Challenges of 21st Century Clinical Research from an Independent IRB's View

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Focuses

- "Professionalization" & Identity of IRBs
- Regulatory Climate and Changes impacting IRBs
- International Research & IRBs

“Professionalization”

- Certification
- Licensure
- **Accreditation**
- **Identity**

Accreditation:

Standards

Standards

- Best Practices
- Measuring Quality & Qualifying Quantity
- NCQA & AAHRPP

Identity of the IRB: The View from Bioethics

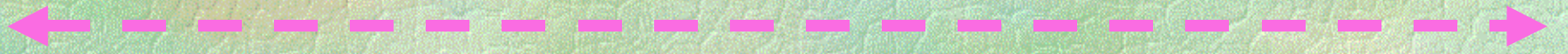
- Part of the public watchdog process
- Advocate for subjects' autonomy
- Monitor of justice concerns
- Assisting in preventing scandals
- Assess scientific merit (but not the main purpose of the IRB, since that function lies elsewhere in the overall human subject protections system)
- Help PIs to identify ethical issues of research

Identity of the IRB: Tensions

Function

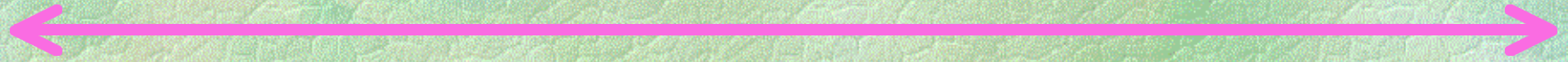
Reviewer Gatekeeper Mediator Arbitrator Advocate Monitor Police

Interaction



Neutrality Advocacy

Power



Advisory Decision-Making

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Regulatory Climate

and Changes

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Pediatric Research

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DHHS/FDA Regulations for Protection of the Rights and Welfare Of Children Involved as Subjects of Research

DHHS/FDA Regulations
Additional Protections for Children

DHHS

- **Subpart D- Children as Subjects in Research**

45 CFR 46.401 – 409

DHHS/FDA Regulations
Additional Protections for Children

FDA

- **Subpart D – Children as Subjects in Research**
  - **21 CFR 50.50 – 56**
  - **Effective April 30, 2001 for new studies**
  - **Effective at time of continuing review for ongoing studies**

DHHS/FDA Regulations
Additional Protections for Children

Additional duties of IRB

- Find (decide) and Document
- Permitted research involving children
  - four categories based on risk to children
  - and anticipated benefit to the individual child
- Permission (consent) of parents and assent by children

DHHS/FDA Regulations
Additional Protections for Children
IRB Determines Level of Risk

Level 1

Not more than minimal risk:

One parent permission + assent

45 CFR 46.404 / 21 CFR 50.51

DHHS/FDA Regulations
Additional Protections for Children
IRB Determines Level of Risk

Level 2

Greater than minimal risk

+ direct benefit to child

One parent permission + assent

(many IND / IDE Studies)

45 CFR 46.405 / 21 CFR 50.52

DHHS/FDA Regulations
Additional Protections for Children
IRB Determines Level of Risk

Level 3

Greater than minimal risk

+ no direct benefit

+ minor increase over minimal risk

Both parents permission + assent

45 CFR 46.406 / 21 CFR 50.53

DHHS/FDA Regulations

Additional Protections for Children

IRB Determines Level of Risk

Level 4

Does not meet above requirements,

DHHS secretary/FDA commissioner decides after expert panel consultation:

Both parents permission + assent

45 CFR 46.407 / 21 CFR 50.54

Subpart D
Additional Protections for Children

Assent of the child

- **IRB determines whether kids are capable of assent**
  - **depends on age, maturity, psychological state**
- **IRB determines adequate provisions made for soliciting assent of children**
- **IRB may waive assent requirement under**
- **Certain conditions**

45 CFR 46.408(a) / 21 CFR 50.55

Subpart D
Additional Protections for Children

- **Kids not capable - age, maturity, psych state**

or

- **The prospect of direct benefit important to health or well being of children and available only in this study**

45 CFR 46.108(a)/21 CFR 50.55(c)

Subpart D
Additional Protections for Children

IRB may determine assent is not required when:

(FDA)

- No more than minimal risk
- Not adversely affect rights and welfare
- Study not practicable without waiver
- Explain to kids after participation

21 CFR 50.55(d)

Subpart D
Additional Protections for Children

Assent of the Child

If assented, IRB determines whether and how assent shall be documented, e.g.

