Vulnerable Populations

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Vulnerable Populations

Who, why and how

Anne Salter, PhD
Who are vulnerable populations?

- In Clinical Trials, people who need special protection to be included as subjects
- Prisoners; Children; Pregnant women and their unborn child; Mentally ill.
- Each group is different.
Prisoners as Subjects
Prisoners

- Federal regulations identify prisoners as vulnerable subjects in need of additional safeguards.
- Prisoners may only be used for research that is material to their lives as prisoners. They may not be used as a convenient population for experimentation. The campus IRB includes an advocate for prisoners as required by federal regulations.
- If a research subject becomes a prisoner during the course of a study, all the special protections and review procedures apply.

http://www.ors.duke.edu/irb/vulnerable/prisoners.html
Drug testing on prison inmates was common until the early 1970s, until revelations of unethical testing, abuse and mistreatment came to light, at which point the practice was stopped and new legislation imposing tight restrictions was passed in 1978.

Prisoners have suffered egregious physical and psychological abuses in experiments that held no promise of treatment. For example, prisoners’ testicles were irradiated in experiments conducted by the Atomic Energy Commission. Prisoners have been used in lieu of animals to test cosmetic products.

http://video.on.nytimes.com/index.jsp?fr_story=350ed2566d929c050153e63a6547e1342538707b

This website has a video to view about the history of abuse with prisoners in clinical trials.
Who is a prisoner?

Defining a Prisoner

"Prisoner" means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

http://www.ors.duke.edu/irb/vulnerable/prisoners.html
What is allowed?

study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults). For research funded by NIH, "the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his intent to approve such research"; or

research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well being of the subject. For NIH funded researcher, "in cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of the intent to approve such research."

http://www.ors.duke.edu/irb/vulnerable/prisoners.html
Protection of prisoners

any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

the risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;

procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

the information is presented in language that is understandable to the subject population;

adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

http://www.ors.duke.edu/irb/vulnerable/prisoners.html
Prisoners and AIDS


**OBJECTIVE:** Is the enrollment of *U.S. prisoners in AIDS-related clinical trials feasible, legal and ethical?* Why does the virtual moratorium on such research persist? What is the experience of clinical researchers who have enrolled prisoners in clinical trials?

**DISCUSSION AND CONCLUSION:** U.S. prisoners are barred on an official or de facto basis from clinical trials in all federal and most state prisons. Research which meets federal safeguards should be open to prisoner enrollment. *Providing access to clinical trials is a component of providing first-rate care to prisoners living with AIDS/HIV.* The underrepresentation of ethnic minorities and IV-drug users in AIDS-related clinical research, and their disproportionate presence in U.S. prisons, makes the inclusion of prisoners in clinical trials valuable to researchers seeking comprehensive data on treatments for this disease.
Mentally incapacitated history of abuse

From 1956 through 1971, residents at the Willowbrook State School for Children with Mental Retardation were infected with live hepatitis in order to develop a vaccine. Parents gave permission for their children to participate in this study, often because it guaranteed acceptance into the overcrowded facility.

Sterilization of the mentally retarded
The Mentally Ill

• Federal regulations do not yet specifically address clinical trials among people whose mental status is impaired

• Who are the mentally impaired? People with substance abuse, mental illness such as schizophrenia, some conditions affecting mental capacities, such as Alzheimer's disease.

• Even subjects who are declared legally incompetent generally maintain their right to refuse participation in trials that involve no potentially beneficial diagnostic or therapeutic procedures.
Children as subjects

with thanks to Martha L. Cruz and Cigal Shaham
Historically, no children in drug development

- Only 20-30% of FDA approved drugs are labeled for pediatrics
- Many drugs carry disclaimers “Safety and effectiveness in pediatric patients have not been established”
- Pediatric care providers use drugs “off label” relying on medical judgment and experience
- So drugs were used anyway – why bother testing on children?
so why do we care?

