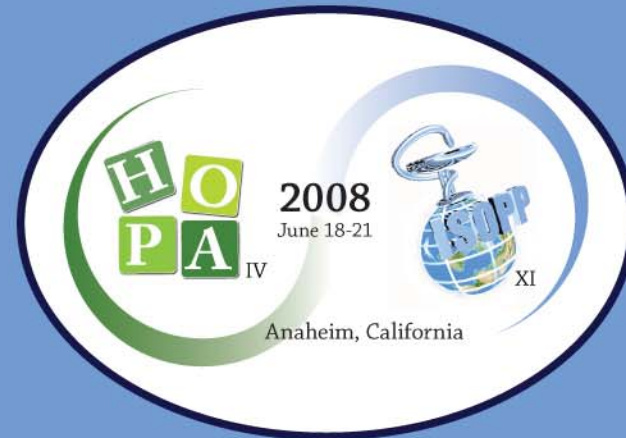


Ethics and Research

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Disclosure

- Jill Davis reports having no real or apparent conflicts of interest

What Is Research Ethics?

- There are four basic principles of research ethics
 - Research merit and integrity
 - Justice
 - Beneficence
 - Respect for persons

Research Merit and Integrity

- Proposed research must have scientific merit
 - Designed using methods that will achieve the aim
 - Based on thorough study of current literature as well as previous studies
 - Justifiable by its potential benefit
 - Designed to ensure respect for participants not compromised by the aims of research or the results
- The researchers who plan to carry out the research must have integrity
 - Persons with experience, qualifications and competence appropriate for the research

Justice

- Research that is just must:
 - Taking into account the scope and objectives of the research, the selection (inclusion/exclusion) of participants is fair and accurately described
 - Recruiting participants is fair
 - No unfair burden of participation on particular groups
 - Fair distribution of the benefits of research
 - No exploitation of participants
 - Fair access to the benefits of research
- Research outcomes should be accessible to participants in a way that is timely and clear

Beneficence

- The likely benefit of the research must justify any risks of harm or discomfort to participants. Benefit may be to the community
- Researchers are responsible for:
 - Designing the research to minimise risks and discomforts
 - Clarifying for participants the potential benefits and risks
 - Ensuring the welfare of participants
- Where the risk of harm is no longer justified by the potential benefits, the research must be suspended

Respect

- A recognition of a person's intrinsic value
 - Abiding by the values of research merit and integrity, justice and beneficence
 - Having due regard for the welfare, beliefs, perceptions, customs and cultural heritage, both individually and collectively of those involved in research
 - Respect the privacy and confidentiality of participants
 - Respect involves giving people the opportunity to make their own decisions
 - Where people cannot make their own decisions, empowering them where possible and protecting them as necessary

Ethical Framework

- In Australia we have two documents that are the basis of our ethical research principles. These are published by the NHMRC (National Health and Medical Research Council)
- National Statement on Ethical Conduct in Human Research – *updated 2007*
- Values and Ethics Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research – *published 2003*. The six values are: *spirit and integrity, reciprocity, respect, equality, survival and protection and responsibility*

Ethics and the Law in Research

- Research involving humans is subject to a variety of legal regulation at Federal, State, and Territory level
- Federal laws include those covering drugs, devices, privacy, health information, and intellectual property
- State and Territory laws regulate access to and the use of health information, consumer protection, and professional conduct
- Where both an ethical and a legal requirement apply, the legal requirement will prevail. When ethical guidelines require a higher standard than that is required by law, researchers should apply the higher standard

Common Ethical Issues

- Including non-English speaking participants
- Identifying potential participants
 - Use of databases
 - Searching medical records
- Genetic testing
- Research where participant consent is not possible eg, children, non-competent adults, emergency situations
- Use of placebo
- Use of a suboptimal control arm

Common Ethical Issues *continued*

- Publication policy
- Research into illegal activities
- Research with no benefit for participants
- Financially reimbursing participants
- Consent to future use of data and tissue in research
- Monitoring of approved research
- Discontinuance of a trial
- Indemnity and insurance

Research, Low Risk, or Quality Assurance

- Research and quality assurance (QA) activities form a continuum and attempts to clearly separate them are difficult and can be artificial and unhelpful
- What really matters is:
 - QA is undertaken for a valid purpose and its outcomes are used to improve health care
 - Those who undertake QA adhere to relevant ethical principles and legislation
 - Where QA proposals could infringe ethical principles that guide human research, independent ethical scrutiny of such proposals should be sought

