Human Subjects Protection:

An OHSU Focus

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OREGON CLINICAL + TRANSLATIONAL RESEARCH INSTITUTE

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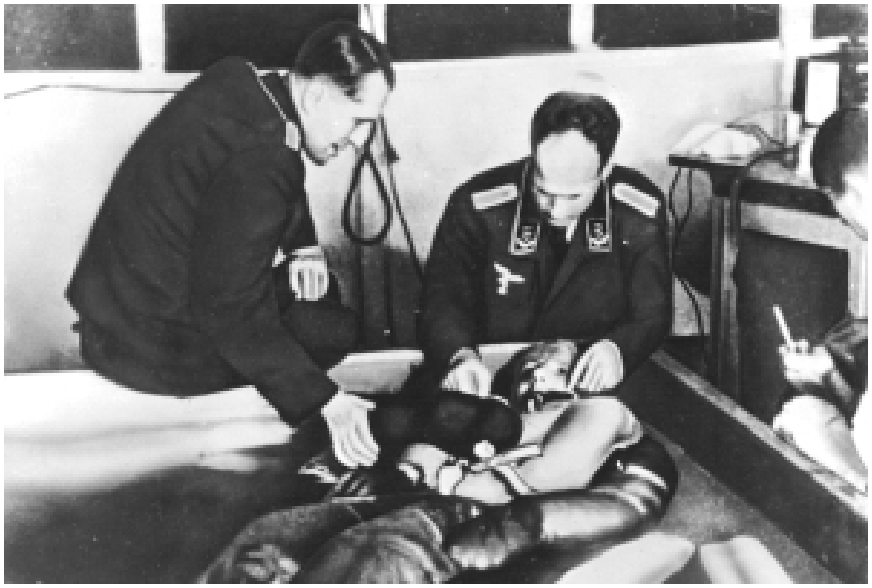
The Development of Protections

Nazi Physicians' Studies: During WWII, prisoners in concentration camps were used as subjects in Nazi experiments involving battlefield medicines, chemicals, and injuries.



Nuremberg Code ('47)

- Voluntary consent
- Risk/benefit assessment

The Development of Protections

- Declaration of Helsinki (‘64)
  - World Medical Association Code of ethics for clinical research
  - Conformance to ***scientific principles***
  - Review and approval by independent committee
  - Conducted by qualified persons
  - Importance of the objective ***in proportion to risk***
  - Informed consent imperative

The Development of Protections

Tuskegee: From 1932-1973, US PHS studied pathogenesis of untreated syphilis in hundreds of black men

- Subjects were not told the true intent of the study
- Did not receive effective treatment when it became available
- Transmitted the disease to others
- Many died from the disease

Development of Protections (cont)

- 1972 - Senate Hearings: Established IRBs
- 1974 -1978 - National Commission: Produced the Belmont Report 1979 - outlines ethical principles
- 1981 - 45 CFR 46 (‘81)
- 1995 - National Commission established by President Clinton to:
  - Review protection provided by IRBs
  - Develop guidelines for use of biological materials in humans
- 1990’s - Shutdowns of major research institutions

Development of Protections (cont)

- Ethical codes:
  - Nuremberg Code
  - Declaration of Helsinki
  - Belmont Report
- Laws:
  - 'Common Rule' – 45 CFR 46
  - 21CFR 50 (Protection of Human Subjects)
  - 21 CFR 56 (IRB)
  - 21 CFR 312 (drugs) and 21 CFR 812 (device)