- Inadequate dosing & failure to develop pediatric formulation
- Why? Children react differently to drugs; not enough to dose per weight
- For example, some children react with aggressive behavior to a popular drug for epilepsy – an adverse event not seen in studies on adults; and this drug has to be given at a higher-than-expected dose to be effective in kids under the age of five.
Just recently, non-prescription infant cold medications were recalled, because they were never tested on that age group.
Why have sponsors been reluctant to test drugs in pediatrics?

- **ECONOMICS**: high cost for trial and small market in children
- **DIFFICULT** recruitment and NON-compliance
- lack of appropriate infrastructure
- **ETHICS**
  - Federal regulations require that clinical trials involving children bear "minimal risk," which is interpreted as barrier to recruiting “healthy” children and adolescents into trials
- **LIABILITY**
  - Perceived risk of excessive legal liability from toxicity in children
Pediatric Research Equity Act of 2003 (PREA)

- Signed in December of 2003
- Mimics Pediatric Rule of 1999 that was overturned - outlines regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients
- Retroactive for all applications back to April 1, 1999
- Gives FDA clear authority to require pediatric studies of drugs when other approaches are not sufficient to ensure that drugs are safe and effective for children.
- Allows for waivers
  - studies are impossible or highly impracticable
  - therapy would be ineffective or unsafe
  - no therapeutic benefit
  - Small patient population
No abuse nor coercion of subjects
Risks to subjects just be minimized …
Risks are reasonable in relation to anticipated benefits
Selection of subjects is equitable
Informed consent sought and documented from each prospective subject
45 CFR 46 D: Children

Classify the trial into one of four risk categories to determine the rules: §46.404 to 46.407:

- §46.404: minimal risk & no direct benefit to subject
- §46.405: greater than minimal risk, but with direct benefit to subjects
- §46.406: greater than minimal risk & no direct benefit to subjects, but likely to yield generalizable knowledge about condition
- §46.407: research not otherwise approvable which represents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children
§46.404: Minimal Risk

Study does not have to benefit the patient

Minimal risk: risks a NORMAL, HEALTHY child would encounter in DAILY ACTIVITIES
§46.405: Greater than Minimal Risk, but with Direct Benefit to Individual Subjects (not as a group)
§46.406: Greater than Minimal Risk & No Direct Benefit to Subjects, but likely to yield Generalizable Knowledge about Disease or Condition

- Only “minor increase” over minimal risk
- Risks are equivalent to the risks **THESE CHILDREN** normally experience
- Knowledge gained must be of vital importance for understanding/ameliorating subjects’ condition
§46.407: Research not otherwise approvable which represents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

- A catch-all category for everything else
  - The IRB must say it fits into this category

- Requires approval by the Secretary of Health and Human Services, after consultation with panel of experts
How can we respect the rights of children in pediatric research?

Societal Protection: IRB approval

Parents: Consent – informed permission

Involve Children: Assent
This means...

- Informed Consent... for pediatric trials

- Parent(s)/guardian must give PERMISSION/CONSENT for their child to participate!

- Children (generally ages 7 to 12) must give child ASSENT to participate!
  - Silence / failure to object is not assent – children have to agree
  - There are exceptions to this rule: life-threatening illness

- Children 12 + give youth assent.

- Requirements for how and when are defined by each individual IRB
  - They consider the study population’s ages, maturity and psychological state

- Generally, children at least 7 years old with normal cognitive development can provide meaningful assent
Permission - parents

• “The agreement of parent(s) or guardian to the participation of their child or ward in research.”

• Who is a parent/guardian?
  – Biological parent
  – Adoptive parent
  – Someone who is authorized under state or local law to consent on behalf of a child to general medical care

• How many parents?
  – one parent: minimal risk (46.404) and more than min. risk with direct benefit (46.405)
  – two parents: more than min. risk, no direct benefit (46.406) and research not otherwise approvable (46.407)
Special Assent Forms

- Permission/Consent
  - Since the language of adult forms have to be at most at an eighth grade reading level

- Assent for Youth (12+)
  - Subjects 12 years old and older

- Assent For Children (7-11)
  - Use most simple language possible, images, etc.
No assent is needed if...

