Definition: Children
§ 46.402(a) and § 50.3(o)

- “Persons who have not attained the legal age for consent to treatment or procedures involved in the research (clinical investigations), under the applicable law of the jurisdictions in which the research (clinical investigation) will be conducted.”

Subpart D:
Categories of Research Risk - Benefit

- Minimal Risk (§ 46.404 & § 50.51)
- Greater than Minimal Risk with Prospect of Direct Benefit (§ 46.405 & § 50.52)
- Greater than Minimal Risk with No Direct Benefit (§ 46.406 & § 50.53)
- Research not Otherwise Approvable (§ 46.407 & § 50.54)
Research Not Greater than Minimal Risk

- All children may participate
- Adequate provisions for obtaining parental permission and assent of the child as delineated in:
  - 45 CFR 46.408 or
  - 21 CFR 50.55

Greater than Minimal Risk: Prospect of Direct Benefit

- Risk is justified by anticipated benefit
- Relation of benefit to risk is at least as favorable as current alternatives
- Permission from a parent and assent of the child
  - 45 CFR 46.408 or 21 CFR 50.55
  - May waive assent

Greater than Minimal Risk: No Prospect of Direct Benefit

- Only a minor increase over minimal risk
- Intervention presents experiences that are commensurate with actual or expected medical, dental, psychological, social or educational situations
- Likely to yield generalizable knowledge about child’s condition or disorder that is of vital importance for the understanding or amelioration of the subject’s disorder
- Permission from both parents and assent of the child
  - 45 CFR 46.408 or 21 CFR 50.55
How do Institutional Review Boards Evaluate Risk?

- How is “minimal risk” defined?
- What constitutes a “minor increase over minimal risk”?
- Do IRBs often rely on intuition when assessing risks?
- Is there a way to standardize risk evaluations?

Categorization of Risk by IRB Chairpersons

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Minimal Risk</th>
<th>Minor Increase over Minimal Risk</th>
<th>More than a Minor Increase over Minimal Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy Skin Testing</td>
<td>23%</td>
<td>43%</td>
<td>27%</td>
</tr>
<tr>
<td>Confidential Survey of Sexual Activity</td>
<td>44%</td>
<td>29%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Shah et al, JAMA 291:476, 2004

§ 46.404 SACHRP Recommendations: Indexing Minimal Risk

- Index risks encountered during daily life of normal, average, healthy, child in safe environment
- Suggests ‘well-child visit’ as reference for routine medical and psychological exam
Dual Standards for Minimal Risk

- Minimal risk is 2 standards, not 1
  - Daily life
  - Routine examination
- Daily life has inherent risks that might not be acceptable in research context
- Routine examination risks are exceedingly low
  - SACHRP only clarifies this aspect of regulation

What are the risks of sports for children > 6 years?

<table>
<thead>
<tr>
<th>Sport</th>
<th>Total</th>
<th>Perm. Disability</th>
<th>Level IV Injuries</th>
<th>Surgery</th>
<th>Broken Bones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Football</td>
<td>3800</td>
<td>42</td>
<td>500</td>
<td>270</td>
<td>910</td>
</tr>
<tr>
<td>Soccer</td>
<td>2400</td>
<td>38</td>
<td>300</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Basketball</td>
<td>1900</td>
<td>58</td>
<td>300</td>
<td>160</td>
<td>180</td>
</tr>
<tr>
<td>Cheerleading</td>
<td>1700</td>
<td>NA</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Baseball</td>
<td>1400</td>
<td>61</td>
<td>200</td>
<td>120</td>
<td>30</td>
</tr>
</tbody>
</table>

- Risks are per 1,000,000 participations
- Level IV means ED, hospital stay, surgery or ongoing PT

Wendler et al, JAMA 294:826, 2005

Minimal Risk Dilemma

- Permitting research equivalent in risk to daily life would allow healthy children to participate in risky studies (Risk of injury 1/250 - 1/500 might permit research riskier than ethically acceptable)
- Limiting research to the routine examination standard would stifle research
- Recognition that the car ride to and from clinic is riskiest part of many research studies
### Examples of Minimal Risk Procedures

- Surveys
- Observations of behavior
- Retrospective chart review
- Non-invasive physiologic measures e.g. BP, HR, RR, SpO2
- Clean catch urine specimen
- Stool samples
- EEG
- Changes in diet or daily routine
- Blood sampling (within certain limits)

### Procedures not Approvable Using Expedited Procedures but Found to be Minimal Risk at CHOP

- Ionizing Radiation: DXA, pQCT, Bone Age, Chest X-Ray
- Skin Punch Biopsy (no suture)
- Additional MRI scan without supplemental sedation
- Blood draw > 2x per week (e.g., PK study)
- Blood draw > 3mL/kg or 50 mL (up to 5mL/kg)

### Examples of Minor Increase over Minimal Risk Procedures

- Lumbar puncture
- Bone marrow aspirate
- Sedation or general anesthesia
  - Depending on the health status of the child could be greater than minor increase
- Magnetic resonance imaging with gadolinium
Component Analysis:
Assignment to Subpart D Category

- Direct benefit studies
  - Intervention + procedures required to monitor intervention
  - Cannot justify components > minimal risk but not needed to assess intervention
- Studies without direct benefit
  - Assessment based on riskiest components
  - Totality of risk from all components

Cumulative Risk

- The cumulative risk burden should be assessed. This is important because research may involve several different procedures that may involve minimal risk or burden individually but that may present more than minimal risk when considered collectively.

IOM, The Ethical Conduct of Clinical Research Involving Children

Systematic Evaluation of Research Risks (SERR) – Proposed 4-Step Process

1. Identify potential harms posed by research intervention
2. Categorize magnitude of each potential harm using a harm scale
3. Quantify or estimate likelihood of each potential harm

Rid et al., JAMA;304:1472, 2010
Systematic Evaluation of Research Risks (SERR) – Proposed 4-Step Process II

4. Compare likelihood of each potential harm from research intervention with likelihood of potential harms of same magnitude in a comparator activity (e.g. activity of daily life); if comparable, risks of research intervention do not exceed risks of comparator activity

Rid et al., JAMA;304:1472, 2010

Feasibility of the SERR approach

- Provides objective standard
- Not possible for every IRB to perform research to obtain necessary data
- Establish national database to collect risk data accessible to IRBs

Case Study I

- **Objective:** Create and maintain an intestinal tissue and stool repository for clinical and basic science researchers
- **Design:** Specimen collection for tissue when subject is scheduled for upper GI endoscopy, sigmoidoscopy, colonoscopy, or intestinal resection; Stool specimen collection either in inpatient or home setting of participant.
- **Population:** Subjects of any age with a confirmed or suspected diagnosis of inflammatory bowel disease
Case Study I

Issues:
- Risks of multiple biopsies (number and locations)
- Frequency of collection
- Prolonged sedation
- Re-consent before every procedure
- Who performs procedure

Case Study II

- **Objective:** Evaluate efficacy, safety, tolerability and pharmacokinetics of study drug for treatment of chronic idiopathic thrombocytopenic purpura (ITP)
- **Design:** Three-part, staggered cohort, open-label and double-blind, randomized placebo-controlled multi-center trial; daily dosing, randomized 2:1 to study drug or placebo; after 7 weeks, all subjects receive study drug open label for a total of 24 weeks on study drug; intensive PK testing at week 6
- **Population:** Subjects 1-17 years old, previously treated for ITP

Case Study II

Issues:
- Are the risks minimized?
  - Pharmacokinetic testing at 6 weeks would include subjects who are on placebo at the time and who would be asked to be in the hospital for more than 8 hours with an indwelling IV catheter, with no benefit to them.
  - Is there a need for pharmacokinetic testing for the subjects receiving placebo?
  - Could PK studies be done when all subjects are receiving study drug?
Case Study III

- **Objective:** Determine whether prenatal surgery for a birth defect improves outcome compared with standard postnatal repair
- **Design:** Observational study; study procedures include urinary catheterization, videourodynamics using x-rays and contrast, MRI of brain and spine under sedation or general anesthesia, spine x-rays
- **Population:** Subjects 5-9 years old, previous participants of prenatal surgery trial

Case Study III

**Issues:**
- Is there a prospect for direct benefit?
- If not, does the cumulative risk of MRI with sedation or general anesthesia, catheterization and contrast for urodynamic testing and X-rays present no more than a minor increase over minimal risk?
- Are risks minimized by using x-ray and contrast urodynamic testing over ultrasound?