The Belmont Report

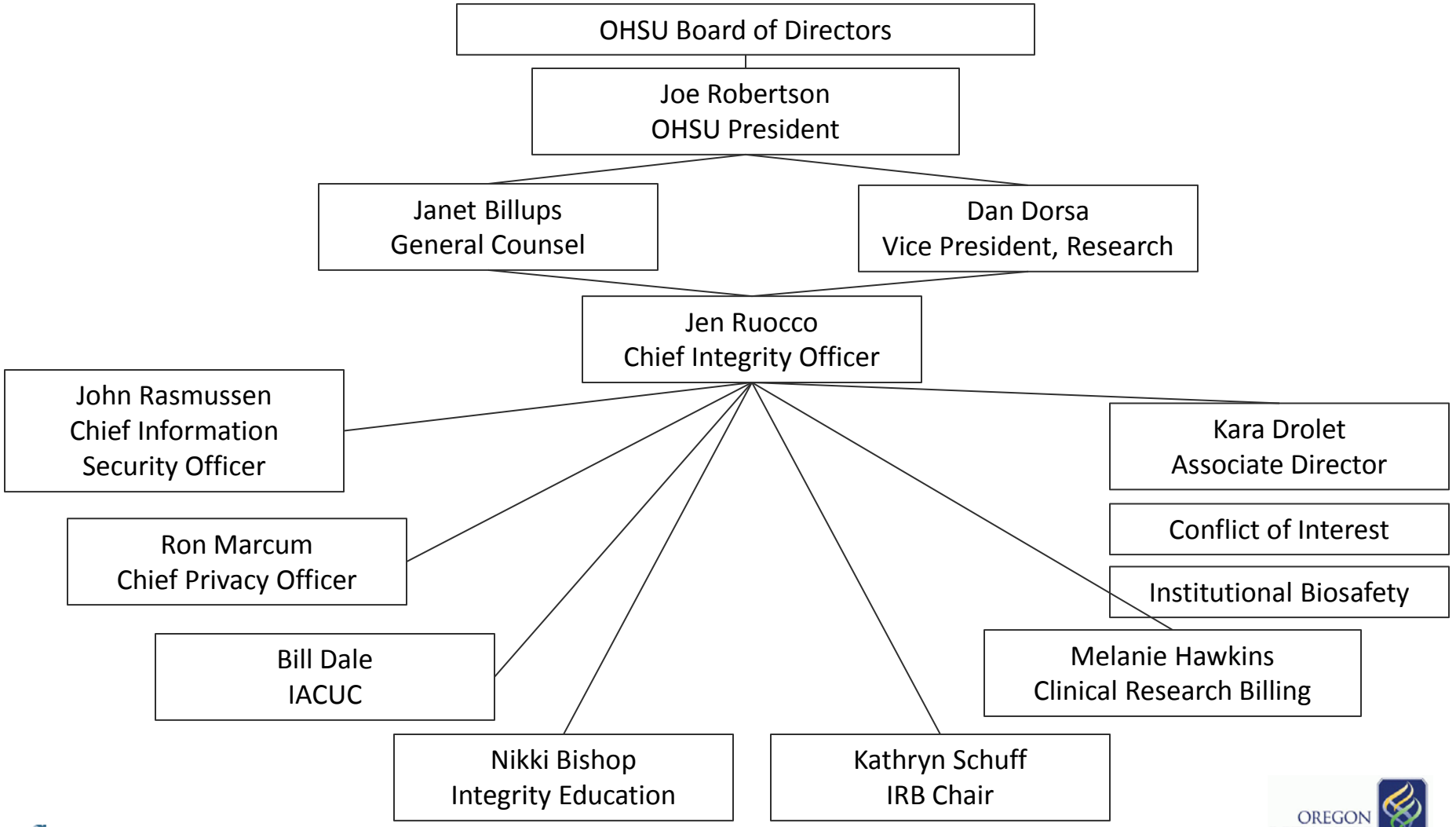
Details the duties that investigators have to research subjects in terms of three ethical principles:

- Respect for Autonomy – recognition of a person's ***right to self-rule*** and dignity; ***special protections*** for those with diminished capacity.
- Beneficence/Nonmaleficence – the obligation to ***maximize benefits and reduce or eliminate harms***.
- Justice – the ***fair distribution of burdens (risks) and benefits*** in research.