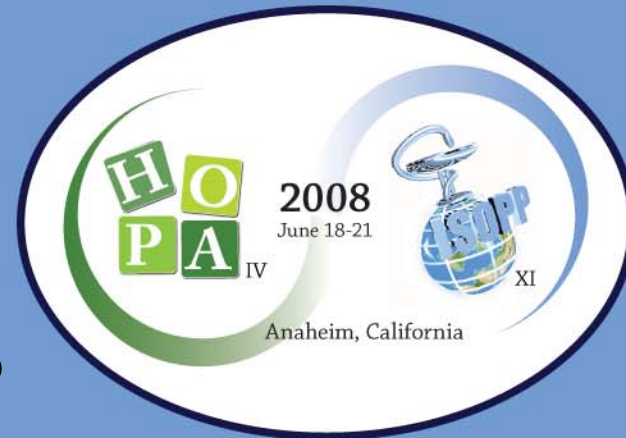
Categories of Proposals

- Research – high risk eg, any drug trial
- Research – low risk eg, study with minimal risk or burden to participants (including the institution)
- QA – high risk eg, an evaluation of a diagnostic technique that requires an extra blood sample; home phone contact to follow up on discharge counseling
- QA – low risk eg, an anonymous patient satisfaction survey of a clinical pharmacy service

So, What Studies Need HREC Review?

- The division between QA and research is very subjective and non-specific. It is just not possible to give a definitive description – all projects will need to be individually assessed
- Each HREC/ IRB needs to define those activities that they consider make a proposal subject to ethical review – whether this be via a full HREC, a sub-committee of the HREC or via an expedited review process
- If it is intended to publish the data collected, it is recommended that the proposal be submitted for ethical review since this is a requirement of many publishers
- Most HRECs will NOT grant retrospective approval

Ethics and Research



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Disclosure

- Mark Holdsworth, PharmD, has no real or apparent conflicts of interest to report

History of Human Subjects' Violations

- Nuremberg trials – 1948
- Tuskegee USPHS syphilis study – 1932-72
- Willowbrook – 1950s
 - “With Tuskegee and Willowbrook, continued deprivation became self-fulfilling; by taking advantage of subjects’ predicament, scientists became accomplices to the problem rather than observers of it”

USPHS = United States Public Health Service.

Alexander L. *N Engl J Med.* 1949;241:39-47; Brandt AM. *Hastings Cent Rep.* 1978;8:21-9;

Rothman DJ. *Hastings Cent Rep.* 1982;12:5-7.

Contemporary Sentinel Ethical Events in Human Subjects Research

- Protocol 126 and “The Hutch” – 1981-93
- Jesse Gelsinger – 1999
- Jolee Mohr – 2007

Ethical Framework

- World Medical Association Declaration of Helsinki
 - Based upon Nuremberg code with 2 additions:
 - That interests of subject have a higher priority than those of society
 - That every subject in research should receive the best known treatment
- Belmont Report – based upon 1974 US National Commission for Protection of Human Subjects of Biomedical and Behavioral Research
 - Recommended establishment of IRBs

Ethical Framework

■ Belmont principles

- (A) Autonomy – respect for persons
 - Providing the necessary information for a subject to make an informed decision
 - Additional protections for those with diminished autonomy
- (B) Beneficence – treating persons in an ethical manner; maximizing benefits and minimizing risk
- (J) Justice – fair distribution of benefits and burdens
 - Don't target certain groups because of easy availability, compromised position, or manipulability

IRB Review Criteria

- IRBs determine that the following are satisfied:
 - Risks to subjects are minimized – B
 - Risks are reasonable in relation to benefits – B
 - Subject selection is equitable – J
 - Informed consent is obtained – A
 - Research plan monitors data to ensure safety – B
 - Adequate provisions for privacy/confidentiality – B
 - Additional safeguards are in place for vulnerable populations – A, B, J

IRB Submission Process

- Exempt research – must fall into specific categories (usually retrospective reviews with no identifiers)
 - Even at this level, apply to the IRB before performing research
- Expedited – no > minimal risk and specific categories
 - Minimal risk – above that encountered by a healthy person in normal daily life
- Full review – > minimal risk or research that doesn't meet exempt/expedited

