D Y PATIL DENTAL SCHOOL

DEPARTMENT OF

PUBLIC HEALTH DENTISTRY

Ethics in Medical Research

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Introduction

- Ethics is defined as "the science of the ideal human character and behavior in situations where distinction must be followed and good interpersonal relations maintained."

Or

- Ethics is the philosophy of human conduct, a way of stating and evaluating the principles by which the problems of behavior can be solved.

Introduction

- Research ethics refers to moral principles guiding research from its inception, through, to completion and publication of the results and beyond.

Importance of ethics in medical research

- Some of these norms promote the aims of research
- Ethical standards promote the values essential to collaborative work.
- Many of the ethical norms help to ensure that researchers can be held accountable to the public
- Ethical norms promote a variety of other important moral and social value.

Historical Background

First century physician 'Celsius'

- Justified experiments on condemned criminals in Egypt

"It is not cruel to inflict on a few criminals sufferings which may benefit multitudes of innocent people through all centuries"

In 1721 - Condemned prisoners in England were offered a reduced sentence if they took part in inoculation trials

Historical Background

Research in 18th century

- Edward Jenner experiments, in which he first tested smallpox vaccines on his son and neighborhood children.
- Johan Jorg - In an instance of self-experimentation, swallowed 17 drugs in various doses to record their properties.

Dr. Walter Reeds Legacy

- 1900
- Dr. Walter Reed was appointed to study the cause of yellow fever
- One set of volunteers were made to sleep on soiled clothes of infected people, no mosquitoes in room.
- Other volunteers – in room with infected mosquito

- Dr. Henry K. Beecher wrote an article in the New England Journal of Medicine describing 22 examples of research studies that he considered to have violated ethical standards

Problems noted:

- Dangerous research
- No or little benefit to subjects
- No informed consent
- Use of coercion or undue pressure
- Use of or exploitation of vulnerable population
- Withholding information about risks
- Withholding available treatment
- Deception
- Risks to subjects outweighing benefits

Ethical violations in research

Experiments during Nazi times

- Freezing / Hypothermia

Victim of a medical experiment immersed in freezing water at the Dachau concentration camp. Germany, between August 1942 and May 1943.

Ethical violations in research

Lost (Mustard) Gas Experiments :

- September 1939 and April 1945
- Sachsenhausen, Natzweiler, and other conc camps
- To investigate the most effective treatment of wounds caused by Lost gas.
- Wounds deliberately inflicted on the subjects were infected with Lost. Some of the subjects died as a result of these experiments.

Ethical violations in research

Sulfonamide Experiments :

- July 1942 to September 1943
- To investigate the effectiveness of sulfonamide
- Wounds deliberately inflicted on the subjects were infected with infected with bacteria such as Streptococcus, gas gangrene, and tetanus.
- Circulation of blood was interrupted by tying off blood vessels at both ends of the wound

Ethical violations in research

- High Altitude experiments

A prisoner in a compression chamber loses consciousness (and later dies) during an experiment to determine altitudes at which aircraft crews could survive without oxygen. Dachau, Germany, 1942. NARA

Bad Blood: The Tuskegee Syphilis Study

- As part of a study conducted in Macon County, Alabama, poor sharecroppers were told they were being treated for "bad blood."
- "The study was conducted to determine from autopsies what the disease does to the human body."

Bad Blood: The Tuskegee Syphilis Study

- 1932: Followed 399 black syphilitic males
- 1933: 201 controls added
- 1943: Penicillin accepted treatment – subjects exempted
- 1947: Nuremberg Code – no connection made
- 1951: Penicillin widely available – treatment withheld –
- 1972: Jean Heller published an article exposing the study
- 1973: Study was stopped, treatment administered
- 1997: Bill Clinton apologized to subjects and families

Bad Blood: The Tuskegee Syphilis Study

- Results
  - Disability .. 100
  - Deaths .. 28
  - Congenital syphilis .. 19

Ethical Issues

- Lack of informed consent
- Deception
- Withholding information
- Putting men and families at risk
- Exploitation of vulnerable group who would not benefit from participation

Bad Blood: The Tuskegee Syphilis Study

- Ad hoc committee formed
- Mandate
  - Federal regulations to protect human research subjects in the future

Thalidomide

- 1950s to early 1960s
- Sold and prescribed to pregnant women, to combat morning sickness and as an aid to help them sleep.
- Before its release, inadequate tests were performed.
- 10,000 children were born with phocomelia