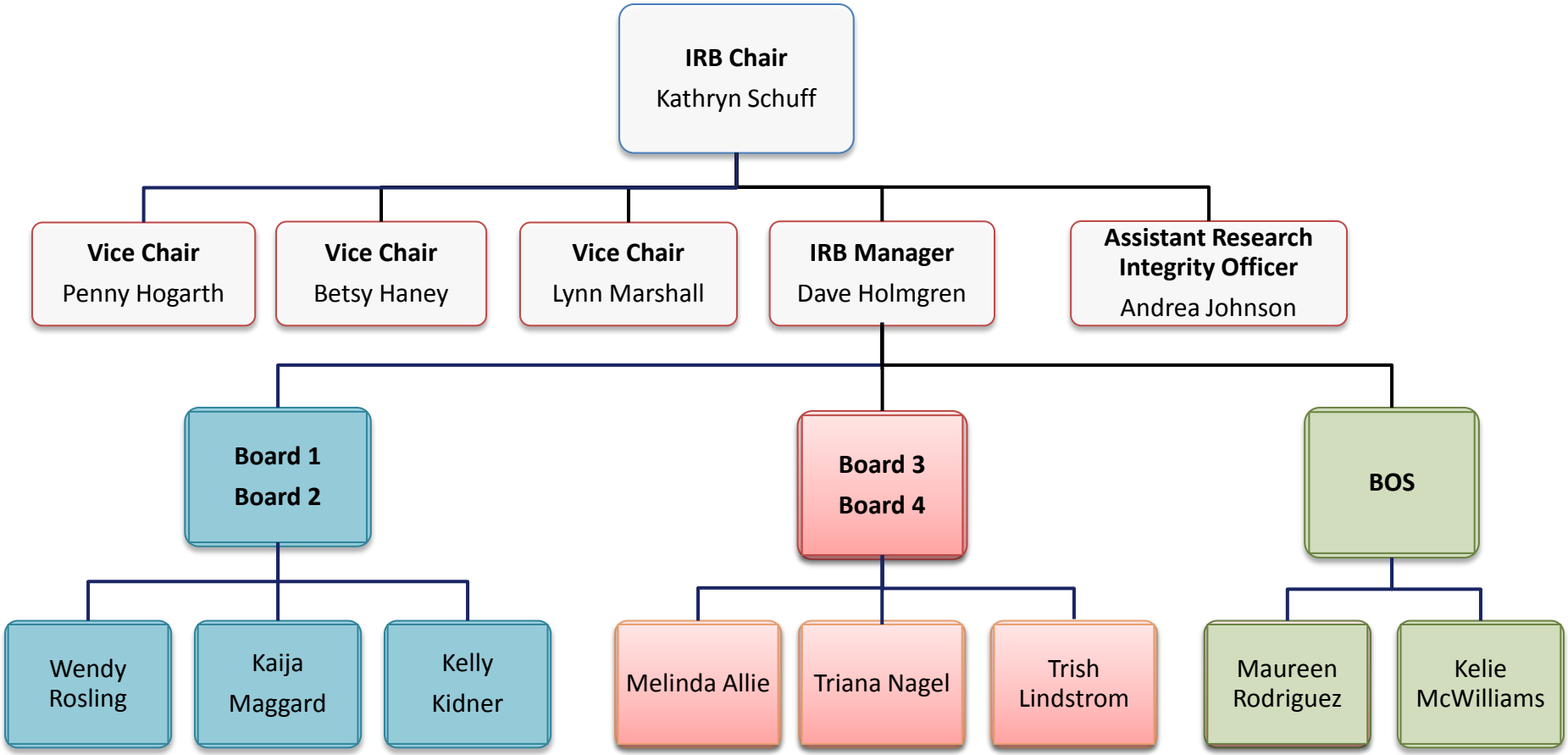
Mandate of the IRB

- Review all research involving human subjects performed by OHSU faculty, research staff, and students
- Charged with the responsibility to protect the rights and welfare of human subjects who participate in research
- Committed to protecting the confidentiality and privacy of subjects

OHSU Research Integrity Structure



IRB Structure



OHSU IRB Composition and Operation

- Composed of at least 5 members
  - Qualified OHSU faculty and community members
  - At least one member who is not affiliated with OHSU
  - At least one member with no medical/scientific background
  - Varying genders and ethnicities
- Quorum required: 50% of committee including nonscientist
- Members appointed by Provost for 3 years, option to renew
- Has final authority to disapprove research
- Members cannot vote or be present for the vote on their own protocols (recusal)
- Four committees, 8-10 meetings a month