- Note in study records
- Signature on assent form
- Signature on the consent form

45 CFR 46.408(e) / 21 CFR 50.55(g)

Subpart D
Additional Protections for Children

Permission of Child's Parents or Guardian

One parent for risk levels 1 and 2

- **both parents for risk levels 3 and 4, unless one is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child**

45 CFR 46. 408(b)/21 CFR 50.55(e)

Subpart D
Additional Protections for Children

Permission of the Child's Parents

DHHS allows waiver of parental permission under specified conditions

- **permission not a reasonable requirement, e.g.,neglected or abused children**

45 CFR 46.408(c)

FDA has not adopted this provision

Subpart D
Additional Protections for Children

Payment to Parents

Any Parental Pay should be based on:

- **Getting child to site. Payable whether or not child signs up for the study.**
- **Pay to child for participation should be separate from getting child to site.**

Subpart D
Additional Protections for Children

Documentation of IRB Decisions

- **In meeting minutes**
- **In letter to investigator**
  (copy to sponsor)

Subpart D
Additional Protections for Children

Documentation of IRB Decisions

Level of Risk

- Minutes should document IRB's decision
- e.g. reference regulation and rationale for meeting the level of risk

The View From OHRP (USA): "Two Cultures"

"Culture of Conscience"

&

"Culture of Compliance"

Dr. Greg Koski

Office for Human Research Protections

U.S. Department of Health and Human Services

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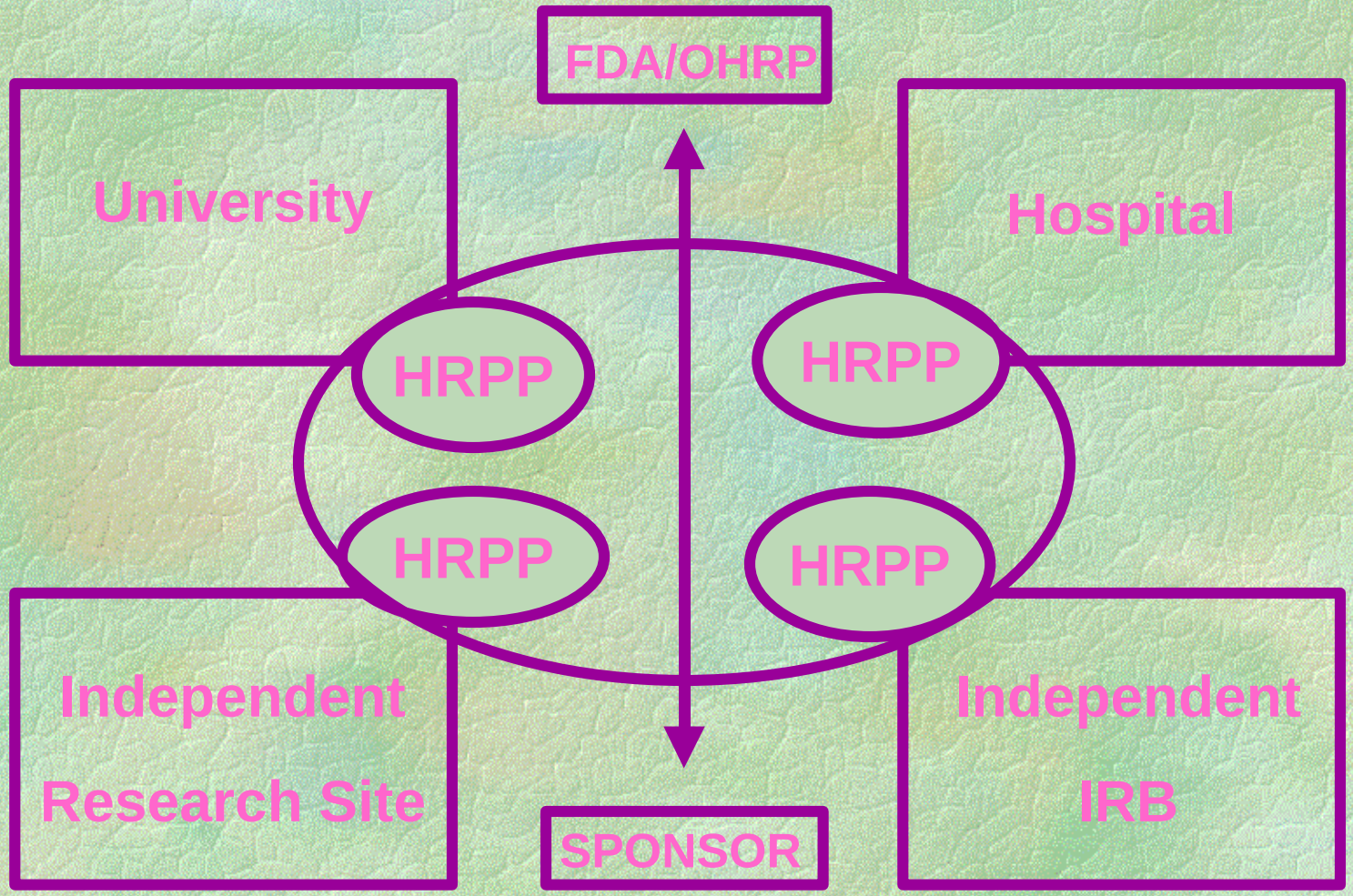
Bridging the "Two Cultures"
The OHRP Modular System