Case Study IV

- **Objective:** Determine safety and efficacy of study drug combination for recurrent, progressive or refractory malignant brain tumor
- **Design:** Phase II open-label multi-center trial; study drugs given IV every two weeks for up to 2 years. In addition to standard MRIs, imaging procedures include two optional PET scans to correlate functional changes in tumor with progression-free survival
- **Population:** Subjects < 21 years old with recurrent, progressive or refractory malignant glioma, medulloblastoma or ependymoma
Case Study IV

Issues:
- PET scans are optional, done for research purposes only
  - Involve > 100mrem radiation exposure
  - No direct benefit to the subject
- Separate risk-benefit determination for main study and optional PET scans

Case Study V

- Objective: Determine safety and feasibility of administration of autologous chimeric antigen receptor T cells, transduced with a viral vector; assess survival of gene modified cells and anti-tumor response.
- Design: Single arm, open-label Phase I/pilot study; lymphodepleting chemotherapy followed by infusion of ex-vivo transduced and expanded T cells
- Population: 1-21 year olds, resistant or refractory leukemia or lymphoma

Case Study V

Issues:
- First in human use of this cell product (viral vector previously used in HIV trial; gene-modified T cells for renal and ovarian cancer, lymphoma and CLL)
- No clinical data in adults; pre-clinical data shows anti-tumor effect in cell cultures and mouse model
- Risks (gene-modified cells, tumor lysis syndrome...)
- Prospect of direct benefit
Case Study VI

- **Objective:** Determine safety and tolerability of subretinal administration of AAV2-hRPE65v2, an adeno-associated virus gene transfer vector, to subjects with Leber congenital amaurosis (LCA) and to assess the objective clinical measures of efficacy in human subjects
- **Design:** Phase I, open-label intergroup dose-escalation trial of AAV2-hRPE65v2; injected into “worse” eye
- **Population:** Children, diagnosed with LCA due to due to RPE65 mutations

**Issues:**
- First in human use (no data in adults; prospect of benefit best in children)
- Prospect of direct benefit in lowest dose (preclinical data in dog model shows restoration of vision at low doses)
- Risks (vector exposure beyond eye; immune response; surgical procedure…)
- Enroll only children who can assent?

Case Study VII

- **Objective:** Evaluate safety, tolerability, and pharmacokinetics of escalating doses of study drug administered as a single intrathecal injection in patients with spinal muscular atrophy (SMA1)
- **Design:** Open-label multi-center trial; four dose levels evaluated sequentially; plasma pharmacokinetics at 1, 2, 4 and 20 hours after dosing
- **Population:** Subjects 2-14 years old, homozygous gene deletion for SMN1
Case Study VII

Issues:
- First in human use (no data in adults) - is it possible to conduct preliminary safety study in SMA adults or health adults?
- Is there a prospect of direct benefit of study participation with a single injection of study drug and is it at least as favorable as available alternatives outside of the research?
- Study procedures include an MRI and two lumbar punctures; all three procedures might require sedation – more than a minor increase over minimal risk?

Case Study VIII

Objective: Evaluate effects of stimulated bone marrow (BM) on event-free survival and engraftment kinetics in children undergoing allogeneic transplantation for leukemias

Design: Phase III trial comparing two graft sources for allogeneic transplantation using HLA identical siblings as donors: bone marrow and filgastrim (recipient receives G-CSF) versus stimulated bone marrow (donor receives G-CSF)

Population: Recipient < 22 years of age with leukemia (for which transplant indicated); Donors > 6 months, matched sibling

Study conducted at CHOP; PCIRB IRB of record

Issues:
- Are donors research subjects
- Risks to donors
- Benefits to donors
- If no direct benefit, is risk only minor increase over minimal
- Commensurability
- Do donors have disorder or condition
- Subject advocate
Why have women of child-bearing potential been excluded from research?

- Fetal risk
- Unreliable contraception
- Available male medical student volunteer
- Variability in hormonal state
- Expense
- Age for inclusion
1960: TRAGEDY IN THE MAKING PROMPTS
FDA ACTION

Est. 8000 "Thalidomide Babies" born
7000 more died in utero. 40 thalidomide cases in US.

Dr. Frances Kelsey
FDA

♂ ≠ ♀

- Size
- Anatomy
- Physiology
  - Absorption, distribution, metabolism and excretion
    - Pharmacokinetics
    - Pharmacodynamics
- Hormones
- Hormonal cycling
- Pregnancy
  - 2 individuals

MAN

Woman
Pregnant Women are Different

- ↑ cardiac output, plasma volume
- ↓ gastric emptying, intestinal transport
- ↑ renal excretion
- ↑ drug metabolism

4 million women pregnant in U.S. each year
Pregnant women use ~ 2 medications during pregnancy
2/3 of pregnant women use > 4-5 medications during pregnancy
Off label use is universal

Maternal Effects:
What we (don’t) know

- 61 articles report relevant PK data
- No consistency of reporting or results
- 2 articles offer evidence-based guidelines

Little, Obstet Gynecol 1999

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>Increase</th>
<th>Decrease</th>
<th>No. Reporting</th>
<th>No. Consistency</th>
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<tr>
<td>ALA</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td>9 (81.8%)</td>
<td>3 (33.3%)</td>
</tr>
<tr>
<td>ASA</td>
<td>11</td>
<td>3</td>
<td>2</td>
<td>10 (90.9%)</td>
<td>3 (30.0%)</td>
</tr>
<tr>
<td>Cm</td>
<td>30</td>
<td>10</td>
<td>7</td>
<td>27 (89.0%)</td>
<td>3 (30.0%)</td>
</tr>
<tr>
<td>CBZ</td>
<td>15</td>
<td>4</td>
<td>3</td>
<td>15 (100%)</td>
<td>3 (33.3%)</td>
</tr>
<tr>
<td>CMX</td>
<td>16</td>
<td>5</td>
<td>5</td>
<td>11 (68.7%)</td>
<td>3 (30.0%)</td>
</tr>
<tr>
<td>CTR</td>
<td>30</td>
<td>10</td>
<td>7</td>
<td>27 (90.0%)</td>
<td>3 (30.0%)</td>
</tr>
<tr>
<td>DHE</td>
<td>15</td>
<td>5</td>
<td>2</td>
<td>14 (93.3%)</td>
<td>2 (16.6%)</td>
</tr>
<tr>
<td>DIB</td>
<td>10</td>
<td>3</td>
<td>2</td>
<td>9 (90.0%)</td>
<td>3 (30.0%)</td>
</tr>
<tr>
<td>DOP</td>
<td>20</td>
<td>10</td>
<td>5</td>
<td>13 (65.0%)</td>
<td>3 (30.0%)</td>
</tr>
</tbody>
</table>
Fetal Effects:
What we (don’t) know