PVAMC/OHSU Joint IRB

- For studies conducted at both OHSU and PVAMC
- Reviewed by OHSU IRB Board 3
- One submission in OHSU's eIRB
  - Start short study title with "PVAMC/OHSU"
  - Complete OHSU eIRQ
  - Upload additional PVAMC forms
- Single review and review memo
- For more information: http://www.ohsu.edu/xd/research/about/integrity/irb/ohsu-and-va-irb-agreement.cfm

Collaborative Research and the Federal Wide Assurance

- Institutions need Federal Wide Assurance (FWA) to receive federal funds for human subjects research
  - Choose to apply regulations equally to all research
  - OHSU FWA = 00000161
- Non-OHSU sites need their own FWA
  - If there is non-exempt research is federally sponsored
  - If employees at the non-OHSU site "engaged in research"
- IRBs will determine if single IRB review is appropriate
  - IAA – IRB Authorization Agreement used to designate which IRB
  - Request a 'Waiver of Oversight' in OHSU eIRB
- Individual Investigators can use an IIA – Individual Investigator Agreement

What is Research?

§46.102 (d) *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge

Research involving human subjects is 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)

§56.102 *Clinical investigation* means any experiment that involves a test article and one or more human

Is it Research? Or not?

Public Health Surveillance?
Quality Assessment/Quality Improvement?
Case Reports?

Questions to consider:

- Will the results be generalizable beyond the population being served?
- Is the intent to generate new knowledge or improve upon an existing principle, theory or knowledge?
- Is the intent to publish or present the results to the scientific community?

What is a human subject?

Human subject means a **living individual** about whom an investigator (whether professional or student) **conducting research** obtains data through **intervention or interaction** with the individual, OR **Identifiable private information.**

What is not a human subject?

- **Data on Deceased Individuals**
  - Note: Still may have HIPAA requirements
- **Deidentified data**
  - No interaction with a human
  - Investigator will not be given access to identifiable data
  - Data does not contain personal identifiers, and
  - A list is not maintained by anyone that can connect data with personal identifiers OR an agreement exists not to share the code

Are you "Engaged" in Research? YES

- Receive funding for research – *even when all the activities involving human subjects happen elsewhere*
- Interact/Intervene with subjects (or environment) for research
  - Blood draws, sample collection- Data collection
  - Administering drug or device - Counseling initiative
- Obtain informed consent
- Obtain, receive or possess individually identifiable private information (directly or indirectly through coding systems)

”Engaged” in Research? No!

- Perform commercial services for other investigators
  - Local lab draw, x-ray, MRI
  - Transcription services (note: may need Business Associate Agreement)
- Special circumstances for temporary coverage
- Inform subjects about research studies, including permission for researchers to contact them.
- Permit facilities to be used by other researchers
- Release individually identifiable private information or specimens
- Use identifiable information only for auditing purposes or satisfying FDA reporting requirements

Exempt Human Subjects Research

- Research in routine educational settings
- Surveys, education tests, observations unless identified/coded AND potential risk of criminal, financial employability or reputation (note: medical info not exempt)
- Publicly available dataset or data recorded in deidentified fashion (no code)
- Public service program evaluations
- Taste and food quality evaluation, consumer acceptance

Determination must be made by OHSU IRB

Exempt Human Subjects Research

- Even if exempt, research must:
  - Respect privacy of subjects
  - Protect vulnerable populations
  - Obtain consent, if appropriate
- All modifications must be submitted to the IRB to ensure the research remains exempt
- No continuing review required, but we check every 3 years to see if the project is ongoing…

Prior to IRB Submission

- Responsible Conduct of Research (RCR) education
  - Link to BigBrain on IRB website
  - Required for all investigators and research staff "engaged in research" (OHSU and Non-OHSU)
  - To fulfill NIH requirement for education in human subjects research:
    - Complete certification letter on Research Grants and Contracts (RGC) forms page
    - Submit the letter to RGC

Prior to IRB Submission (cont.)