IRB Oversight

- Humanitarian device exemptions
- Emergency use of investigational drug/device
- Pilot studies and some case studies (check if $n > 2$)
- Data and biospecimen repositories in which identifiable information is being retained
- Most IRBs have become the de facto entity responsible for enforcing HIPAA

Submission Requirements

- Most IRBs require some investigator training
 - May be online (eg, CITI)
- Additional review
 - Departmental scientific review
 - COI committee review
 - Radiation subcommittee
- Paperwork requirements
 - Application, protocol, consent/HIPAA forms

Submission Requirements

- Key information in an IRB application:
 - Details re: subject population, enrollment #s and vulnerable populations
 - Details re: methodology: randomization, # of visits, description of assessments (eg, copies of surveys)
 - Description of standard of care
 - Details re: privacy and confidentiality
 - Documentation for INDs and IDEs
 - DSMP for > minimal risk studies

IRB Problems

- Turnaround time
- Expertise
- Independence?
- Focus of reviews
 - Consent form wording vs consent process
- Inability to alter design of multicenter studies
 - No clearinghouse of data from IRB rejections
- Central IRBs – to decrease variability
 - ? Vulnerability to influence/domination
- Consent forms – ↑ in length/complexity but without any analysis of how this impacts the subject

Dilemmas in Clinical Research

- Dual roles of clinician and researcher
 - May compromise a patient's care by tolerating or rationalizing certain research activities
- Therapeutic misconception
 - Belief by a patient or researcher that the purpose of clinical research is to benefit the patient
 - Clinical research goal – develop generalizable knowledge to improve future medical care
 - Clinical care – promote best interests of patients by providing best known standard care

Dilemmas in Clinical Research

Concept	Definition	Ethical Significance	Example
Therapeutic Misconception	The research subject conflates research with clinical care	<i>Rarely</i> tolerable because understanding the nature of research is necessary for an autonomous decision to participate in research	Mark believes that the purpose of the Phase 1 cancer trial is to help him personally
Therapeutic Misestimation	The research subject underestimates risk, overestimates benefit, or both	<i>Sometimes</i> tolerable because understanding the exact probability of harm and benefit may not be necessary for an autonomous decision to participate in research	Susan estimates that she has a 30% chance of benefit in the Phase 1 cancer trial. A meta-analysis of similar studies shows that benefit accrues to 5% of subjects
Therapeutic Optimism	The research subject hopes for the best personal outcome	<i>Always</i> tolerable because hope does not compromise the autonomy of a decision to participate in research.	Thomas hopes that he will be one of the 5% who benefit from the Phase 1 cancer trial

Dilemmas in Clinical Research

- Privatization of science
 - Research outcomes
 - Publication of results – positive > negative
 - COX-2 inhibitors
 - Pediatric SSRI data
 - Disclosure of results – during vs after trials
 - COIs – eg, economic studies of oncology drugs
 - Industry sponsored studies less likely to report unfavorable results (1/20 vs 9/24)
 - Industry sponsored studies not more likely to exaggerate results (6/20 vs 3/24)

Dilemmas in Research

■ Injuries

- Subjects/insurers often required to pay costs
- In the US, research subjects are more likely to be uninsured