<table>
<thead>
<tr>
<th>Length of time since FDA approval (y)</th>
<th>None, minimal, or undetermined (%)</th>
<th>Small, moderate, or high (%)</th>
<th>Undetermined (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>91.0%</td>
<td>2.4%</td>
<td>6.4%</td>
<td>100.0%</td>
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<tr>
<td>5-10</td>
<td>85.0%</td>
<td>2.6%</td>
<td>12.4%</td>
<td>100.0%</td>
</tr>
<tr>
<td>&gt;10</td>
<td>69.0%</td>
<td>3.8%</td>
<td>27.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total</td>
<td>80.4%</td>
<td>3.2%</td>
<td>6.4%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Lo and Friedman, Obstet Gynecol 2002

Distributive Justice
Fair allocation of the benefits and burdens of research

Rationale for Including Pregnant Women in Research
- Medical conditions (e.g., HIV) in women who become pregnant
- Medical conditions unique to pregnancy (e.g., preeclampsia)
- Conditions that threaten the successful course of labor (e.g., preterm labor)
- Physiologic changes of pregnancy and lactation
- Safety of medication during pregnancy and breast feeding

ACOG Committee opinion, Sept 2007
Consequences of Understudy of Therapies in Pregnant Women

- Dosing errors
- Unrecognized toxicity
- Reticence to prescribe or take beneficial therapies

Dosing Error Examples

- Amoxicillin
  - Treatment for anthrax exposure
  - PK studies suggest concentrations not achievable for prophylaxis

Fetal Toxicity

- THALIDOMIDE
  - 1960 in Europe and Canada for morning sickness
  - More than 10,000 children around the world born with major abnormalities (limbs)
- DES
  - 1938-1971 for the treatment of miscarriages and PTL
  - About 4 million women were exposed in the US
  - Development of fetal reproductive system anomalies
**FDA Categories**

- The FDA system not intended to estimate teratogenic risk
- The FDA categories based largely on data from unpublished premarketing animal studies.
- Animal teratology studies are not always predictive of either teratogenic risk or safety in human pregnancy.
- In addition, FDA categories take into account both the potential benefit and the potential risk of drug treatment during pregnancy.

**Under-utilization of Beneficial Therapies**

**Imatinib (Gleevec) Example**

- Treatment for CML
- Discontinued during pregnancy
- 40% relapse with therapy interruption

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>maternal</td>
<td>blood</td>
<td>195</td>
</tr>
<tr>
<td>cord blood</td>
<td>GPF/TNB</td>
<td>51</td>
</tr>
<tr>
<td>umbilical cord blood</td>
<td>3</td>
<td>175</td>
</tr>
<tr>
<td>GPF/TNB</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>placenta</td>
<td>transfer</td>
<td>242</td>
</tr>
<tr>
<td>cord milk</td>
<td>transfer</td>
<td>152</td>
</tr>
</tbody>
</table>

Minimal placental transport

**Presumed Inclusion**

- The committee recommends that pregnant women be presumed eligible for participation in clinical studies.
- “Vulnerable” implies less autonomy and ability to make decisions
- Robust informed consent process is vital

---

IOM Committee on Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Research, 1994
Criteria for Exclusion

- No prospect of medical benefit to pregnant woman
- Risk of significant harm to offspring is known or can be plausibly inferred
  - Animal studies,
  - in vitro studies or
  - previous clinical experience

IOM, 1994

45CFR46 Subpart B
Conditions for Research

- Pertinent preclinical (pregnant animals) and clinical (nonpregnant women)
- Any fetal risk holds prospect of direct benefit to woman OR fetus, OR risk minimal AND purpose important AND no alternative
- Any risk is least possible
- Informed consent (with paternal consent if benefit solely to fetus)
- Pregnant children (see Subpart D)
- No inducement to terminate
- Investigators have no role in decisions on termination or determination of viability

27

Double-blind, Placebo-controlled Pilot Trial of X to Promote Smoking Cessation During Pregnancy

- 50 smoking pregnant women, 14-26 weeks
- Smoking risks
  - Maternal – respiratory, cardiac
  - Fetal child – low birth weight, respiratory, SIDS, ADD and neurocognitive
- X is FDA-approved for smoking cessation, but not in pregnancy
- Pregnancy class C (dose-related risk in animals, especially 1st trimester)
- DSMB

30
Double-blind, Placebo-controlled Pilot Trial of X to Promote Smoking Cessation During Pregnancy

- Clinical equipoise?
- Potential benefit
  - Urgency of fetal (vs. childhood) smoking risk
  - Urgency of maternal smoking risk
- Appropriate DSMB surveillance
- Long-term outcome analysis

Cord Blood Bank

- Collection of umbilical cord blood to supply BM transplant recipients (supplementing ethnic minorities)
- Harvesting post-partum at discretion of OB
- Recruitment in L&D while comfortable and not in active labor
- Screening for inherited diseases, HIV, syphilis, HTLV, CMV, WNV

Cord Blood Bank

- No physical risk to mother or infant
- Opting out of personal CB banking
  - Possibility of opting back in?
- Site of recruitment
- Can consent process be improved?
Double-blind, Placebo-controlled, Parallel-group Study of Y as Adjunctive Therapy for Refractory Partial Seizures

- Novel antiepileptic agent with minimal toxicity in animal/human trials (anticipate class B)
- Women of child-bearing potential excluded and must use 2 BC methods
- Approved SOC agents are pregnancy class C-D

Double-blind, Placebo-controlled, Parallel-group Study of Y as Adjunctive Therapy for Refractory Partial Seizures

- Distributive justice?
- Should pregnant women be excluded?
- Should WCP be excluded?
- Would the inclusion of a small # of pregnant women be meaningful in a pivotal trial?
- Should WCP and pregnant women be targeted for study prior to FDA approval?
Introduction

- Historically women have been omitted from clinical research.
- In an effort to protect the vulnerable population of pregnant women, the unintended consequence has been that women remain underserved in the area of clinical research.
- The Office of Research on Women's Health (ORWH) was established in September 1990 to ensure that women's health research is part of the scientific framework at the NIH—and throughout the scientific community.

Current Perinatal Research at the University of Colorado

- The establishment of ORWH 22 years ago, new mandates from the NIH and a growing interest in lifespan research has increased interest in women's health and pregnancy-related research.
- Around Campus:
  - 32 active pregnancy studies
  - 10 active NICU studies
  - A growing interest in perinatal research
- In 2010, the Department of Obstetrics and Gynecology identified a growing need to develop a coordinated infrastructure to conduct perinatal research at the University of Colorado School of Medicine.
To establish a research database that is linked to clinical, bio-bank, ultrasound, mental health, neonatal and other study specific data of women who initiate early (<23 weeks gestation) prenatal care at the University of Colorado Hospital (UCH) and plan to deliver their babies at UCH.

Baby Blanket expands on the historical success of the Perinatal Database by providing a coordinated infrastructure for conducting perinatal research studies at UCH.