- Conflict of Interest in Research (CoIR)
  - All staff with direct involvement with the project
  - Before starting any research project, annually, any changes
  - Online system also in BigBrain
  - If potential conflict disclosed
    - Reviewed by committee
    - May require divestment or management plan
- To check RCR/CoIR, ORIO Compliance Records : http://ozone.ohsu.edu/research/rda/apps/eirbinfo/index.php or Visual CoIR in eIRB

Types of Initial Applications

- Full Board Review
  - Includes all investigational biomedical studies
- Expedited Review – reviewed by a designated member of the IRB
  - "Minimal Risk" studies
- Exempt Determination
- Request for Waiver of IRB Oversight
- Request for Determination
  - Non-human subjects research, not engaged in HS research

Minimal Risk

The probability and magnitude of harm or discomfort anticipated in the research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

45 CFR 46.110

Minimal Risk

- FDA approved drug/device
- Blood samples by finger stick, heel stick, venipuncture
  - Healthy, non-pregnant adults > 100 lbs
  - Not more than 550 ml/8 wks
  - Not more than 2X per week
  - Other adults/children < 50 ml or 3 ml/kg
- Noninvasive biological specimens
  - Teeth, placenta, saliva, buccal swab, urine

Minimal Risk

- Materials already collected for non-research purposes (e.g., medical records)
- Voice or video recordings
- Research on individual or group behavior/characteristics, or survey/interview/focus groups, program evaluation or QA methodologies
- Continuing review when above minimal risk activities completed
- Research determined by the full board IRB to be minimal risk

Initial Application Contents

- Proposed Project Questionnaire (PPQ) – ePPQ, eCRIS, or paper (TTBD, unfunded, or VA-only funding)
- Initial Review Questionnaire (IRQ)
- Protocol
- Brief Protocol Description
  - Explain purpose of study and design to IRB community member
  - Nontechnical/nonmedical/nonjargon language
- Consent Documents (as needed)
  - Consent Forms and Information Sheets
  - Assent Forms (children 7-15 years old)
- Recruitment Notices, Flyers, Ads

Initial Application Contents (cont.)

- Attachments (as needed)
  - Grant application (if NIH funded)
  - Investigator's Brochure or package insert (for drugs and devices)
  - Manufacturers purity and pyrogenicity testing (if herbal/dietary supplement)
  - Letters or approvals from other sites (unless industry multicenter study)
  - Questionnaires, Surveys
  - Data & Safety Monitoring Plan (DSMP)

§46.111 Criteria for IRB approval

- Risks to subjects are minimized
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.
- Selection of subjects is equitable. In making this assessment the IRB should take into account:
  - The purposes of the research
  - The setting in which the research will be conducted
  - Particularly cognizant of the special problems of research involving vulnerable populations (children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons)

§46.111 Criteria for IRB approval (cont.)

- Informed consent will be sought from each prospective subject or the subject's legally authorized representative.
- Informed consent will be appropriately documented.
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

Vulnerable Populations

- Some classes of research subjects are considered to be more vulnerable to coercion and in need of additional protections. These include:
  - Children
  - Persons with Reduced Capacity to Consent
  - Prisoners
  - Fetuses and Pregnant Women
  - Terminally Ill
  - Students
  - Employees

Who is a child in Oregon?

Under age 18 except:

- Legally emancipated minors
- Married individuals
- All subjects in studies of venereal disease, birth control information or services
- Individuals 14 yo or older in research of mental or emotional disorder, chemical dependency (excluding methadone maintenance)
- Individuals 15 yo or older in research involving hospital care or medical/surgical diagnosis/ treatment

Children's Issues

Categorization of children's research:

- §46.404 or §50.51: Minimal risk
- §46.405 or §50.52: More than minimal risk but potential for direct benefit
- §46.406 or §50.53: Minor increase over minimal risk, yield knowledge about subject's condition
- §46.407 or §50.54: Not approvable by the IRB, requires governmental panel

Children's Issues

- Soliciting assent
  - Based on capacity of child
  - Not required if direct benefit only available in research
- Soliciting permission of each parent or guardian
  - One sufficient for minimal risk or research with direct benefit
  - Can be waived in special situations
- Waiver of parental or guardian permission
- Protections for wards of state or any other agency, institution or entity

Decisionally Impaired

- Consider impact of DI on risks/benefits of the study, and need for safety or monitoring procedures
- Assessing decision-making capacity – may fluctuate
- Consent – Legally Authorized Representative
  - Health care representative
  - Court-appointed guardian
  - Spouse/registered domestic partner
  - Adult child
  - Either parent
  - Adult sibling
- Assent

Certificates of Confidentiality

- A major barrier to participating in some types of research is fear of loss of confidentiality of sensitive information.
- Certificates of Confidentiality protect against compelled disclosure in any federal, state, or local civil, criminal, administrative, legislative, or other proceeding.
- CoCs issued by a variety of federal agencies: NIH, FDA, CDC
- No cases of successful subpoena of CoC protected information.
- Note: Do not protect against public health reporting, or domestic or child abuse reporting.

