UTHealth™
The University of Texas
Health Science Center at Houston

Ethics of Clinical Trials

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Foundations of Cancer Therapeutics
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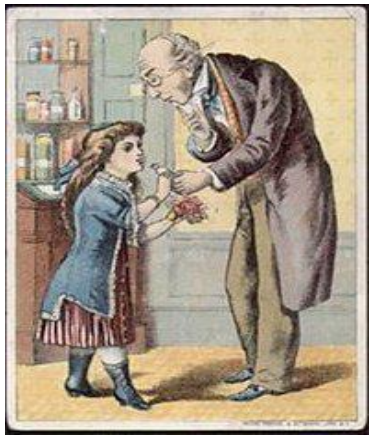
OBJECTIVES

- Learn about regulatory requirements that apply to clinical trials
  - Define ethical values and principles and explain how they differ from laws, policies, and codes of conduct.
  - Describe the ethical oversight regulations and guidance.
- Apply basic regulatory knowledge to illustrate ethical considerations made by IRBs in reviewing human subjects.
- Identify common ethical challenges that arise in research.

History of Clinical Trials



6th Century BC

Book of Daniels

Meat vs Vegan

1st century BC

Cleopatra

Gender experiment

1537

Surgeon Pare

Wound care – Boiling Oil vs Egg yolks, rose petals and turpentine

1747

James Lind

Scurvy Trial

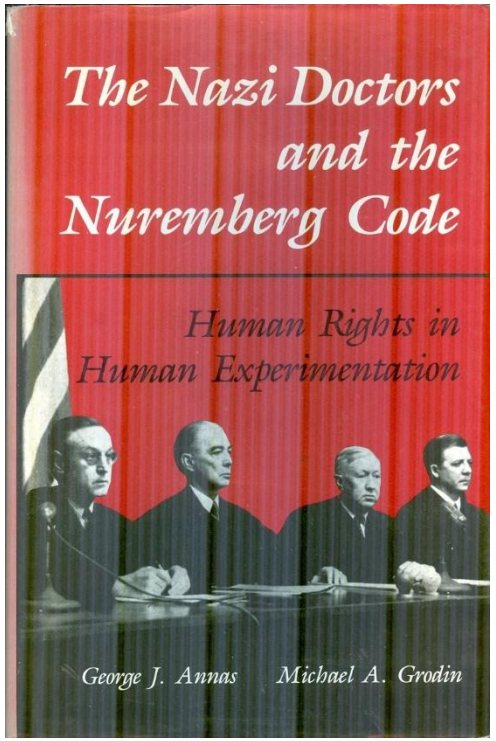
1863

Austin Flint

Placebo Effect of Mint Water for Rheumatic Fever

Nuremberg Experiments

- The doctors accused of performing medical and pseudo-medical experiments on prisoners in the concentration camps with no consideration for their health or even survival.
- Experimentation with vacuum chambers, head injury, freezing experiments, malaria, sulphonamide, poisons, seawater experiments etc.
- 20 doctors Nazi regime tried in Nuremberg August 1947.



"It was the Nuremberg Code that first specified that experiments could not be conducted on people without their consent"

Christiane Druml, UNESCO Chair in Bioethics at MedUni Vienna

https://history.nih.gov/display/history/Nuremberg+Code

Ethics and Clinical Research

The New England Journal of Medicine

Volume 274 JUNE 16, 1966 Number 24

Reprinted from pages 1354-1360.

SPECIAL ARTICLE

ETHICS AND CLINICAL RESEARCH*

HENRY K. BEECHER, M.D.†

BOSTON

HUMAN experimentation since World War II has created some difficult problems with the increasing employment of patients as experimental subjects when it must be apparent that they would not have been available if they had been truly aware of the uses that would be made of them. Evidence is at hand that many of the patients in the examples to follow never had the risk satisfactorily explained to them, and it seems obvious that further hundreds have not known that they were the subjects of an experiment although grave consequences have been suffered as a direct result of experiments described here. There is a belief prevalent in some sophisticated circles that attention to these matters would "block progress." But, according to Pope Pius XII,[1] ". . . science is not the highest value to which all other orders of values . . . should be subordinated."