- October 2005: official start of data collection
- March 2012: over 20,000 records currently in the database
Baby Blanket Partners

Anschutz Medical Campus
- School of Medicine
  - Department of OB/GYN
  - Department of Pediatrics and the section of Neonatology
- College of Nursing
- School of Public Health
- Child Maternal Health Program of the Colorado Clinical and Translational Sciences Institute (CCTSI)

University of Colorado Hospital (UCH)
- University Nurse-Midwives
- Women's Care Clinic

Children's Hospital Colorado (CHC)
- Perinatal CTRC

Community Partners
- Metro Community Provider Network (MCPN)

Consenting of Subjects into the Baby Blanket Protocol
Patient Flow at Recruitment Visit

Protecting the Vulnerable Patient Population of Pregnant Women: Campus-wide Concerns

Study Overlap and Competition for Recruitment: an increase in the number of approved perinatal research protocols at the Anschutz Medical Campus resulting in a growing competition for research subjects and a need for “traffic control” in the recruitment of research participants in the Prenatal Clinic, on Labor & Delivery and in the Neonatal Intensive Care Units.
**Addressing Campus-wide Concerns**

**Study Overlap and Competition for Recruitment**

**Solutions:**
- Promote use of existing campus resources
  - Perinatal Database
  - Biorepository
- Development of a Research Facilitation Core
  - Perinatal Research Facilitation Committee
  - Triage Committee
- Development of Research Recruitment Forms through the Research Facilitation Core to assist researchers in recruiting pregnant women

**Research Facilitation**

**Perinatal Research Facilitation Committee**
- Composed of senior faculty and administrators from across campus
- Meets bi-annually to discuss major issues related to perinatal research

**Triage Committee**
- A sub-group of the Perinatal Research Facilitation Committee
- Meets monthly to review new perinatal research protocols

**Goals of the Triage Committee**
- Determine feasibility of proposed research
- Assure awareness of existing data, recruitment database, and biobank
- Identify overlap with ongoing studies
- Foster collaboration
- Establish priorities for protocols
- Direct investigators to alternative resources and/or research sites
- Major resource is the department of Ob/Gyn Perinatal Database
Case Study: Competition for Cord Blood

- Issues with co-enrollment and the collection of cord blood:
  - Unreasonable amounts of cord blood requested in protocols
  - Delayed cord clamping
  - Cord blood banking
- Solutions:
  - Oversight by the CTRC team on Labor and Delivery and by the Triage Committee
  - Memoranda of understanding (MOU) and promotion of co-enrollment
  - Task force developed to explore aliquoting samples of cord blood
  - Campus-wide awareness of this problem

Research Recruitment Forms

Women can choose whether or not they would like to be contacted for inclusion in pregnancy related studies

Women who mark 'YES' will be pre-screened for research studies following inclusion in the Baby Blanket Research Recruitment Database

Recruitment Forms Collected in 2011

- Records are shared by 5 NIH sponsored studies

UCH CLINIC
- FRONT DESKS
- UCH PRENATAL DIAGNOSIS
- BABY BLANKET PARTICIPANTS
- CHC CAMP CLINIC
- LOWRY CLINIC
- MCPN

RECRUITMENT DATABASE
1,480
Case Study: Clinical Trials Core

Study Aims:
- Overall goal is to evaluate the effects of low dose aspirin (LDA) on reproduction, specifically on conception and pregnancy
- Study Type:
  - Multi-center, randomized, placebo-controlled, double-blind clinical trial sponsored by the NICHD

High Risk Target Population
- Women of childbearing age, 18-40
  - Who live in the Denver metro area
  - Who have experienced one or two spontaneous pregnancy losses in the past
  - Who are thinking of becoming pregnant again

Community Based Study
- Print
- Radio/TV
- Neighborhood recruitment
- Social Networking
- Word of Mouth
COMIRB’s Involvement

- Targeting a very high risk vulnerable population
- Potential participants may be desperate to become pregnant
  - Even the name of trial, EAGeR, suggests the patients vulnerability
- Language used in national publications for the study were questionable in wording
- Multiple IRBs in the local area

Solutions:

- Worked with COMIRB on modifying language of brochures and other media related materials
- Scripting for all media
- Address sensitivity issues
- Additional training of research staff
- A marketing consultant who worked alongside PI and team
- Maternal-Fetal Medicine specialist on team
- Perinatal-loss nurse as part of the team

Campus Publications

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Facebook Campaign

Targeting: women who live within 50 miles of Denver, ages 22 to 40.
Campaign reaching 311,520 unique Facebook users

KCFR 90.1FM Colorado Matters

Study Looks At Link Between Aspirin and Healthy Pregnancy
Researchers at the University of Colorado Denver School of Medicine are studying whether aspirin can contribute to a healthy pregnancy. Ryan Warner speaks with Anne Lynch, who is heading up the study.

Colorado & Company Interview

The EAGeR Study was featured on the 9News morning show Colorado & Company.
Where We Are Now...

Supportive Infrastructure:
- The Clinical Core Team:
  - Supports recruitment into the Baby Blanket clinical program
  - Enrolled 415 women into the program in 2011
- The Database and Analysis Core Team:
  - Worked with 36 investigators in 2011
- The Biorepository Core Team:
  - Manages all aliquoted biological samples from the Baby Blanket program as well as other study specific biospecimens
  - Assisted 8 investigator initiated projects in 2011
- The Research Facilitation Core:
  - Reviewed 18 new perinatal protocols in 2011
- The Clinical Trials Core:
  - EAGeR
  - The Maternal Fetal Medicine Network Units (MFMU) Studies

Acknowledgements:
- Nanette Santoro, MD
  Chair of Department of OB-GYN
- Ron Sokol, MD
  Director and Principal Investigator of the CCTSI
- Bill Hay, MD
  Director of the Child Maternal Health Program of the CCTSI
- Alison Lakin, RN, LLB, LLM, PhD
  Assistant Vice Chancellor for Regulatory Compliance
- Warren “Cappy” Capell, MD
  Director of COMIRB
- Baby Blanket Research Team
- EAGeR Trial Research Team
Why Are We Here?

Understand the responsibility to ensure the protection of human-research subjects and the legal liability when this fails to occur

Overview

- Vulnerability in human subjects research
- Laws affecting human clinical trials
- Concerns prompting litigation
- Causes of Action
- Cases
- Impact of Litigation
If we knew what it was we were doing, it would not be called research, would it?

-Albert Einstein (1879-1955)

1. To be susceptible to something, (a bad something)
2. To be capable of being physically or emotionally wounded

Precisely who are the Vulnerable?

In clinical research, the term vulnerable generally is applied to individuals who are unable to give informed consent or who are susceptible to coercion.
“Special justification is required for inviting vulnerable individuals to serve as research subjects and, if they are selected, the means of protecting their rights and welfare must be strictly applied.”


Who are the Vulnerable?

Current Regulation (45 CFR 46)

46.102 Human Subject is a living individual about whom an investigator obtains data through intervention or interaction with the individual or the individual’s identifiable private information

The Common Rule (45 CFR 46, Subpart A)

46.111 The Institutional Review Board (IRB) in approving research must assure:

3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

Who are the Vulnerable?

46.111 7 (b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

46.201-207 Subpart B Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

46.301-306 Subpart C Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

46.401-409 Subpart D Additional Protections for Children Involved as Subjects in Research
Although the Common Rule specifies certain vulnerable categories, the guidelines were not intended to be exclusive, leaving open the interpretation of vulnerability.