Certificates of Confidentiality

- Common Uses of CoCs:
  - Substance abuse
  - Sexual attitudes/practices
  - Illegal behaviors (not drug-related)
  - HIV status
  - Psychological well-being
  - Domestic violence

IRB Responses

- Approved as presented
  - No changes needed
  - Very rare for initial reviews
- Approved with changes
  - Minor changes needed
  - Administrative re-review
  - Most common response
- Deferred
  - Major changes needed
  - Requires full IRB re-review
- Disapproved (rare)

How to Respond to an IRB Review

- Three options:
  - Make all suggested and required changes
  - Provide a detailed justification for changes not made
  - Negotiate with the IRB
- Making Changes:
  - All means all. Don't skip any requirements
  - If the request is confusing, ask the analyst
  - Neatness counts. Typos, formatting, and spelling errors will hold you up

How to Respond to an IRB Review (cont.)

- Justifications:
  - Be respectful
  - Explain why the change is unnecessary to protect the subjects
  - Explain why the required change is an error
  - Mark any material in the protocol the reviewer missed
- Compromising:
  - Go to the analyst first. Go to the chair second
  - Put it in writing and get it in writing
  - Request a meeting with staff or reviewer as appropriate
  - Ask to attend or call into the IRB meeting

Modifications

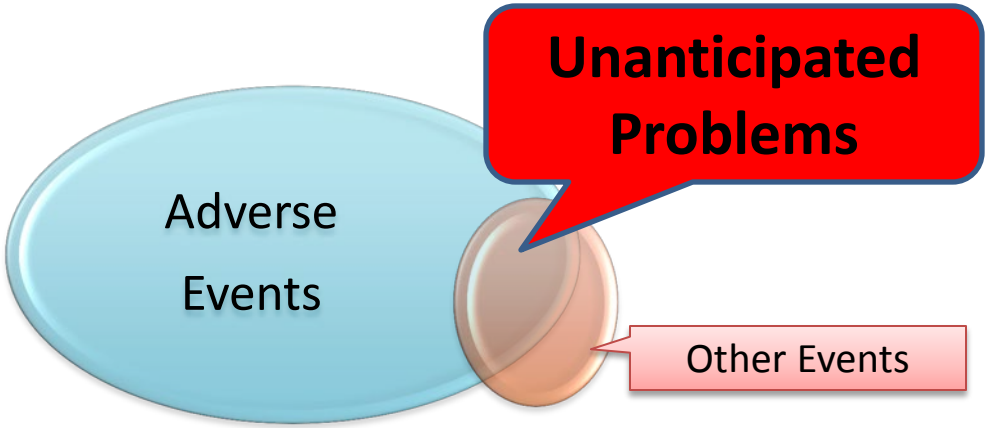
- All changes to the research must be reviewed and approved by the IRB
- Ensure that criteria for approval are still met
- Submit:
  - Modification request
  - Revised document(s) with tracked changes
- Changes cannot be implemented until IRB approved except to prevent immediate harm to subjects (call us if it's an emergency)

Continuing Review

- HS research must receive continuing review (CR) and approval at intervals appropriate to the degree of risk, but not less than once per year.
- Continuing review provides for ensuring criteria for approval still met:
  - Reassessing risks & benefits
  - Ongoing determination of the adequacy of the informed consent process and form
  - Adverse Event Reporting
  - Data Safety & Monitoring
- Cannot enroll subjects and collect/use date collected during a lapse in IRB approval

Adverse Events and Unanticipated Problems

- One of the most critical aspects of the ethical conduct of human subjects research is the reporting and evaluation of adverse events.
- Problem: Adverse Events happen. A lot.
- What we care about are Unanticipated Problems
- Mission: Determine which AEs represent UP's