I am aware that these are troubling charges. They have grown out of troubling practices. They can be documented, as I propose to do, by examples from leading medical schools, university hospitals, private hospitals, governmental military departments (the Army, the Navy and the Air Force), governmental institutes (the National Institutes of Health), Veterans Administration hospitals and industry. The

Experimentation in man takes place in several areas: in self-experimentation; in patient volunteers and normal subjects; in therapy; and in the different areas of *experimentation on a patient not for his benefit but for that, at least in theory, of patients in general.* The present study is limited to this last category.

REASONS FOR URGENCY OF STUDY

Ethical errors are increasing not only in numbers but in variety – for example, in the recently added problems arising in transplantation of organs.

There are a number of reasons why serious attention to the general problem is urgent.

Of transcendent importance is the enormous and continuing increase in available funds, as shown below.

MONEY AVAILABLE FOR RESEARCH EACH YEAR

	MASSACHUSETTS GENERAL HOSPITAL	NATIONAL INSTITUTES OF HEALTH*
1945	$ 500,000†	$ 701,800
1955	2,222,816	36,063,200
1965	8,384,342	436,600,000

*National Institutes of Health figures based upon decade averages, excluding funds for construction, kindly supplied by Dr. John Sherman, of National Institutes of Health.

†Approximation, supplied by Mr. David C. Crockett, of Massachusetts General Hospital.

Liver Cancer Study

- The Jewish Chronic Disease Hospital in Brooklyn
- Study of immunity to cancer
- Live cancer cells injected into 22 humans
- Subjects did give consent – they were told “they would be receiving some cells”

“It was not necessary to tell them that the substances were cancer cells because they are harmless. As expected, they were rejected by the patients' bodies. It was the rate of rejection that was sought.”

Dr. Chester Southam, January 1964

TUESDAY, JANUARY 21, 1964. The New York

HOSPITAL ACCUSED ON CANCER STUDY

Live Cells Given to Patients Without Their Consent, Director Tells Court

ALLEGATION IS DENIED

Chronic Disease Institution Defends Action—Value of Tests Is Praised

By JAMES P. McCAFFREY

The Jewish Chronic Disease Hospital in Brooklyn was accused yesterday of permitting cancer cells to be injected into noncancerous patients without their consent during experiments.

William A. Hyman, a director of the hospital, made the charge before Justice Lewis W. Olliffe in Brooklyn Supreme Court in an application to obtain the records relating to the research project. He pleaded for all "the medical records of the patients who were used as guinea pigs."

As a result of the accusation, the Memorial Sloan-Kettering Cancer Center disclosed the nature of the experiments, saying they had helped demonstrate that cancer victims may lack "an immune mechanism present in other individuals." It added that the "nature of this deficiency is now being sought."

19 Patients Tested

The statement said that 19 volunteer patients with advanced chronic diseases other than cancer had been given cultured human cancer cells under the skin of the thigh and that all had rejected the transplants as promptly as healthy individuals.

The center, which was not involved in the court action, said it had provided the serum for the experiments as part of a research program it began in 1954. It said the tests had provided "new and significant information."

Mr. Heyman, who said he was

Determined Union Rebels Lock Out Everyone—But the Law S

Men of dissident faction of Local 1101 of Communications Workers of America bar entry to lawyer representing parent union at local's office in Forrest Hotel, 224 West 49th St.

Local member bolted door.

Phone Rebels Barricade Office To Keep Out the Union They Left

By JOHN C. DEVLIN

A determined rebel group, on guard behind barricaded doors, yesterday balked an attempt by the Communications Workers of America to occupy a midtown union headquarters.