Other ‘Vulnerable Subjects’
Special Classes of Subjects
IRB Guidebook, OHRP Chapter VI
Traumatized and Comatose Patients
Human In Vitro Fertilization
Terminally Ill Patients
Women
Elderly/Aged Persons
Minorities
Cognitively Impaired Persons
Students, Employees, and Normal Volunteers
International Research

What makes a Subject Vulnerable?
Forms of Vulnerability

- Cognitive
- Environmental
- Institutional
- Deferential
- Medical
- Economic
- Social

Despite its vagueness, “vulnerability remains a useful concept, and the attempts to define it in regulations show that we should in fact regard every research subject as vulnerable, unless and until proven otherwise on an individual basis.”

Richard Nicholson

Regulations want to both **include** and **protect** vulnerable subjects
Dangers exist in both too many and too few protections

Emerging Trends in Litigation

- Diversified types of legal claims
- Changes in the number and types of defendants named in lawsuits
- Emergence of class action lawsuits

Targets of Liability

- Researcher
- Institution
  - IRB
- Others:
  - Sponsors
  - Patient advocates
  - Bioethicists
Laws Affecting Human Clinical Trials

- 1949 Nuremberg Code
- 1964 Declaration of Helsinki
- 1974 National Research Act
- 1979 Belmont Report
- 1981 Federal Policy for the Protection of Human Subjects
- FDA regulations
- 1991 Adoption of the ‘common rule’

Concerns Prompting Litigation

Sources of Risk:
- IRB workloads
- Resources
- Multicenter trials
- Conflict of Interest
- Ignorance
- Suitability of site

Clinical Trial Litigation

- Abney vs. Amgen
- Suthers/Martin vs. Amgen, Inc.
- Scheer vs. Burke, et al.
- Hamlet vs. Fradin, M.D., et al.
- Steubing v. Kornak et al.
- Quinn v. Abiomed et al.
- Steubing v. Kornak et al.
- Robertson et al. v. McGee et al.
- Wright v. Fred Hutchinson Cancer Research Center et al.
- Berman v. Fred Hutchinson Cancer Research Center et al.
- Adlerman v. Trustees of the University of Pennsylvania
- Beth Wade v. Oregon Health And Science University
- Dagosto, Mariam v. FHCRC
Causes of Action

- Battery
- Negligence
- Strict Liability
- Fraud
- Breach of the right to be treated with dignity
- Violation of Anti-kickback statutes

What Can be Done?

- Be clear about conflicts of interest
- Pay attention to process through which subjects informed consent is obtained
- Designing and conducting trials carefully
- Monitoring studies closely for injuries to subjects

Impacts

- Increase cost of research
- Discourage research
- Chilling effect on individual willingness to serve on IRB's
- Potential to lead to worse not better decisions about the ethics of research studies
- Potential to create incentives for more careful research
- Greater human subjects protections
The moral test of any society is how it cares for the people in the dawn of life: the children; the twilight of life: the elderly; and the shadows of life: the sick and disenfranchised.

Hubert H. Humphrey
Parental Permission and Waiver of Parental Permission

Nuremberg Code: 1947

1. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice…; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision.

2. Children would be universally excluded.

Declaration of Helsinki: 1964

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative.

These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
Declaration of Helsinki, 1964

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject’s dissent should be respected.

45 CFR 46 & 21 CFR 50: Subpart D Categories of Research Risk – Benefit

- Minimal Risk (§ 46.404 & § 50.51)
- Greater than Minimal Risk with Prospect for Direct Benefit (§ 46.405 & § 50.52)
- No Direct Benefit (§ 46.406 & § 50.53)
- Research not otherwise approvable (§ 46.407 & § 50.54)

Respect for Children: Permission and Assent

- Parents grant permission for their child’s participation in research
  - Presumed to act in child’s best interests
- Children assent to extent possible given their capacity to make choices
  - Honors the choices of persons with diminished autonomy
Requirements for Parental Permission

- § 46.408(b) …the IRB shall determine, in accordance with and to the extent that consent is required by § 46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian.

Permission Requirements: Research approved under 45 CFR 46.404 or 405

- § 46.408(b)…Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under § 46.404 or § 46.405.
- May find means that the IRB must make an active decision
- The IRB may find that 2 parents permission is needed

Permission Requirements: Research Approved Under 45 CFR 46.406 or 407

- § 46.408(b)…Where research is covered by § 46.406 and 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.
What are the requirements for permission?

- The content of the permission form are identical to the requirements for consent 45 CFR 116(a) and (b)
- The requirements for HIPAA authorization are the same

When is the requirement for parental permission not enough?

- Child dissent
- This can take the form of:
  - Failure to assent (passive dissent)
  - Active dissent
  - Withdrawal of assent

Recommendation 5.4

- IRBs should consider granting waivers of parental permission for adolescent participation in research when
  - the research is important to the health and well-being of adolescents and it cannot be reasonably carried out without the waiver (consistent with § 46.116(d) or § 46.408(c)); or
– the research involves treatments that state laws permit adolescents to receive without parental permission (consistent with the definition of children at 45 CFR 46.102(a) and when
  • the investigator has presented evidence that the adolescents are capable of understanding the research and their rights as research participants and
  • the research protocol includes appropriate safeguards to protect the interest of the adolescents consistent with the risk presented by the research.

IOM Ethical Conduct of Clinical Research Involving Children

Waiver of the Requirement for Parental Permission

- 45 CFR 46.116(d)
- 45 CFR 46.408 (c)
- 45 CFR 46.402(a) (not an actual waiver)
- 21 CFR 50.24 (emergency research)
Waiver of Parental Permission Under 45 CFR 46.116(d)

- Waiver criteria are the same as for the waiver of consent
  1) ...involves no more than minimal risk...
  2) ...will not adversely affect the rights and welfare of the subjects
  3) research could not practicably be carried out without the waiver or alteration;
  4) ...provided with additional pertinent information after participation

Common Examples: Waiver of Parental Permission Under § 46.116(d)

- Research involving existing records or specimens
- Prospective research such as:
  - Research involving data gathered during Quality Assurance activities
  - Research involving a large number of subjects
  - Need 100% participation to ensure scientific validity

Case Study 1: Resuscitation Performance in Pediatric Trauma

- **Objective**: to identify patient or provider factors associated with delays in care
- **Design**: exploratory cohort study
- **Population**: MDs, RNs and children videotaped in the ED during Level I or II trauma activations
Case Study 1: Waiver of Parental Permission Under § 46.116(d)

- **Minimal risk**: videotapes already being obtained for QA purposes
- **Rights and welfare**: no additional procedures performed, no disclosure of information
- **Practicability of obtaining consent**: parents not generally available, most subjects severely ill, loss of some subjects would bias the study results

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Case Study 1: Waiver of Parental Permission Under § 46.116(d)

- Records and videotapes from the resuscitation bay gathered for QA purposes
  - Review of these records for research purposes poses no additional risk
  - Omission of some subjects would bias the research
  - Parents stressed by the clinical circumstances

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Case Study 2: Resuscitation Performance in Pediatric Trauma

- **Objective**: to determine if pop-up reminders to clinicians influences % of children who receive influenza vaccine
- **Design**: cluster-randomized trials
- **Population**: 250 pediatrics and ~50,000 children seen in primary care practices
Case Study 2: Basis for Waiver of Parental Permission Under § 46.116(d)

