Grimes versus Kennedy Krieger Institute and the ethics of non- therapeutic research

- Project to test the relative effectiveness of lead paint abatement
- Certain homes undergo only partial lead abatement
- Required landlords to rent premises to families with young children
- Encouraged families to remain in those houses and children‘s blood tested over time
- Only low income families involved
- In return – free food, stamps, money

- 2 cases filed. One child had dangerously high lead levels

- Plaintiff's argument: The researchers failed to notify parents in a timely manner; and failed to provide parents with a complete and clear explanation of the research

The court's view

- " In our view, otherwise healthy children should not be the subjects of non-therapeutic research that has the potential to be harmful to the child.
- It is, first and foremost, the responsibility of the researcher and the research entity to see to the harmlessness of such non-therapeutic research.
- Consent of parents can never relieve the researcher of this duty"

Glantz L. Am J Public Health 2002 ; 92(7): 1070–73.

- Paul Ramsey: Use of young children as research subjects when they could derive no benefit from participating is never justified

- Richard McCormick : Research on children is ethically permissible so long as it involves “no discernible risks, no notable pain, [and] no notable inconvenience

WLs issued to IRBs by the US FDA

- 40 WLs
- 9 (23%) for drug and 23 (58%) device related research

- Failure to follow SOPs and maintain documentation (93%)
- Inappropriate membership, quorum (60%)
- Failure to address informed consent issues (47%)
- Failure to address risk minimization and protect vulnerable participants (13%)

- *Gogtay NJ, Doshi BM, Kannan S & Thatte UM. A Study of Warning Letters issued to Clinical Investigators and Institutional Review Boards by the United States Food and Drug Administration. Ind Jr Med Ethics 2011; VIII(4): 211-14.*

- IRBs failed in their primary responsibility to protect the rights, safety and well being of participants in research.

  Gogtay NJ et al. Ind Jr Med Ethics 2011; VIII(4): 211-14.

- IRBs are plagued with

-Inconsistencies in decision making

-Reliance on vagaries of intuition to interpret federal regulation on acceptable risks and potential benefits

Weijer C & Miller PB. When are research risks reasonable in relation to anticipated benefits? Nature Medicine 2004; 10: 570- 73.

Ethics and non-therapeutic trials

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Outline of presentation

- What is non- therapeutic research ?
- Historical evolution and the Declaration of Helsinki
- The role of IRBs and the concept of risk
- Non therapeutic studies in children
- Studies in oncology
- Factors that motivate participation in non-therapeutic studies
- Summary

ICH-GCP 1996

- A non-therapeutic trial is a trial in which there is no anticipated direct clinical benefit to the subject)
- Examples : Phase I trials, bioavailability and bioequivalence (BABE) studies

Non-therapeutic research

- Therapeutic procedures are justified by their potential to benefit the subject, while non-therapeutic procedures are justified by their potential to generate knowledge. These two types of benefit are largely incommensurable.
- Non-therapeutic procedures are not administered with therapeutic warrant and are administered in the interest of answering the research question.

Weijer C. The Ethical Analysis of Risks and Potential Benefits in Human Subjects Research (Research Involving Human Participants V2) . Online Ethics Center for Engineering.

Non-therapeutic research

- 1960s: Sea change in research
  - randomized clinical trial
  - AIDS and cancer research

- Changing boundaries
  - therapy versus research
  - patient versus subject
  - physician and investigator

- The distinction between therapeutic and non-therapeutic research became subject of debate

Historical evolution

- Declaration of Helsinki (DOH : 1964)

  …In the field of clinical research a fundamental distinction must be recognized between clinical research in which the aim is essentially therapeutic for a patient, and clinical research the essential object of which is purely scientific and without therapeutic value to the person subjected to the research……

- Structure

  I. Basic principles', 'II. Clinical research combined with professional care' and 'III. Non-therapeutic clinical research'

- DOH (2000)

-No specific section dealing with non-therapeutic research

-Para 8: those who do not stand to benefit from the research are “vulnerable”

-Para 16: Use of healthy volunteers as subjects permissible

-Para 18: Healthy volunteers is a group where the importance of weighing risks and burdens is especially important

Thus no longer a section dealing with research where there is no potential benefit to the participants

- DOH (2000, 2008)

-Para 6: 'The primary purpose of medical research involving human subjects is to improve diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease.

-Even the best proven prophylactic, diagnostic and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality'

- How does one balance ‘the protection of, and respect for, research patients and healthy volunteers with the necessary freedom of research to facilitate scientific progress as a public good’?

The role of IRBs

- Ensure that

- risks to subjects are minimized
- risks to subjects are reasonable in relation to anticipated benefits, if any, and the importance of the knowledge that may be reasonably expected to result [45 CFR, 46.111 9a) (1,2)].

What is risk?

- Risk is a multidimensional concept: involves both probability and magnitude of harms
- A risk of death of one in one million should be treated differently than a risk of death of one in ten.
- Benefit, on the other hand, is the magnitude of a positive outcome without reference to its probability.

Weijer C. The Ethical Analysis of Risks and Potential Benefits in Human Subjects Research (Research Involving Human Participants V2) . Online Ethics Center for Engineering.