The rebels used triple bolts and locks on the hinge side as well as the latch side of some doors to the six rooms Local 1101 occupies in the Forrest Hotel, 224 West 49th Street, between Broadway and Eighth Avenue. In one case a hole was punched in a wall dividing two rooms and a timber thrust through it and across the doors

assets of Local 1101 from various banks.

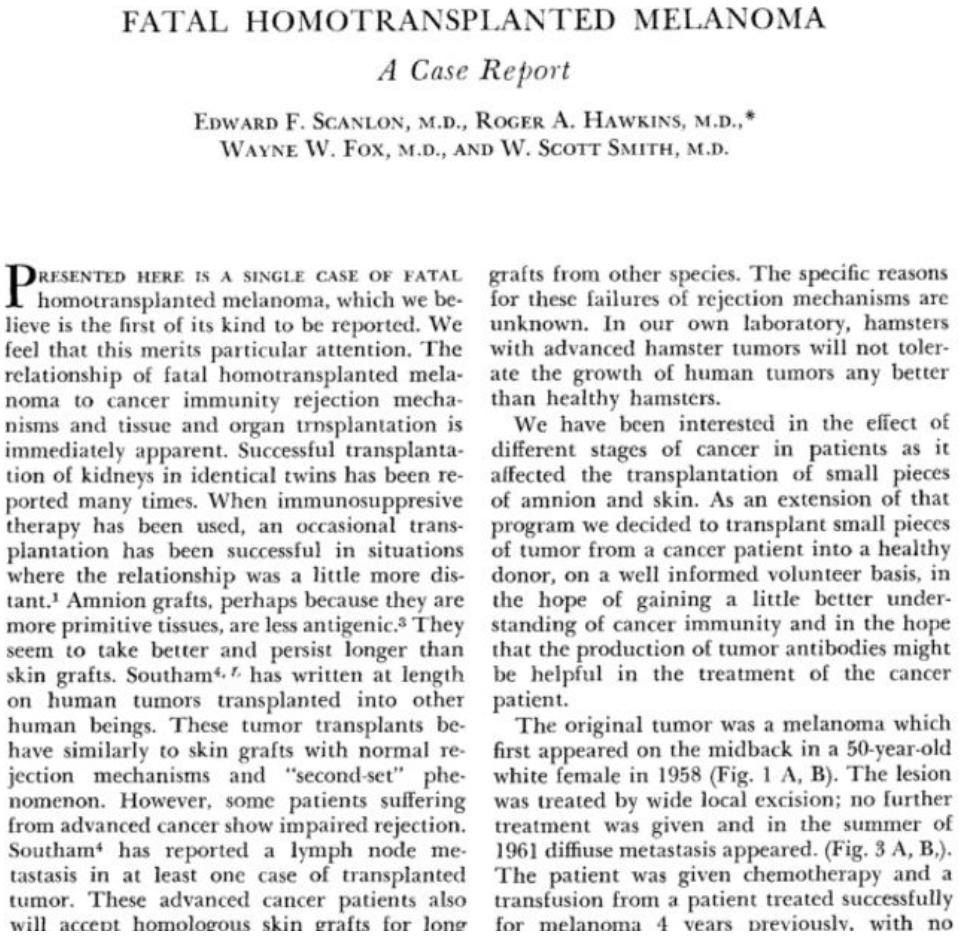
The rebels' counsel, Ernest Garb, said he had advised his clients, members of the Local 1101 executive committee, to comply with the court order. There appeared to be some belief, however, that other members of the local were not involved in the court's decision, which was rendered late Friday and might not comply.