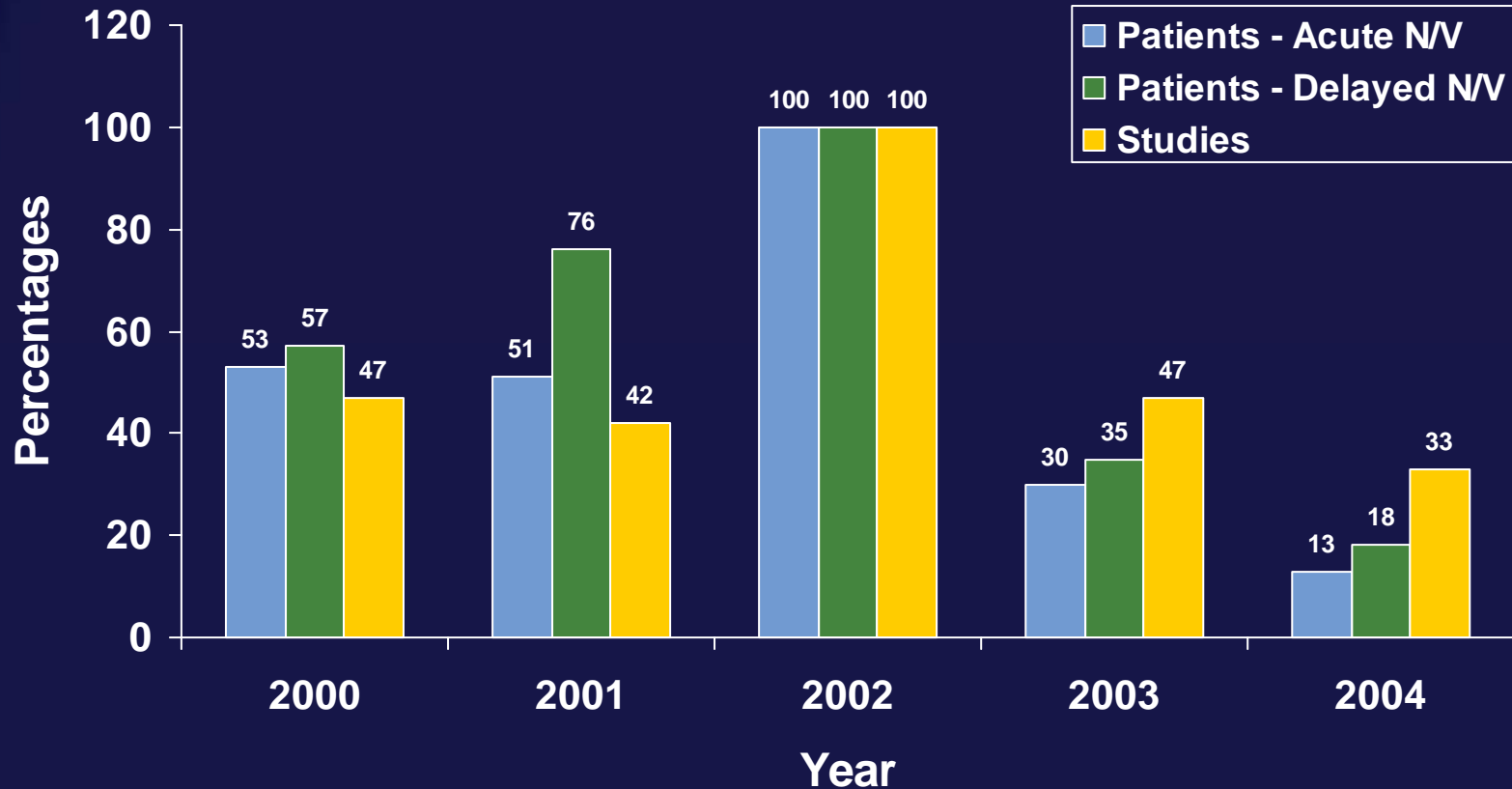
■ Exclusions

- Women – especially pregnant women
- Children
 - Majority of drugs without FDA approved labeling
 - Incentives for pharma to conduct pediatric research are perverse
 - Patent exclusivity at end of product patent life
 - Requiring PK studies for agents in common use in pediatrics for >7 years (eg, ondansetron)

Contemporary Ethical Issues

- Use of placebos and suboptimal controls
 - Examples:
 - Studies of new bisphosphonates for osteoporosis vs placebos or vitamin D/calcium
 - Studies of new antidepressants vs placebo
 - Studies of new meds vs placebo with all other meds washed out for fibromyalgia patients
 - Chemotherapy-induced N/V (CINV) trials
 - Comparing newer agents vs placebo or vs suboptimal controls
 - Most common suboptimal control is failure to administer dexamethasone

CINV Trials



N/V = nausea/vomiting.

Holdsworth MT, Vo-Nguyen T. *Ann Pharmacother.* 2005;39:1903-10.