- The child is incapable of participating
- The proposed treatment "holds out a prospect of direct benefit that is important to the health or well-being of the child and is available only in the context of the research." (for example, in a recurrent cancer where standard treatment is known to have poor results – and a new promising drug is only available through a clinical trial)

But parent permission is still needed.
AIDS treatment

- between 16 and 22 percent of pediatric AIDS patients were children in foster care in 1989 – most born to parents using drugs
- at that point, most state laws allowed only for “standard medical treatment” for children in foster care
- however, no standard treatments for HIV-infected children existed, so there wasn’t much care for them.
- in states that had a mechanism for foster children to enroll in clinical trials, many required biological parents’ signature.

source: http://www.hhs.gov/ash/testify/t050518.html
Ward of state

- Additional protections for children who are wards of the State or any other agency, institution, or entity.
- Two categories of research or clinical investigations:
  - 1) research or clinical investigations that involve greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research or clinical investigation (research/clinical investigations approved under 45 CFR 46.406 or 21 CFR 50.53); or
  - 2) research or clinical investigations determined by the IRB not to meet the conditions of the HHS regulations at 45 CFR 46.404, 46.405, or 46.406, or FDA’s regulations at 21 CFR 50.51, 50.52, or 50.53, but found to present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children (research/clinical investigation approved under 45 CFR 46.407 or 21 CFR 50.54).
Before children who are wards of the State or any other agency, institution, or entity can be included in either of the two categories of research or clinical investigations described above, the research must meet the following conditions:

- the research must be either related to the children’s status as wards; or conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards; and
- the IRB must require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis.

One individual may serve as advocate for more than one child, and must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child’s participation in the research. The advocate should represent the individual child subject's interests throughout the child's participation in the research. The HHS and FDA regulations further require that the advocate not be associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.
Lesson Learned

- Pharmacokinetics are more variable than anticipated
- Adverse reactions that are pediatric specific are being defined
- Trial designs are being modified as more is learned from submitted studies
- Ethical issues have to be reassessed from the pediatric perspective
Recruitment: Perceived problems - parents

- Fear of harming or hurting child
- Objections to using children as “guinea pigs”
- Time required to participate in trials
- Interference with school
- Transportation issues
- Language barriers
Recruitment: Perceived Problems by the Child

- Fear of procedures
  - Blood draws/ staying overnight at the hospital

- Fear of being stigmatized by classmates/friends/family
  - Child does not consider herself “sick”
  - Child does not like to be identified as being “overweight” and “needing” help
Recruitment

Would you allow YOUR child to participate in a Clinical Trial?
Pregnancy and in-utero babies

I don’t want to take any medications while pregnant.

There’s a problem, you need to take XXX.
Need for research for treatment of problems during pregnancies

- Few prescription drugs are specifically labeled for use during pregnancy
- Most women take at least one prescription drug during a pregnancy
- Pregnant women react differently to drugs than non-pregnant women
- Unknown effects on fetus
Why is it different?

• Changes in absorption, distribution, metabolism and elimination of drug during pregnancy
• Fetus and placenta also active ‘management’ of the drug
• Fetal susceptibility to the drug varies based on gestational age
So what do we study?

- Which drugs to study?
- Who should be studied (all pregnant women? The ones needing a similar drug?) and when in their pregnancy?
- What effects should we look at?
- How should we obtain data?
Which drugs?

- Ones treating complications/problems of pregnancy only (e.g. Spina Bifida detected in utero)
- Ones treating problems often occurring during pregnancy (e.g. nausea in 1st trimester)
- Ones that are used to treat conditions often encountered in women of child-bearing age (e.g. migraine)
- Known teratogens should be excluded

When?