The court order cited Henry F. (Hank) Habel, president of Local 1101; Carmine Mazzarella, secretary-treasurer; Arthur McGovern, vice president; and James Corey, James I

https://www.nytimes.com/1964/01/21/archives/hospital-accused-on-cancer-study-live-cells-given-to-patients.html

Melanoma Study

- Research study to gain better understanding of cancer immunity and in the hope that production of tumor antibodies might be helpful in the treatment of the cancer patient at Northwestern University in 1965.
- Melanoma transplanted from daughter to mother.
- Daughter died day after the transplant
- Primary implant was widely excised on the 24th day after it had been placed in the mother
- Mother died from metastatic melanoma a year after transplantation



FATAL HOMOTRANSPLANTED MELANOMA

A Case Report

EDWARD F. SCANLON, M.D., ROGER A. HAWKINS, M.D.,*
WAYNE W. FOX, M.D., AND W. SCOTT SMITH, M.D.

PRESENTED HERE IS A SINGLE CASE OF FATAL homotransplanted melanoma, which we believe is the first of its kind to be reported. We feel that this merits particular attention. The relationship of fatal homotransplanted melanoma to cancer immunity rejection mechanisms and tissue and organ trnsplantation is immediately apparent. Successful transplantation of kidneys in identical twins has been reported many times. When immunosuppresive therapy has been used, an occasional transplantation has been successful in situations where the relationship was a little more distant.[1] Amnion grafts, perhaps because they are more primitive tissues, are less antigenic.[3] They seem to take better and persist longer than skin grafts. Southam[4, 7] has written at length on human tumors transplanted into other human beings. These tumor transplants behave similarly to skin grafts with normal rejection mechanisms and "second-set" phenomenon. However, some patients suffering from advanced cancer show impaired rejection. Southam[4] has reported a lymph node metastasis in at least one case of transplanted tumor. These advanced cancer patients also will accept homologous skin grafts for long grafts from other species. The specific reasons for these failures of rejection mechanisms are unknown. In our own laboratory, hamsters with advanced hamster tumors will not tolerate the growth of human tumors any better than healthy hamsters.

We have been interested in the effect of different stages of cancer in patients as it affected the transplantation of small pieces of amnion and skin. As an extension of that program we decided to transplant small pieces of tumor from a cancer patient into a healthy donor, on a well informed volunteer basis, in the hope of gaining a little better understanding of cancer immunity and in the hope that the production of tumor antibodies might be helpful in the treatment of the cancer patient.

The original tumor was a melanoma which first appeared on the midback in a 50-year-old white female in 1958 (Fig. 1 A, B). The lesion was treated by wide local excision; no further treatment was given and in the summer of 1961 diffiuse metastasis appeared. (Fig. 3 A, B,). The patient was given chemotherapy and a transfusion from a patient treated successfully for melanoma 4 years previously, with no

https://doi.org/10.1002/1097-0142(196506)18:6%3C782::AID-CNCR2820180616%3E3.0.CO;2-%23

Clinical Trial Regulations

1945	Nuremberg Code
1962	Kefauver Harris Amend.
1964	Declaration of Helsinki
1979	Belmont Report
1981	Human Subjects Regulations
1996	International Council For Harmonization

What Makes Clinical Research Ethical?

- Value
- Validity
- Fairness
- Risk Benefit Assessment
- Independent Review
- Informed Consent
- Respect for Participants