Protocol Deviations

- Deviations happen

- Report what happened
- Determine how to prevent it from happening again

- Federal reporting: Serious or continuing noncompliance

Study Termination

- IRB must be informed when studies are terminated
- Termination = no study related activity
  - If analyzed by OHSU investigators: After all analyses are complete
  - Multicenter studies: When all data has been collected from OHSU subjects and forwarded to the collaborating/parent site
  - Industry studies: After closeout visit performed
- If reanalysis or resumption of study activities is required after termination, submit new study or request exception
- If study expires and not terminated by investigator, $550 fee for administrative termination
- If specimens or data from study may be used for future research, must hold in a repository

Coordination with Other Units

- OHSU Knight Cancer Institute Clinical Research Review Committee
  - Reviews all projects involving cancer
  - Submit in eIRB – will automatically go to Knight first
  - Knight will review first and forward when approvable
- Oregon Clinical & Translational Research Institute (OCTRI) Administrative Review
  - Cost estimates, protocol refinement and study planning
  - Submit in eIRB - Review concurrently with IRB review

Other Compliance Committees

- Reviews concurrent, but IRB approval held for approval of all relevant "ancillary" committees
- Institutional Biosafety Committee (IBC):
  - Recombinant DNA, infectious agents, or biologically derived toxins (incl select agents and infectious proteins, cells, viruses, bacteria, etc.)
- Radiation Safety Committee
  - If study uses ionizing radiation for research purposed (beyond what would be received for clinical care)
  - State review required if study involves screening radiation
- Conflict of Interest In Research
  - If potential conflict disclosed

Informed Consent Requirements

- Informed consent must be obtained from **each subject** or subject's legally authorized representative participating in the clinical study – UNLESS the IRB has approved a waiver or alteration of consent.
- Consent must be **documented** by use of written consent form approved by IRB and signed by subject or subject's legally authorized representative
- **Copy** of signed form given to subject and original retained as documentation
- Consent form must be written in **lay language** (8th grade) and **native language**

Problems with Informed Consent

- Therapeutic misconception
  - Research is not medical treatment
- Therapeutic misestimation
  - Overestimate benefits/underestimate risks
- Therapeutic optimism
  - Hope for best personal possible outcome
- Unrealistic optimism
  - More likely to experience positive outcomes

  (or less likely for negative outcomes than others)

Caregiver	→	Patient
=		=
Researcher	→	Subject

Consent Form Writing Tips

- Do not start with sponsor consent form template
- Choose the appropriate OHSU template, delete and fill as appropriate
- Covers federal/state law, institutional policy
- Start with the protocol
- Use standard language when specified in template
- See handout regarding readability and lay language (8th grade reading level) tips
- For optional substudies, consider a separate consent form

OHSU Consent Form Template (cont.)

- Purpose
  - "You have been invited to be in this research study because … The purpose of the study is to…"
  - Minimum necessary to understand
  - Investigational (experimental) device, procedure, or drug to be used if applicable
  - Number of subjects at OHSU and elsewhere

OHSU Consent Form Template (cont.)

- Procedures
  - "Stuck and Stuck": How long will be stuck at the clinic and how many times will be stuck with a needle
  - List in chronological order research related procedures
  - Treat events within each visit as they will happen
  - Indicate how much time participation in study will take (each visit and total)
  - Standard language for placebo, blinding, randomization, and radiation safety

OHSU Consent Form Template (cont.)

- Risks/Discomforts
  - Describe
  - Use standard wording provided where applicable
  - Warning signs of serious trouble first
  - Most common to least common
  - Similar problems together
- Benefits
  - Standard statement

OHSU Consent Form Template (cont.)

- Alternatives
  - List reasonable non-research alternatives
  - Include subject need not participate in research to receive same treatment if applicable
- Confidentiality
  - Indicate recipients of confidential information
  - Indicate who may review and copy records
- Costs
  - Select appropriate statement regarding costs to subject
  - At minimum, study must cover all costs outside of standard of care at OHSU

OHSU Consent Form Template (cont.)