Risks

(1) Physical

(2) Psychological

(3) Social

(4) Economic

When are research risks reasonable in relation to anticipated benefits?

Non-therapeutic trials in children

- Federal regulations do allow non- therapeutic research on children if an IRB determines that the research presents "no greater than minimal risk" to the children
- minimal risk "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

The Context for Nontherapeutic Research with Children. ACHRE report.

- Chairpersons of German RECs generally tend to accept non-therapeutic research with minors if the apparent risk for the participating children is low. If the risk is clearly higher than ‘‘minimal’’, the chairpersons’ decisions differ widely.

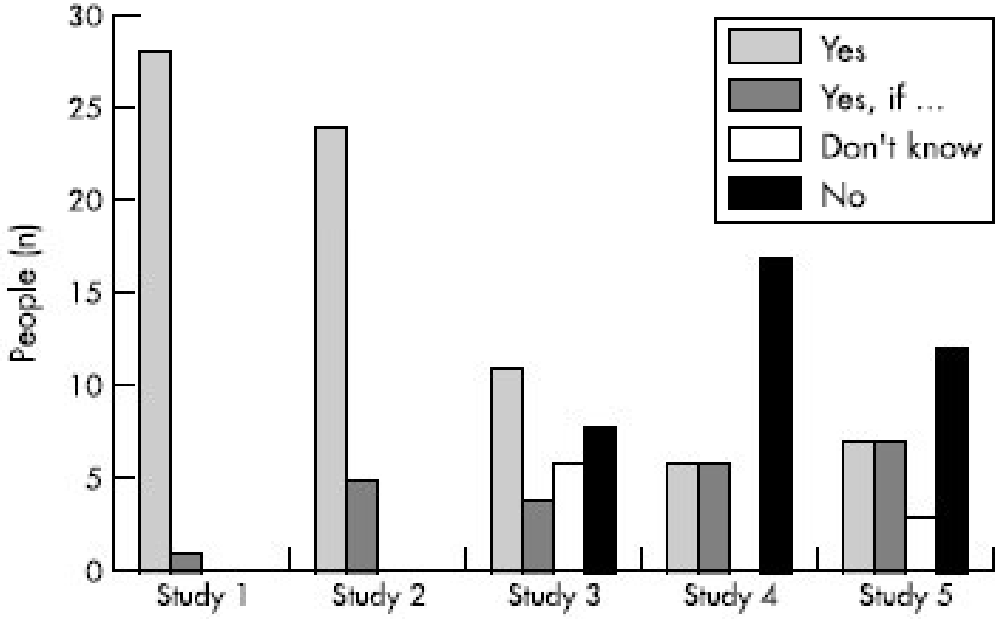


Figure 1 Evaluation of five different studies by chairpersons of German research ethics committees (n = 29).

Lenk et al. Non-therapeutic research with minors: how do chairpersons of German research ethics committees decide? J Med Ethics 2004; 30:85–7.

Benefits

Three types:

(1) Direct

(2) Collateral or indirect

(3) Aspiration

Benefits in Phase I oncology trials-1

- 1974 -1982
- 187 trials
- 54 drugs
- 6447 patients
- Complete Response – 0.7%;
- Partial Response -3.5%

Cancer Treat Rep. ***1986*** *Sep;70(9):1105-15*

Benefits in Phase I oncology trials-2

- 1972 - 1987
- 211 phase 1 oncology trials
- 87 drugs
- 6639 patients
- Complete Response – 0.3%;
- Partial Response-4.2%;
- Toxic deaths – 0.5%

Ann Oncol. ***1990****;1(3):175-81*

Benefits in Phase I oncology trials

- NCI's CTEP
  - 1991 – 2002
  - 460 trials
  - 10, 402 patients for clinical response
  - 11,935 patients for toxicity

	New investigational agent	Approved standard
Complete response (%)	1.5	5.6
Partial response (%)	4.4	16.4
Stable disease (%)	40.8	31.3
Death (%)	0.57	0.77
Grade IV toxicity (%)	15	14.5

Horstmann *et al*. Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002. NEJM 2005;352:895-904

Informed consent document

"Informed consent documents make phase one studies sound like the cure for your cancer"

- Le Roy Wallers (2000)

Benefits in Phase I oncology trials

- Jan 1999 – Dec 2010
- 41 phase 1 oncology trials
- 602 patients
- Overall response- 8.6%
- Complete Response – 1.27%;
- Stable disease- 40.3%;
- Treatment related mortality– 1.2%

Swami *et al*. Journal of Clinical Oncology 2011; 29

The challenges for IRBs

- Which risks must be minimized?
- To what extent must they be minimized?
- Which risks and which benefits are to be considered in the “reasonableness” determination?
- By what measure does one determine that the risks are reasonable in relation to the potential benefits?
- By what measure does one determine that the risks are reasonable in relation to the knowledge that may result?