Table 2. Seven Requirements for Determining Whether a Research Trial Is Ethical*

Requirement	Explanation	Justifying Ethical Values	Expertise for Evaluation
Social or scientific value	Evaluation of a treatment, intervention, or theory that will improve health and well-being or increase knowledge	Scarce resources and nonexploitation	Scientific knowledge; citizen's understanding of social priorities
Scientific validity	Use of accepted scientific principles and methods, including statistical techniques, to produce reliable and valid data	Scarce resources and nonexploitation	Scientific and statistical knowledge; knowledge of condition and population to assess feasibility
Fair subject selection	Selection of subjects so that stigmatized and vulnerable individuals are not targeted for risky research and the rich and socially powerful not favored for potentially beneficial research	Justice	Scientific knowledge; ethical and legal knowledge
Favorable risk-benefit ratio	Minimization of risks; enhancement of potential benefits; risks to the subject are proportionate to the benefits to the subject and society	Nonmaleficence, beneficence, and nonexploitation	Scientific knowledge; citizen's understanding of social values
Independent review	Review of the design of the research trial, its proposed subject population, and risk-benefit ratio by individuals unaffiliated with the research	Public accountability; minimizing influence of potential conflicts of interest	Intellectual, financial, and otherwise independent researchers; scientific and ethical knowledge
Informed consent	Provision of information to subjects about purpose of the research, its procedures, potential risks, benefits, and alternatives, so that the individual understands this information and can make a voluntary decision whether to enroll and continue to participate	Respect for subject autonomy	Scientific knowledge; ethical and legal knowledge
Respect for potential and enrolled subjects	Respect for subjects by (1) permitting withdrawal from the research; (2) protecting privacy through confidentiality; (3) informing subjects of newly discovered risks or benefits; (4) informing subjects of results of clinical research; (5) maintaining welfare of subjects	Respect for subject autonomy and welfare	Scientific knowledge; ethical and legal knowledge; knowledge of particular subject population

*Ethical requirements are listed in chronological order from conception of research to its formulation and implementation.

Ezekiel J. Emanuel, M. D. (2000, May 24). *What makes clinical research ethical?* JAMA.

INSTITUTIONAL REVIEW BOARDS

https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html

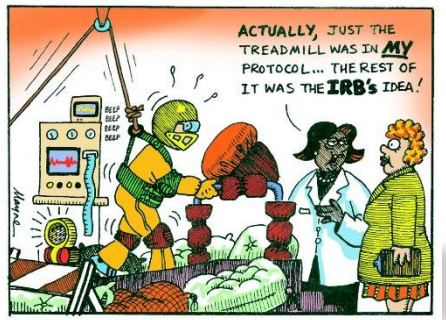
The Belmont Report

	• individuals should be treated as autonomous agents • persons with diminished autonomy are entitled to protection
	• do not harm • maximize possible benefits and minimize possible harms.
	• to each person an equal share according to individual need, individual effort, societal contribution and merit.

https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

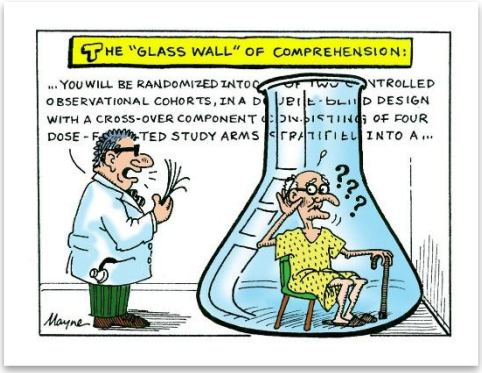
Criteria for Approval

Risks are reasonable
Risks and benefits that may result from the research.
Do not consider possible long-range effects of applying knowledge gained in the research as among those research risks.



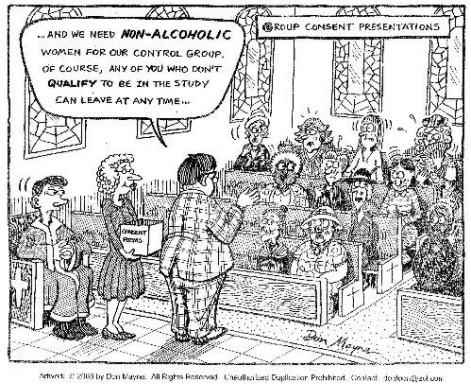
Risks are minimized
Evaluate if the research design is sound.
Evaluate if subjects will be exposed to unnecessary risks.

Subject selection is equitable
Review eligibility criteria.
Consider if research burdens and benefits are distributed fairly.



Informed Consent
Consider if information provided is adequate.
Consider who is giving consent and who is obtaining consent.
Consider documentation of consent.