Placebo Controls in Asthma Research

Study	Subjects	Total Sample Size	Age Range, y	Mean FEV ₁ * at Study Entry, % Predicted	Study Arms	Trial Duration, wk
Lavolette, et al. (study 1)	History of at least 1 yr of intermittent or persistent asthma	642	15-78	72	(1) Beclomethasone dipropionate + montelukast sodium (n = 193) (2) Beclomethasone dipropionate (n = 200) (3) Montelukast sodium (n = 201) (4) Placebo (n = 48)	16
Kavuru, et al. (study 2)	History of asthma for at least 6 mo requiring therapy	354	12-70	64	(1) Fluticasone propionate + salmeterol (n = 92) (2) Fluticasone propionate (n = 92) (3) Salmeterol (n = 90) (4) Placebo (n = 82)	12
ZuWallack, et al. (study 3)	History of chronic asthma requiring therapy for 6 mo prior to enrollment	253	12-69	67	(1) Fluticasone propionate, 250 µg twice daily (n = 86) (2) Fluticasone propionate, 500 µg once daily (n = 83) (3) Placebo (n = 84)	12

Arguments for Placebo

■ Assay sensitivity

- To avoid attributing a placebo response to an active agent
- To show the actual response and to distinguish active from inactive treatments

■ Dosing

- To provide information on the lowest effective dose

■ Cost?

- To decrease the number of subjects that need to be studied

Research in Developing Nations

- Some recent research raises ethical concerns
 - Eg, short course zidovudine to prevent vertical transmission of HIV in Africa and Thailand
 - ACTG 076 not used as the control, but rather placebo
 - Double standard for research in developed vs developing nations?
 - Argued as justifiable since no treatment was available/affordable and therefore impractical
 - Modern day Tuskegee?

Study of Vulnerable Populations

■ Psychiatric patients

- Psychiatric symptoms can affect or impair informed consent
- When/if symptoms worsen, do such patients remain autonomous re: making appropriate decisions re: withdrawal?

■ Children

- When can children apply risk/benefit in making decisions?
- Can parents enroll children against their wishes?
 - Phase I?
- Are parents of very sick children also vulnerable?

Exempt vs Expedited Research

Case Study of a Problem

- CQI project by Johns Hopkins conducted at multiple hospital ICUs in Michigan
 - JH IRB judged the study to meet exempt criteria and didn't require informed consent
 - Evaluated impact of routine implementation of 5 evidenced-based procedures to reduce central line infections
 - Also implemented a checklist to ensure protocol adherence
 - Demonstrated major reduction in catheter-related infections from baseline

Exempt vs Expedited Research

Case Study of a Problem

- The problem:
 - Publication of the results triggered an OHRP investigation
 - OHRP claimed the project was human subjects research and that the IRB had “failed to ensure that the requirements for obtaining ... informed consent ... were satisfied.”
 - Should this project have undergone full or expedited IRB review instead?
 - Was informed consent required?

Exempt vs Expedited Research

Case Study of a Problem

■ Analysis:

- IRB determination of exemption was based on category of research involving collection/study of existing data
 - Not correct, as project employed a prospective design
- Expedited review could have been performed – posed no > minimum risk
 - Eg, collection of data through noninvasive procedures routinely employed in practice OR research involving data collected for nonresearch purposes
 - IRB could decide to waive informed consent in an expedited project
 - Would informed consent make sense for CQI research?

CQI Research and Informed Consent

- Arguments for consent waiver
 - Ethical purpose of consent is “to protect subjects from exposure to research risks that they have not agreed to”
 - CQI does not typically include experimental procedures – such projects can be conducted without research
 - Only component that is research is the systematic measurement of the outcome (catheter infections), which doesn’t involve risks to subjects
 - If consent were required, sampling bias would result in studies such as this, as well as many epidemiologic studies (eg, ADE studies) being unable to be conducted in a valid manner ~ harming through overprotection

Waiver of Informed Consent

■ Criteria

- Research poses no $>$ minimum risk
- Waiver will not adversely affect rights/welfare of subjects
- Research could not be practicably carried out otherwise
- Whenever appropriate, subjects are provided with additional pertinent information

Conclusions

- IRB scrutiny of research is increasing within the US
 - Federal regulations that went into effect in the 1980s >>> actual routine enforcement in the late 1990s >>> increases in IRB staff/policies and now are at the point where over-regulation occurs at times
 - Paperwork requirements are now substantial
 - Consent forms are now at the point where they read more like real estate contracts
 - ↑ Federal scrutiny has not ↓ unethical research
- Many researchers remain unfamiliar with the regulations
- Early consultation with IRB staff is essential