- Drug safety demonstrated in rest of population
- Potential significant therapeutic use for pregnant women specifically
- Not expected to pose undue risk to unborn child

On whom?

- Women having this condition and needing treatment
- Not healthy pregnant women
- Look at post-partum data as well
§ 46.204 Research involving pregnant women or fetuses (full text)

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

(c) Any risk is the least possible for achieving the objectives of the research;

(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

(j) Individuals engaged in the research will have no part in determining the viability of a neonate.
(a) Previous research has been done, including studies on nonpregnant women, to assess potential risks
(b) Either of these: prospect of direct benefit to woman or fetus, or risk no greater than minimal.
(c) Any risk is the least possible for achieving the objectives of the research;
(d) Proper informed consent for woman.
(e) If possible direct benefit solely to the fetus, consent by both parents (unless rape or incest)
(f) Informed of reasonably foreseeable impact of the research on the fetus or neonate;
(g) If pregnant child, assent and permission obtained.
(h) No inducements to terminate pregnancy
(i) Researchers make no decision about terminating pregnancy (timing, method, or procedures)
(j) Researchers will have no part in determining the viability of a neonate
The fetus as a subject

• Only two circumstances when this is ethical
  • 1. to promote life or health of fetus
  • 2. to give the mother information regarding the health of the fetus so she can make decisions regarding treatment and or termination of pregnancy
Questions?
**Consent Requirements for Medical Treatment of Minors**

<table>
<thead>
<tr>
<th>IF MINOR IS:</th>
<th>Is parental consent required?</th>
<th>Are parents responsible for costs?</th>
<th>Is minor's consent sufficient?</th>
<th>May M.D. in minor's name treat without parental consent?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmarried, no special circumstances</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Unmarried, emergency care and parents not available [Business and Professions Code § 2397]</td>
<td>No</td>
<td>Yes</td>
<td>Yes, if capable</td>
<td>Yes</td>
</tr>
<tr>
<td>Married or previously married [Family Code § 7002]</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Emancipated (declaration by court, identification card from DMV) [Family Code §§ 7002, 7050, 7140]</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Self-sufficient (15 or older, not living at home, manages own financial affairs) [Family Code § 6922]</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Not married, care related to prevention or treatment of pregnancy, except sterilization [Family Code § 6925]</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Not married, seeking abortion</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Not married, pregnant, care not related to prevention or treatment of pregnancy and no other special circumstances</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>On active duty with Armed Forces [Family Code § 7002]</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>12 or older, care for communicable reportable disease or condition [Family Code § 6926]</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Probably Yes</td>
</tr>
<tr>
<td>12 or older, care for rape [Family Code § 6927]</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes, usually</td>
</tr>
<tr>
<td>Care for sexual assault [Family Code § 6928]</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes, usually</td>
</tr>
<tr>
<td>12 or older, care for alcohol or drug abuse [Family Code § 6929]</td>
<td>No²</td>
<td>Only if parents are participating in counseling</td>
<td>Yes</td>
<td>Yes, usually</td>
</tr>
<tr>
<td>12 or older, care for mental health treatment, outpatient only [Family Code § 6924]</td>
<td>No</td>
<td>Only if parents are participating in counseling</td>
<td>Yes</td>
<td>Yes, usually</td>
</tr>
<tr>
<td>17 or older, blood donation only [Health and Safety Code § 1607.5]</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes, usually</td>
</tr>
</tbody>
</table>

¹ Special requirements apply. See Chapter 2 of the Consent Manual or Chapter 4 of Minors & Health Care Law.

² Parental consent is required for a minor's participation in replacement narcotic abuse treatment using methadone or levoalphaetylmethadol (LAAM) program licensed pursuant to Health and Safety Code § 11875 et. seq. [Family Code § 6929(e)]

Reference: Welfare and Institutions Code § 14010

Minors are defined as all persons under 18 years of age.