- Liability
  - Select appropriate standard statement
  - Note that adverse events for industry sponsored studies are not billed to the subject or their insurance (see policy)
- Payment
  - How, when will the subject be paid
  - Payment must be prorated
  - SSN and tax reporting

OHSU Consent Form Template (cont.)

- Participation
  - Standard language
  - Include the Principal Investigator's name and phone number
  - State the circumstances under which the subject may be withdrawn from the study and what will happen
  - State subject will be informed of new findings if applicable
- HIPAA Authorization
  - Update to HIPAA law March 2013 allows combined consent-HIPAA

Signature and Date Lines

- Subject
- Parent or Legal Guardian
  - Children, cognitively impaired
- Person Obtaining Consent
  - Preferably investigator
- Witness
  - Not required by OHSU, but may be included
  - Define what they are witnessing

Consenting Non-English Speakers

- Qualified interpreter facilitates consent discussion with:
  - IRB-approved fully translated consent form OR
  - IRB-approved translated short consent form
- Provide subject with CF used for discussion
  - Translated CF -OR- English CF and short form
- Signatures:
  - Subject: Translated consent form or translated short form
  - Person obtaining consent: Long consent used for consent discussion (translated or English)
  - Interpreter or other impartial individual: Witness on long consent (translated or English CF and short form

Waiver of Consent (& Authorization)

- Rarely given for studies involving treatment or interaction with subjects
- Waivers must be explicitly requested and justified in the protocol
- Granted mostly for records review/preexisting specimens
- Waiver of *signed* consent is not waiver of *all* consent
- Waiver of authorization is not the same as waiver of consent – may need both.

Waiver of Consent

For minimal risk research, consent may be altered in 4 ways:

- Waiver of documentation of consent: Use of Information Sheet instead of a signed consent form. Still has full consent process
- Alteration of consent: Some required elements may be altered or waived
- Waiver of consent: Requirement to obtain consent may be totally waived

The IRB must ensure that:

- The waiver or alteration will not adversely affect the rights and welfare of the subjects
- The research could not practicably be carried out without the waiver or alteration.

Waiver of Consent

- For research that is **greater than minimal risk,** there are three modifications that may be made to the mandated consent process.
  - Waiver of requirement to document consent, used if:
    - Only record linking the subject and the research would be the consent document AND
    - Main risk is harm is from breach of confidentiality
  - Oral consent process with use of a short form to document consent.
  - Exception from informed consent requirements for emergency research – replaced with community notification

HIPAA

- Privacy Rule – Requires research subject authorization to use and disclose their protected health information
- Provision of Notice of Privacy Practices
- Applies to Protected Health Information (PHI)
- Identifiable data (18 elements)
- Security Rule – Sets standards for protecting the integrity and security (e.g., confidentiality) of electronic protected health information

HIPAA: How to use PHI in Research

- Deidentified
- HIPAA Authorization
  - What information will be collected and why
  - How long will data be kept
  - Who will that information be shared with
  - Access to information (remember CLIA)
  - Authority to revoke
  - Redisclosure, restricted information
- Limited Data Set with Data Use Agreement
- Waiver of Authorization
- Prep to research
- Decedents attestation

Investigator's Role in Human Subject Protection

- Primary responsibility for protecting the rights and welfare of human subjects
- Conducting research according to IRB-approved protocol
- Complying with IRB determinations
- Ensuring that subjects understand the research
- Knowledgeable about human subjects regulations, State and local laws, institutional policies and procedures
- Reporting progress according to IRB requirements
- Providing a copy of the IRB approved consent document to each subject or legally authorized representative, unless waiver alteration granted by IRB
- Promptly reporting proposed changes in IRB-approved research prior to initiation of the change, except to eliminate apparent immediate hazards to subjects
- Promptly reporting to the IRB any unanticipated problems involving risks to subjects or others

IRB Education

- Website: IRB Policies and Forms
  - http://www.ohsu.edu/xd/about/services/integrity/policies/all-irb-documents.cfm
- Training courses:
  - http://www.ohsu.edu/xd/about/services/integrity/training/irb-education.cfm
- IRB Brown Bags:
  - 9/25: STudents as ResearcherS: STARS in the IRB Sky
  - 11/17: VA Update
- Communications:
  - IRB Notes
  - Research News
  - RAIN

Thank You!