Adequate provisions for confidentiality
Consider if only minimum necessary data is collected.
Evaluate plan for access control, security – electronic and physical.

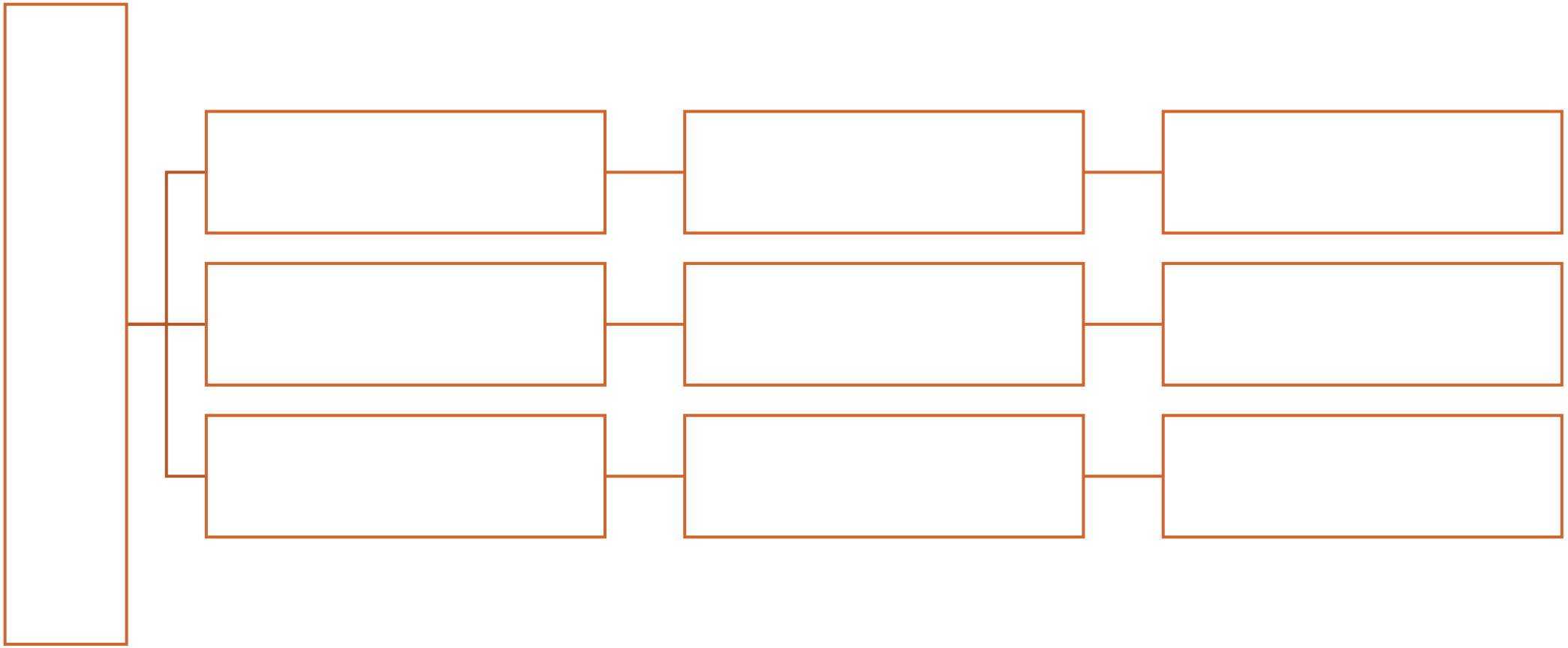


Adequate provisions for privacy
Privacy refers to persons and their interest in controlling access to themselves.
Consider recruitment strategy.

Data and Safety Monitoring
DSMP for all studies greater than minimal risk.
Consider if safety and efficacy data will be reviewed, frequency of review and who will review this.

