to OHRP/FDA
  - OHRP: "...the following noncompliance is always considered serious and therefore needs to be reported:
    - Nonexempt human subjects research conducted without IRB review and approval;
    - Research conducted without appropriate informed consent; and
    - Substantive changes made to research without prior IRB review and approval (when those changes are not required to eliminate apparent immediate hazards to subjects.)"
- If the problem is significant enough to result in an FDA Warning Letter, then OHRP needs to be notified as well



# Case Studies

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## Case Study Disclaimer

- The case studies are based on generally available information. I have not personally researched the accuracy of the information presented as factual.
- The conclusions regarding what went wrong are mine. The entities in question may well disagree.
- We have the advantage of hindsight. It is much harder to anticipate possible problems at IRB review.
- The entities at which the case studies occurred are reputable institutions, which had unfortunate events. We all make mistakes. I offer these case studies in the hope that we can learn from them, and continually improve human subject protection.



# Case Study: Gelsinger

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- Jesse Gelsinger was an 18 year old diagnosed with ornithine transcarbamylase deficiency, which adversely impacts ammonia metabolism. Jesse's illness was under control at the time of the research. The trial used adenovirus as a vector to deliver genetically altered material to the liver.
- Jesse was the last of 3 patients in the 6<sup>th</sup> cohort of the trial.
- Within hours of receiving the infusion, Jesse was critically ill with DIC, renal failure, and jaundice. He developed MODs and eventually died.



# Case Study: Gelsinger

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## FDA Findings:

- Prior study participants had experienced Serious Adverse Events, which should have caused study termination
- Enrollment criteria were violated, leading to enrollment of higher-risk subjects
- Revisions to the protocol were not submitted to the FDA, and thus not validly approved
- Protocol changes were "obscured" from the IRB and FDA by not listing them on the change summary
- Failure to perform certain tests required by the Protocol
- The PI failed to report adverse events to the IRB
- Failures of informed consent
  - Failure to mention reproduction risk
  - Failure to warn patients of higher risk associated with certain medications



# Case Study: Gelsinger

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■ Gelsingers' attorneys also alleged that:

- the risks of the toxic effects of the injection of the adenovirus particles were understated;
- no mention was made that monkeys injected with the virus had become ill and/or died;
- no mention was made that patients who had previously participated in the trial suffered serious adverse effects;
- the representation was made that efficacy had been attained with respect to the treatment of OTC; and
- A conflict of interest situation involving the PI and University was not adequately disclosed.

■ Some of these issues were mentioned in the FDA investigation letter, but not in the final letter.



# Case Study: Gelsinger

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Where did the IRB go wrong?

- Protocol amendments were improperly approved, either because the IRB failed to read the revision, or didn't understand the clinical implications of the amendment:
  - Changes in enrollment criteria (male vs. female, add to cohort for AE, ammonia results)
  - Study hold if 2 subjects develop mild toxicity
  - Study halt if Grade III or higher toxicity develops
  - Study halt if 3 subject develop high titer neutralizing antibodies
  - Removed requirement for IRB and FDA consult if 2 subjects developed Grade II AEs
- Changes to the protocol required by the FDA in the IND process were not incorporated. IRB failed to note this.



# Case Study: Gelsinger

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Where did the IRB go wrong?

- Annual review paperwork reflected average lab results. This obscured the high toxicity subjects labs.
- Annual review documentation was incomplete and inaccurate.
- Deviations from protocol were not reported to the IRB or FDA.
- Animal studies with similar SAEs were occurring during the human trials, but animal SAEs were not timely reported – or demanded.
- There were significant undisclosed conflicts of interest between the University, the PIs, Genovo, and Institute for Human Gene Therapy, which sponsored the trial.
- Individuals who did not meet inclusion criteria were enrolled.



## Case Study: Hexamethonium

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Johns Hopkins: "Mechanisms of Deep Inspiration-Induced Airway Relaxation"

- Part of a NIH funded study exploring how normal airways maintained bronchodilation despite bronchoconstrictive stimulus
- Involved inhalation of hexamethonium, a ganglionic blocker
- Mentioned as a planned study in a continuation application to NIH; reviewed as "consistent with the original goals" of the study, but not otherwise reviewed scientifically.
- A healthy volunteer study subject died of MODs after inhaling hexamethonium



## Case Study: Hexamethonium

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### Hexamethonium Study – What went wrong?

- PI cited research using inhaled hexamethonium which demonstrated inconsistent results
- Limitations on the literature search resulted in failure to identify earlier studies which identified lung damage as an adverse effect of hexamethonium
- Available research addressed hexamethonium chloride; PI used hexamethonium bromide
- An earlier study subject had developed a non-productive cough 8 days after hexamethonium inhalation; the patient was followed, but the possible AE was not reported to the IRB
- No IND was obtained for use of hexamethonium bromide



# Case Study: Hexamethonium

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Hexamethonium Study – What went wrong?