Patients have different perceptions than healthy people

- Seriously ill patients – willing to take more risks
- Even families – overestimate symptoms and underestimate satisfaction and quality of life

Treatment choices at the end of life: a comparison of decisions by older patients and their physician-selected proxies. Gerontologist. *1989 Oct;29(5):615-21*

Patients willing to undergo more risk than healthy people

- Accept great risk for a very small benefit
- 1% chance of benefit to want an intensive chemotherapy regimen described with many side effects
- Nurses needed 50% chance, and doctors needed a 10% chance, general public needed 50% chance of benefit.

Attitudes to chemotherapy: comparing views of patients with cancer with those of doctors, nurses, and general public. BMJ. 1990 June 2; 300(6737): 1458–60.

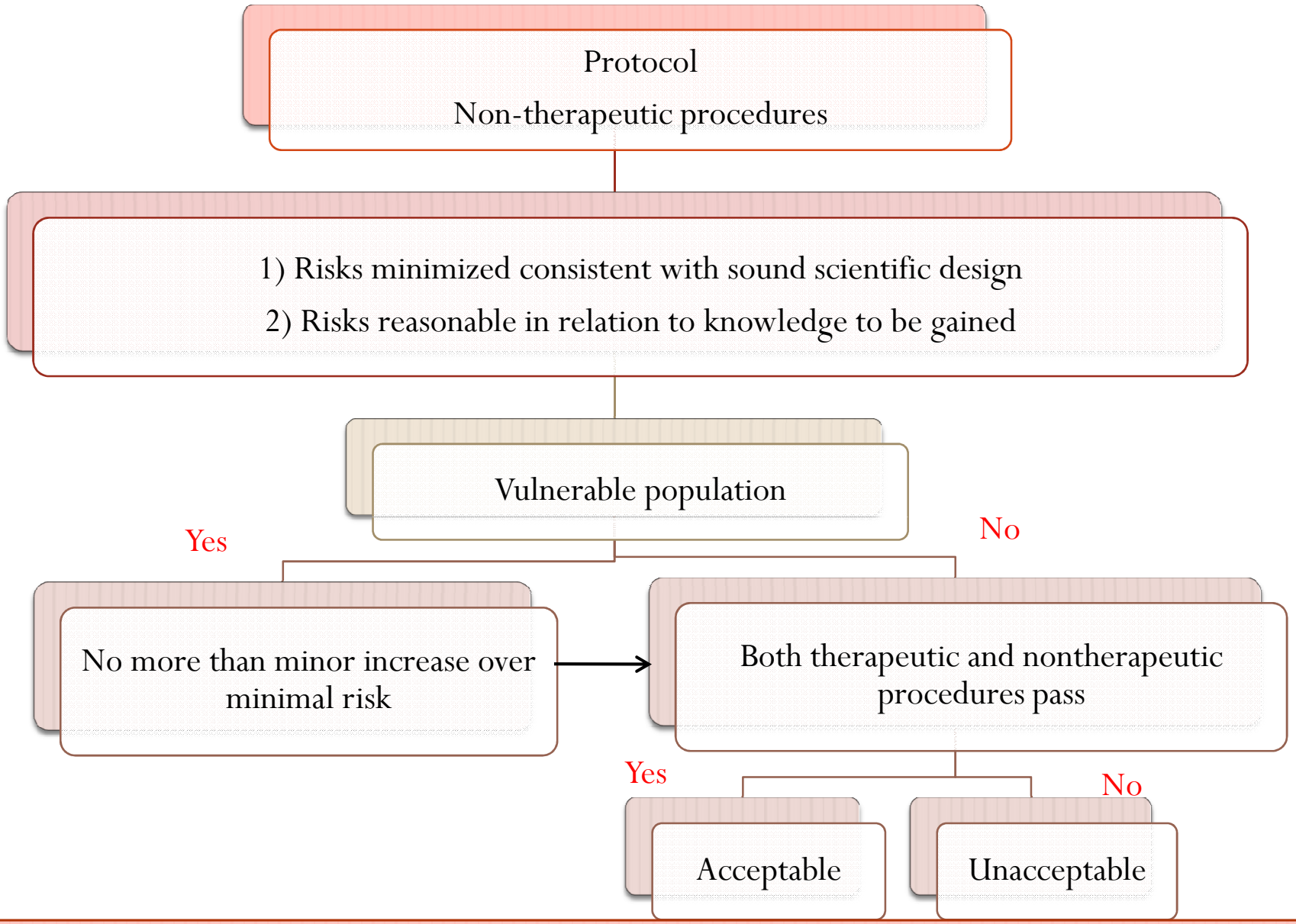
Therapeutic misconception

- Phase 1 oncology trials
- Terminally ill participants – Exhausted of standard treatments
- Especially when the scientific investigator is the treating physician for the patient

Risk-benefit analysis

- A systematic approach to the ethical analysis of risks and potential benefits in research is called “component analysis”.
- Built on the recognition that clinical research often contains a mixture of therapeutic and non-therapeutic procedures and that separate moral standards are required for each.

Weijer et al.When are research risks reasonable in relation to anticipated benefits? Nature Medicine 2004;10(6):570-3



Weijer et al.When are research risks reasonable in relation to anticipated benefits? Nature Medicine 2004;10(6):570-3

- What factors motivate participants to consent for non-therapeutic studies?