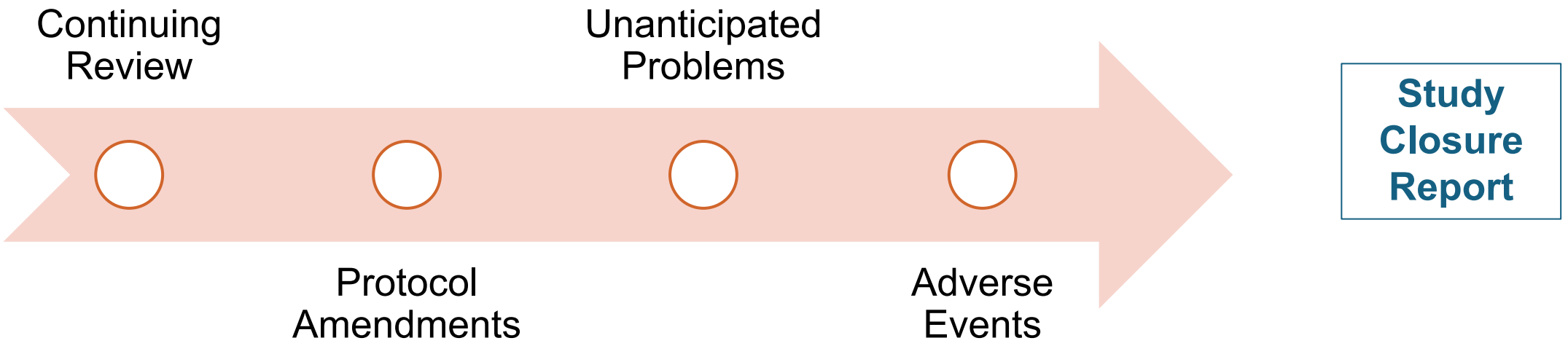
Additional protections for vulnerable populations.
Children – parental permission – one or both parents, assent. Risk category – no greater than minimal risk (404), greater than minimal risk with prospect of direct benefit to participant (405), minor increase over minimal risk with no prospect of direct benefit (406).
Pregnant women – is there a prospect of biomedical benefits?
Prisoners- specific regulatory criteria – refer to policy.

IRB Review Process



Approved; Approved Pending Modifications; Deferred; Disapproved

IRB Oversight



GOOD CLINICAL PRACTICE GUIDELINES

References

- OHRP Regulations - 45 CFR 46
- OHRP Guidance for Investigators
- FDA Regulations - 21CFR 50 ; 21 CFR 56
- FDA Information Sheets – IND
- FDA Information Sheets - IDE

PHASES of a CLINICAL TRIAL

Preclinical
LABORATORY STUDIES
Duration: Several years

- ✓ Provide information on dosing and toxicity levels

Phase 1
SAFETY
Duration: Several months

- ✓ Evaluate safety
- ✓ Gather information about how a drug interacts with the human body

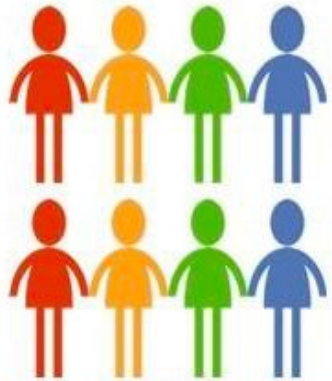
Phase 2
SAFETY AND DOSING
Duration: Several months

- ✓ Further evaluate safety
- ✓ Monitor side effects
- ✓ Check which dose works best
- ✓ Check effectiveness

Phase 3
SAFETY AND EFFICACY
Duration: Several years

- ✓ Confirm effectiveness
- ✓ Monitor safety

FDA APPROVAL



Phase 4
POST MARKETING SAFETY AND EFFICACY

- ✓ Gather information on the drug's effect in various populations and any side effects associated with long-term use

https://www.slhn.org/cancer/clinical-trials