- **Minimal risk**: each child's care determined by their pediatrician; computerized records recording outcomes prepared by an honest broker
- **Rights and welfare**: no additional procedures performed
- **Practicability of obtaining consent**: not possible to obtain consent from 50,000 parents

Waiver of Requirement for Parental Permission

45 CFR 408(c)

Waiver of Permission Under 45 CFR 408(c)

- (c) … the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph…
Protective Mechanism for Waiver of Permission Under 45 CFR 408(c)

- ...provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted…
- The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

Case Study 3: Adolescent's Knowledge About Emergency Contraceptives Pills

- Objective: to assess adolescent girls’ knowledge, attitudes and subjective norms related to ECPs
- Design: cross-sectional study
- Procedures: interview and survey
- Population: teenage girls obtaining care in the ED of a pediatric hospital

Case Study 3: Basis for Waiver of Parental Permission Under § 46.408(c)

- Understanding attitudes towards seeking ECPs was determined to be important for health and welfare of adolescent girls and prevention of unwanted pregnancy
Case Study 3: Protective Mechanism

- Assent was determined to provide sufficient to protect the interests of the participants

Case Study 4: Attitudes of Teen Drivers

- **Objective**: to evaluate the effectiveness of the National Teen Driver Effectiveness Week
- **Design**: school-based cross-sectional study.
- **Procedures**: questionnaires
- **Population**: high school teens age 13 – 18 y

Case Study 4: Basis for Waiver of Parental Permission Under § 46.408(c)

- Car accidents are a major cause of morbidity and mortality for teens
- Understanding the effectiveness of national campaigns is vital for the health and welfare of teens
Case Study 4: Protective Mechanisms

- Parents sent a letter explaining the study
  - Phone number provided to allow parents to opt-out
- Adolescents provided assent for study participation

Case Study 5: Driving Performance of Novice Drivers

- **Objective**: to evaluate the effectiveness of novice drivers on a standardized course compared to more experienced drivers
- **Design**: prospective observational trial
- **Procedures**: on-road driving assessment
- **Population**: novice drivers 16 – 17 year old and experienced drivers 25+ years old

Case Study 5: Basis for Waiver of Parental Permission Under § 46.408(c)

- Car accidents are a major cause of morbidity and mortality for teens
- Understanding on-road driving skills of novice drivers is vital to understanding the factors leading to teen traffic fatalities
Case Study 5: Protective Mechanisms

- Adolescents provided assent for study participation
- On-road test on city streets is comparable to typical driving situations
- Adolescents who drive can come to research without their parents
- Experienced driving instructor in the car during the on-road test

Minors Who Aren’t Children Under 45 CFR 46.402(a)

When Subpart D Does Not Apply

Definition: Children § 46.402(a) and § 50.3(o)

- Persons who have not attained the legal age for consent to treatment or procedures involved in the research (clinical investigations), under the applicable law of the jurisdictions in which the research (clinical investigation) will be conducted.
When is a minor not a child?

- Whenever the minor may consent under state law to the treatment or care related to the research, they may consent research related to their treatment
- If the minor can consent to treatment, they are not children as defined by § 46.402(a) and Subpart D protections do not apply

Requirements for Minor Consent to Treatment Vary State by State

- Age of majority = 18 years in most states
- Age of majority > 18 years
  - Alabama (19)
  - Nebraska (19)
  - Mississippi (21)
  - Puerto Rico (21)

When can minors consent for treatment in Pennsylvania?

- 18 years of age
- **Mature Minors**
  - Pregnant or have ever been pregnant
  - Married or have been married
  - Graduate from high school

**Specific Conditions**
- STDs & HIV testing, treatment, prevention
- 50+ reportable infectious diseases
- Emergency care
- Blood donation
- Mental health services (14+)

### When can minors consent for treatment in New Jersey?
- 18 years of age
- **Mature Minor**
  - Pregnant or have ever been pregnant
  - Married or have been married

### Specific Conditions
- STD testing/treatment
- Alcohol or drug abuse
- Emergency care for a sexual assault
- Blood donation

### When can minors consent for treatment in Delaware?
- 18 years of age
- **Mature Minor**
  - Pregnant or have ever been pregnant
  - Married or have been married

### Specific Conditions
- STD testing or treatment (12+)
- HIV testing (12+)
- Family planning (12+)
- Alcohol or drug abuse treatment (14+)
- Blood donation (17+)

### Case Study 6: Sexually Transmitted Infections in HIV+ Teens
- **Objective**: describe the prevalence of sexually transmitted co-infections
- **Design**: prospective cross sectional study
- **Population**: HIV+ teens
- **Procedures**: questionnaire, blood tests, cultures
Case Study 6: Right to Consent to Treatment and Research
- Majority of teens at CHOP attend HIV clinic without their parents
- Permitted to consent to diagnosis, prevention or treatment of HIV on their own
- Those who obtain care without their parents are not children and may consent to participate in the study

Case Study 7: Phase II Trial of Monovalent H1N1 Vaccine in HIV+ Children and Youth
- **Objective**: immunogenicity and safety of influenza vaccine in HIV+ children & teens
- **Design**: open-label clinical trial
- **Population**: HIV+ children & teens
- **Procedures**: FDA-approved vaccine (unapproved indication), blood tests

Case Study 7: Right to Consent to Treatment and Research
- If children attend clinic with their parents, then Subpart D applies
- Teens who obtain care for HIV without their parents permitted to consent to a clinical trial related to HIV
- Influenza is a reportable disease in PA
- May participate in clinical trial of influenza vaccine without parental consent
Outline

- Cost of Doing Business in the Pharmaceutical World
- Distribution of Clinical Trials
- Efficiencies Using The Pyramid
- What are Metrics - What are their Values?
- Different Types of Metrics
- Working Smarter
  - Using METRICS to Manage Investigator Performance
  - Using LEADING QUALITY METRICS to Manage Investigator Performance
  - Move to Increased METRIC UTILIZATION
- Metrics Champion Consortium
- Summary
Cost of Doing Business in the Pharmaceutical World

- **R&D Global Spending**
  - 2002 = $69 Billion
  - 2010 = $127 Billion
  - 17% of total sales

- **Drugs in Active Development**
  - 1995 = 5,000
  - 2010 = 9,600

- **Industry Launches**
  - 2002 = 47
  - 2008 - 2012 = 37

- **Mean Cost per Patient** *
  - Phase I = $19,345
  - Phase II = $14,703
  - Phase III = $12,852
  - Phase IV = $6,254

- **Cost to develop a new drug (including Phase IV)** ** = $1,129 BILLION (2010 US$)

- **Average time** from idea to FDA approval = **12.4 YEARS**

- **Attrition Rate** from FIH → Approval = **85%**

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*Parexel Biopharmaceutical R&D Statistical Sourcebook 2011-2012

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*2003 Tufts Center for the Study of Drug Development Analysis, DiMasi et al.

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**Distribution of Clinical Trials**

<table>
<thead>
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<th>PII</th>
<th>PIII</th>
<th>PIV</th>
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<td>64%</td>
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<td>US – based</td>
<td>6,000</td>
<td>14,000 (96% → 54%)</td>
</tr>
<tr>
<td>Non-US – based</td>
<td>hundreds</td>
<td>12,000</td>
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</table>

*Parexel Biopharmaceutical R&D Statistical Sourcebook 2011-2012

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*2003 Tufts Center for the Study of Drug Development Analysis, DiMasi et al.
Efficiencies using ‘The Pyramid’

What it takes to get the job done!!