## Problems with Informed Consent

- Did not advise that hexamethonium was no longer approved by the FDA for clinical use
- Did not mention that approved hexamethonium was a different salt (bromide); also, no hexamethonium salt had never been approved for inhalation
- Did not mention prior experience with longer-term oral hexamethonium and pulmonary fibrosis
- Did not reveal that the evidence on the safety of hexamethonium was based solely on reports involving a total of 20 patients
- Did not mention possibility of unknown adverse events, or that SAE which could result in death or disability was possible



# Case Study: Hexamethonium

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## Hexamethonium Study – What went wrong?

### Problems with Safety/Science

- IRB did not address whether studies looking at only 20 subjects were sufficient to establish safety of inhaled hexamethonium
  - The review committee felt it was inadequate and further information was necessary
- The IRB did not require the PI to seek an IND from the FDA
  - In fairness, the FDA had been asked for guidance on when an IND was appropriate; the response had been pending for literally years
- The earlier possible AE was not timely reported to the IRB
  - PI stated that he thought it was standard URI; others in the area had similar symptoms
- Because hexamethonium (in any form) was not at the time of the study approved for marketing, it was obtained from a chemical supplier. Inadequate information regarding preparation and stability was provided to the IRB.



# Case Study: TGN1412

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## ■ TeGenero TGN1412

- A new-class monoclonal antibody intended to modulate immune responses in CLL and RA
- Double-blind, randomized, placebo-controlled, single escalating dose study
- First-in-man trials in the UK in March, 2006, resulted in SAE for 6 trial participants
  - Severe cytokine storm, resulting in MOD
  - Developed headache (1hr), N/V/D, fever (4hr), hypotension (4hr), tachycardia (4hr) resp. distress (5hr)
  - Admit to ICU at Hours 12-16
- Media reports conflict and incomplete protocol information is available, which makes analysis



## Case Study: TGN1412

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### TeGenero TGN1412 Protocol (partially redacted)

- "Results of the analysis of cytokines in serum within 4 hours following single-dose administration of TGN1412 will determine the further time points of assessments. In case, [sic] an acute release of pro-inflammatory cytokines will be observed within 4 hours post-dose, all further samples for optimal measurement will be examined..."
- "Although not to be expected after TGN1412 administration, a 'cytokine burst' or anaphylactic reactions [sic] theoretically could occur within the first few hours after infusion..."



## Case : TGN1412

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### TeGenero TGN1412

- Protocol on MHRA site is redacted, but reports in the media and the TeGenero website state that the protocol provided that the drug should be administered "within a period of 2 hours."
- Reportedly, there was only a 2 minute time lapse between infusions
- NEJM article states that there was a 10 minute lapse between infusions

MHRA: SAE appears to have been an unanticipated biological response



## Case Study: TGN1412

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### TeGenero TGN1412 – What Went Wrong?

- This was a very novel drug – first in class, first in man, new mechanism of action.
- Preliminary tests in non-human primates showed some immune response, but no SAEs
- Immune system is very species-dependent; much more so than other systems. Predictive accuracy of animal studies is therefore unclear.
- Studies indicated that TGN1412 had a very long half-life (8 hours)
- The possibility of a cytokine "burst" was acknowledged, but downplayed.



## Case Study: TGN1412

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### TeGenero TGN1412 – What Went Wrong?

- Common sense suggests stringent controls and precautions when conducting first-in-man studies on novel drugs.
- Given a half-life of 8 hours, does dosing 6 volunteers over a total of 2 hours make sense?
- Informed consent unjustifiably downplayed the risk of cytokine "burst" or storm, and didn't give worst case scenario
- Subject compensation: Approx. \$3,500 U.S.  
Reasons for volunteering? Vacation, computer.



## Conclusion

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- The regulations governing human subject research are relatively broad, and don't contain much detail
- Look to regulatory agency guidance for additional information
- OHRP Determination Letters and FDA Warning Letters indicate common issues
- OHRP and FDA personnel are valuable resources
- When in doubt, make decisions and act in the best interest/greatest protection of the research subject.



# Conclusion

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"The scientific research enterprise, like other human activities, is built on a foundation of trust. Scientists trust that the results reported by others are valid. Society trusts that the results of research reflect an honest attempt by scientists to describe the world accurately and without bias. The level of trust that has characterized science and its relationship with society has contributed to a period of unparalleled scientific productivity. But this trust will endure only if the scientific community devotes itself to exemplifying and transmitting the values associated with ethical scientific conduct."



**QUESTIONS???**