Adopted from Dr. Greg Koski; OHRP Presentation Pretoria, S. Africa 2001

International Research

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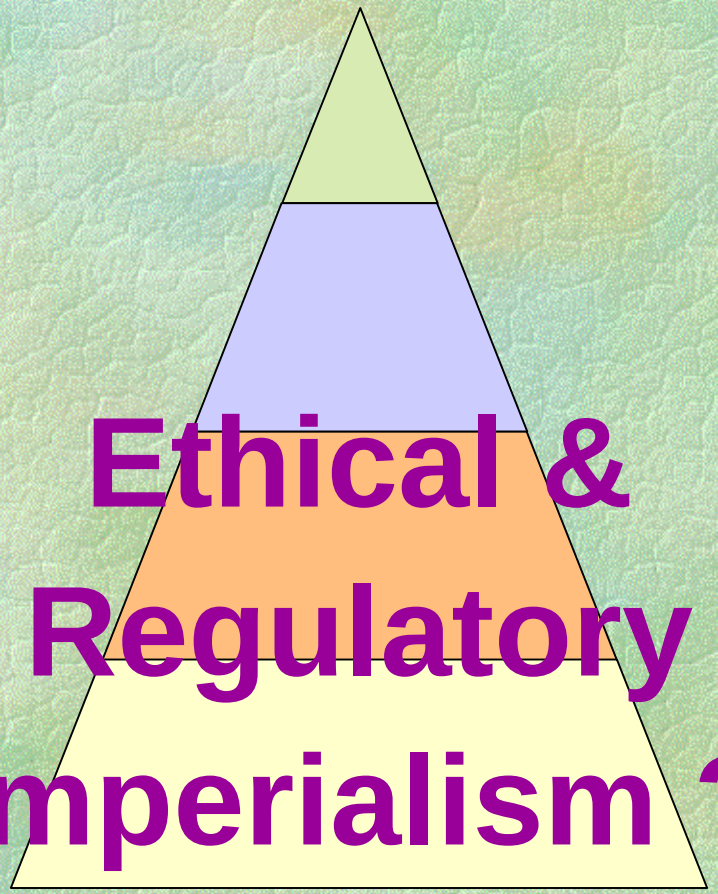
Key International Ethical Issue



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Common Ethical Issues

Conflicts of Interest

(Interest of subject vs. interest of institution)

Fraud

(e.g., falsifying data)

Coercion

(e.g., subject recruitment)

Privacy/Confidentiality

(e.g. genetics research)

The following three slides are taken from:

Ethical and Policy Issues in International Research:
Clinical Trials in Developing Countries

(www.bioethics.gov)

On Equivalent Protections

Current U.S. regulations allow for the Office for Human Research Protections (OHRP) to determine whether another country's guidelines provide protections for research participants that are equivalent to those provided by the U.S. regulations. If so, the other country is free to follow its own guidelines instead of the U.S. regulations. NBAC found that, to date, OHRP has neither provided criteria for determining what constitutes equivalent protections nor made any determinations of equivalence. The Commission recommends that the U.S. government identify criteria and a process for determining whether the human participants protection system of a host country or a host country institution has achieved equivalent substantive ethical protections.

On Ethical Review

Efforts to enhance research collaboration must account for the capacity of ethics review committees in developing countries to review research, and the need for U.S. researchers and sponsors to ensure that their research projects are conducted according to the ethical standards applied in the United States. To accomplish this, NBAC recommends that protocols must be reviewed and approved by a U.S. Institutional Review Board and by an ethics review committee in the host country, unless the host country or host country institution has in place a system of equivalent substantive ethical protections.

On Substantive Ethical Requirements

- prior review by ethics review committees;
- minimization of risk and having a reasonable risk::benefit
- voluntary informed consent by each participant; and,
- an equitable distribution of burdens and benefits of research

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