$
What are Metrics - what are their Values?

What are metrics:
Snapshots in time which show performance in chosen areas

What are their values?
- Give the ability to compare in a consistent manner
- Help to identify trends
- Promote metric-based communication
- Offer a competitive environment

Different Types of Metrics

**SOFT**: difficult to define in a number (quality, hidden value...)

**Vs.**

**HARD**: easily defined in a number (# of days, $ per item...)

**LAGGING**: reporting what happened yesterday (# of those who attended; last year’s budget spend...)

**Vs.**

**LEADING**: reporting what is happening now - based on ‘cause & effect’ (customer satisfaction survey)

WORKING SMARTER!

Using **METRICS** to
Manage Investigator Performance
Site Performance Metrics

- **Operational**
  - Start-up cycle time (contracts, IRB approvals, etc.)
  - Screening, randomization and dropout rates

- **Quality**
  - Protocol deviation scores
  - AE reporting: time from investigator awareness to report to sponsor
  - Data query responsiveness
  - Process compliance

- Both categories are important for assessing and improving performance

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Operational Metrics

- **Money Spent**
- **Time Spent**
- **Enrollment**

Compare to expectations or industry benchmarks to keep projects on track and on budget.

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Quality Metrics: Process Compliance

- Check the box
- Take the course
- Read and apply
- Pass the test
- Review the document
- Approve the document
- File the document

% Completed
% Completed on Time
% Passed / Failed
% Missing

Document compliance with regulatory expectations
Using Metrics for a Holistic Look at Performance

- Total # of protocol deviations
- Total # of protocol deviations divided by # of patients
- Days from subject visit to data entry
- Actual and Planned
- Screened vs. enrolled

Historical Data: Lagging Metrics

Question: How well did site perform on a study? How well might they perform on the next study?

Best Use:
In site selection as predictor of future good performers or to avoid poor performers

Caveat:
Site performance data must be considered relative to the performance of other investigators in the same study and/or geographic profile.

WORKING SMARTER!

Using LEADING QUALITY METRICS
to Manage Investigator Performance
Leading Quality Metrics

Question: How well is someone performing on our study?

The best quality metrics on site performance are leading indicators to ensure:
1. Site is protecting patient safety
2. Site is in compliance with protocol
3. Site is producing quality data

Leading quality measures are detection mechanisms, used to prevent further degradation with quick action and remediation.

The Quality Management Process

Plan. Identify the factors that are critical to quality and determine metrics
Do. Conduct clinical trial
Check. Use CTQ metrics to monitor performance
Act. Identify cause of deviation and take action to improve quality

Plan: What is ‘Critical to Quality’?

The key measurable characteristics of a process whose performance standards or specification limits must be met in order to satisfy the customer
**Do: Conduct Clinical Trial**

In process monitoring of "critical to quality" measures

**Check and Act: Control Plan**

**Example**

<table>
<thead>
<tr>
<th>Critical to Quality</th>
<th>Threshold</th>
<th>Unit of Measure</th>
<th>Who Will Record</th>
<th>How Often Recorded/Where</th>
<th>Who Responds</th>
<th>What Will They Do</th>
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</thead>
<tbody>
<tr>
<td>Subjects have signed updated ICD</td>
<td>1 missed consent</td>
<td>Eligible Subject</td>
<td>Monitor</td>
<td>At each monitoring visit</td>
<td>Monitor</td>
<td>Retrain site on ICD process; escalate as necessary</td>
</tr>
</tbody>
</table>

Predetermine what will be measured, what are limits and what action is taken

**WORKING SMARTER!**

Move to Increased Metric Utilization
Our mission is to help sponsor and service provider organizations industries improve their overall clinical trial development processes through the utilization of MCC standardized clinical trial performance metrics (time, cost & quality) by:

• Supporting the ongoing collaborative development of standardized performance metrics and process improvement tools
• Encouraging the continuous implementation of the metrics and tools among MCC members
• Providing a collaborative learning environment for members to share best practices, discuss challenges and industry trends
• Offering live and online educational opportunities to support the use of performance metrics and tools in member organizations

Summary

• Increasing R&D costs require greater efficiency
• Metric utilization expanding in management of clinical trials
• Can look at operations but also quality
• Leading metrics afford the opportunity to intervene and influence
Bertha deLanda, CIP
IRB Training Specialist
April 2012

Stanford University –
Post-approval Monitoring

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Overview - Stanford University IRB

STANFORD HRPP mandates:

- **Training** requirements (CITI, SIR, etc.)
- **Support and education** (Research Compliance Office, Stanford Clinical and Translational Education and Research, Stanford Cancer Institute)
- **Periodic reviews** (Results of reviews can be sent to the IRB)
Examples of Post Approval Monitoring

A. Consent Form Review
   • Documentation and signature

B. Consent Observations
   • Observation of consent process between prospective participants and Person Obtaining Consent (POC)

C. Sponsor-Investigator Research (SIR) Review
   • Review of studies where Stanford Investigators hold IND or IDE

“ALCOA” Review Standards

A – Attributable: accountability
L – Legible
C – Contemporaneous: temporally documented; “of the present time” and not long after the fact
O – Organized
A – Accurate

A. Consent Form Review

• Schedule time to meet with investigator
• IRB Staff looks for:
  • Participants’ or LARs’ signature/dating of:
    o Consent Form
    o HIPAA Authorization
  • Approved text, correct approval/expiration dates, Person Obtaining Consent (POC) signature
• In-person reviews provide opportunities to:
  • reinforce the available resources
  • educate research group on compliance requirements (HRPP, GCP, …)
Consent Form Reviews

Focus on:

- Approval/expiration dates on signed informed consent forms were the same as those on the IRB-approved form
- Text on signed consent forms was the same as approved language
- HIPAA authorization was dated/signed
- Person obtaining consent (POC) signature was obtained
- Consent forms were organized/easily retrievable

B. Consent Form Observations

IRB staff observes the consenting process to determine whether:

- Informed consent process is appropriately conducted and documented
- Participant is provided sufficient time to consider participation
- No evidence of coercion during the consenting process
- Info presented reflects content of the consent form and is conveyed in understandable language

Consent Observations

Focus on:

- Modifications were reviewed and approved by the IRB prior to implementation
- Latest version of consent form was downloaded from the electronic protocol system (best practice)
- Potential participants were given a copy of the consent form during the consent discussion so they can keep pace with the conversation
Tools – Consent Observations

- Checklists and procedures are provided to staff and investigator

<table>
<thead>
<tr>
<th>Observation</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the consent form the most recent IRB-approved version?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PIC mention that the study involves &quot;research&quot;?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PIC describe the study procedures (following the consent document)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If study involves an unapproved agent (e.g., not FDA approved), does the PIC explain why?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PIC exist and sufficiently answer questions?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C. Sponsor/Investigator Research (SIR)

- **Periodic** review of each study
- **Cancer Center** performs reviews for Cancer Center studies
- **CQI** (Continuous Quality Improvement) performs reviews of non-cancer studies
- Both entities use the same review document; follow the same criteria
- **Documentation and procedures** are reviewed

Documentation Expectations - Examples

- Correspondence/Communications between investigator and:
  - FDA
  - IRB
  - Study Team
  - Monitors or Contract Research Organization
Procedural Expectations - Example

- Delegation of Authority for Dispensation of Drug

Delegation of Authority lists investigator as performing dispensation.

Dispensation Log states research coordinator performed dispensation.

SIR Reviews
Focus on:

- Documentation of Investigator qualifications (e.g., training, licenses, financial disclosure forms)
- Organization of records
- Implementation/process
- Submission of protocol modifications to the IRB and/or FDA, when necessary
- Adherence to GCP

Tools – SIR Reviews

Checklists are provided for staff/investigator

SIR/IND Checklist:
- basic info
- required documentation
- qualifications of investigators
- reporting/monitoring requirements
- etc.

http://pronto.dxcathabs.gov/foaa.htm
Cut – Click to follow link
Good Practices for Post Approval Monitoring Review

- Reinforce resources
- Provide job aids and checklists - add hyperlinks to the regulations and/or HRPP
- Provide feedback about the reviews
- Emphasize the need for readiness for external inspections
  - Share examples of corrective action plans/warning letters
Barbara N. Hammack, PhD  
Research Subject Advocate

Post Approval Monitoring

Colorado Clinical and Translational Sciences  
Institute Organizational Pillars

- Child and Maternal Health Research
- Community Translation
- Discovery Translation Research CTRCs CTOs BERD Regulatory Knowledge & Support
- Translational Research Informatics
- New Methods and Technologies Pilot Projects Translational Technology Cores New Methods
- Education, Training and Career Development
- Evaluation and Tracking

Affiliated Institutions

- UCB
- UCD Denver
- NJH
- Anschutz
- UCH & CHC
- Denver Health
- VAH
- KP
**Active CTRC Protocols by Site**

- Year 4 projected: 425 Yr. 4 Protocols

**CTRC Outpatient Visits by Site**

- Year 4 projected: >25,000 Yr. 4 Outpatient Visits

**CTRC Inpatient Visits by Site**

- Year 4 data projected

*Note: Year 4 data projected*
Distribution of CTRC Investigators

- Biochem
- Exercise
- PT
- Anesthesia
- CV
- Pharmacol
- Diabetes
- Endocrine
- Gastro
- Allergy
- Anesthesia

Percent of Investigators (n=293)

- Genetics
- Allergy
- Behavior
- Nutrition
- Psychology
- GI
- Immunology
- HIV
- Liver
- Nephrology
- OB-Gyne
- Pulmonary
- Otolaryngology
- Psych
- Urology
- Nursing
- Eye
- CAM

Structure of CTRC Network

- Controlled environment
  - Inpatient units/outpatient clinics
- Clinical Services/ Nursing
- Core Laboratories
- Bionutrition
  - Metabolic kitchen
- Informatics
- RSAs

RSAs

- Champion the mission of the safe and ethical conduct of human subject research within the CCTSI.
  - RSA role was defined and incorporated only recently (2001)
- Dual role
  - Monitoring
  - Subject advocacy
    - Ensure participants have full understanding of what is clinical research, the risks involved, and their rights as volunteers.
    - Serve as objective witness to the consent/assent process
RSA Involvement During Life of Study

- Work closely with CCTSI investigators in study design, Data and Safety Monitoring Plan, approval, and oversight.
- Members Scientific Advisory & Review Committee
- Oversight IRB submission process
- Address safety and human subject issues at preliminary PI meeting
- Provide training and education for research participants, parents, investigators and co-investigators, study coordinators, and CTRC staff members.
- Research participant advocacy
- Rounds on Pediatric/Adult Inpatient Units
- Policy development related to the protection of human research subjects for review by Oversight Committee

Relationships

Post Approval Monitoring Goals

- Enhance protection of research subjects
- Serve as resource for investigators and participants
- Enhance regulatory compliance
- Enhance education program
Vulnerable Research Populations

- Pediatrics
- Pregnant women
- Cognitively impaired
- Substance abuse
- Nursing home residents
- ICU patients

Risk Assessment by Site and Role of RSA

University Hospital
- Adult; various populations
- Liaison to IRB
- Study Monitoring Committee
- Observe consent process

Children’s Hospital Colorado
- Vulnerable population
- Rounding daily
- DSMB boards
- PI monitored

University of Colorado Boulder
- Adults; normal healthy controls
- Safety Monitoring Committee
- RSA liaison to Boulder IRB

National Jewish Health
- Mostly adults
- Lung disease – asthma, COPD
- Bronchoscopies
- DSMB

RSA Resources - Summary

- Safety monitoring committees
- DSMB boards
- PI meetings
- Participant advocacy
  - Rounds, brochures
  - Liaison role with IRBs, oversight committees, nursing, core labs
- CTRC website
  - Research participants/investigators/study team members
  - Policies/procedures
  - Educational materials/references, virtual tours
- Required to report SAEs to NCRR
David Rickaby, Ph.D.
Research Compliance Officer

Post-approval Monitoring in the Department of Veterans Affairs

VA Research Program: Overview

VHA Office of Research & Development

Establish Policy
- R&D Series of Handbooks:
  - Human Protections
  - Animal Care and Use
  - Laboratory Safety

Fund
- Biomedical Laboratory R&D
- Clinical Science R&D
- Health Services R&D
- Rehabilitation R&D
All protocols must be audited once...

...and at least once every 3 years.
**GCP-HRPP Audit Tool**

**Informed Consent Actions**
- Revisions approved
- IRB stamp on forms
- Re-consent if needed

**SAEs, UPRs, DMC Reports**
- Event, date, subject ID
- Reported to the IRB
- Categorized by IRB
- Reported to ORO

**Staff Qualifications/Training**
- Training up-to-date
- Before participation
- Scope of Practice on file

**Subject Record Review**
- 10% (10 min, 30 max)
- Consented prior to study
- Inclusion criteria met
- Exclusion criteria met

**Informed Consent Audit Tool**
All signed consent forms...

...must be audited.
Informed Consent Elements

For Each Consent Form (by Subject ID number):

- Was signature & date of POC present?
- Was date of subject signature present?
- Was signature of subject present?
- Was correct version of the ICF used?

Audit Reports

- Routine reporting by RCO to the IRB and IO
- Reporting "apparent" serious or continuing non-compliance
  - by RCO to the IO and IRB within 5 days
  - by IO to ORO within 5 days of notification
  - IRB evaluates, makes determination
- Annual Summary Report to ORO
Findings (2010): Informed Consent

For 89,216 consent forms from 3,563 protocols:

- Incorrect consent form used: 2.4%
- Not signed/dated by subject: 0.22%

Findings (2010): Triennial Audits

For 2,102 protocols audited at 107 VA Hospitals:

- Initiated prior to IRB approval: 0.14%
- Halted for safety or PI concerns: 2.8%
- Serious/unexpected/related AEs: 25 events
Findings (2010): Triennial Audits
For 1606 protocols requiring continuing review:

- Lapse in IRB continuing review: 6.0%
- Continued activities during lapse: 0.32%

Findings (2010): Triennial Audits
For 11,387 subject case histories reviewed:

- Procedures initiated before consent: 2.2%
- No inclusion/exclusion documentation: 2.4%

Findings (2010): Triennial Audits
For 6,787 research staff members:

- Working without Scope of Practice: 7.6%
- Working outside Scope of Practice: 0.15%
- Required training not current: 5.9%
“With Thanks…”

VA research is possible because of the participation of thousands of Veterans across the country. Their partnership with us has resulted in new diagnoses, treatments and cures that contribute to the good health of fellow Veterans and the community at large.

We are deeply grateful to every Veteran who has participated in a clinical research study.