Brooklyn Cancer Experiment

- 1960 at Jewish Chronic Disease hospital
- Dr. Chester Southam and Emannuel Mandall
- In order to study the immune response, live cancer cells were injected into 26 geriatric non consenting patients, without their knowledge.
- Justification given by the researcher
  - Believed that the cells would be rejected and it would frighten them unnecessarily

Willowbrook Hepatitis Experiment

- 1963-1966
- Dr.Saul Krugmann
- Purpose was :
  - To follow the natural history of viral hepatitis
  - Test the effectiveness of gamma globulin against hepatitis

Willowbrook Hepatitis Experiment

- Group of mentally retarded children who lived at Willowbrook state hospital , were deliberately infected with hepatitis virus; early subjects were fed with extracts of stools from infected individuals and later subjects received injections of more purified virus preparations.

Willowbrook Hepatitis Experiment

- Consent obtained from parents

  Hazards not fully informed

- Coercion

  Undue pressure on parents

  To obtain consent

Vipeholm studies

- 1945-1953
- Mentally retarded patients were divided into 7 groups and 6 groups were fed with diet containing sugars.

Vipeholm studies

Ethical Issue :

- Mentally retarded children
- Coercion – No informed consent
- Hazards not informed

Cincinnati radiation experiments

- Dr. Saenger
- Purpose of the "treatments" was to determine how much radiation a solider could take before being disabled
- At least 111 cancer patients were subjected to whole-body irradiation at the public hospital in Cincinnati during the years 1960 to 1971
- The patients thought they were receiving treatment
- 21 of them died

Mustard gas experiments

- British military scientists tested a chemical weapon on Indian colonial troops during World War Two.
- Many Indian and British soldiers were exposed to mustard gas in tests conducted in Rawalpindi, which was then part of Britain's Indian colony
- Severe pain and burns on the soldiers' skin

Gas experiments

- 1993 – Prison camp 22 North Korea
- Dr. Lee Sun Ok
- Chemical experiments being carried out on political prisoners in specially constructed gas chambers.

The Nuremberg Code (1947)

- The voluntary consent of the human subject is absolutely essential.
- The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

The Nuremberg Code (1947)

- The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results justify the performance of the experiment

The Nuremberg Code (1947)

- The experiment should be so conducted as to avoid unnecessary physical and mental suffering.
- No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

The Nuremberg Code (1947)

- The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
- Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death.

The Nuremberg Code (1947)

- The experiment should be conducted only by scientifically qualified persons.
- During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

The Nuremberg Code (1947)

- During the course of the experiment the scientist must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the subject.

Declaration of Helsinki

- Adopted by 18th World Medical Association in 1964.
- The Declaration of Helsinki was revised in 1975, 1983, 1989, 1996, and 2000.
- Clarifications were given in 2002 and 2004
- 32 principles

Declaration of Helsinki

Basic principles for medical research

- Duty of the physician to protect the life, health, privacy and dignity of the subject.
- Research should conform to accepted scientific principles, be based on thorough knowledge of scientific literature and adequate lab and animal experiments

Declaration of Helsinki

- Research protocols should be reviewed by an independent committee
- Research protocols should be conducted by medically/scientifically qualified individuals
- Risks and burden to the participant should not outweigh benefits
- Researcher should stop study if risks are found to outweigh potential benefits

Declaration of Helsinki

- Research is justified only if there is a reasonable likelihood that the population under study will benefit from the results
- Participants must be volunteers and informed in research project
- Every precaution must be taken to respect privacy, confidentiality, and participant's physical and mental integrity

Declaration of Helsinki

- Assent must be obtained from minors, if child able to do so
- Investigators are obliged to preserve the accuracy of results; negative and positive results should be publicly available
- Appropriate caution must be exercised in the conduct of research.

National Research Act -1974

- The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- Identify the basic ethical principles that should underlie the conduct of research involving human participants and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles.

Belmont Report (1974)

Principal	Application
Respect for Persons - Individuals should be treated as autonomous agents - Persons with diminished autonomy are entitled to protection.	**Informed Consent** - Participants, to the degree that they are capable, must be given the opportunity to choose what shall or shall not happen to them - The consent process must include three elements: ○ Information, ○ Comprehension, and ○ Voluntary participation
Beneficence - Human participants should not be harmed - Research should maximize possible benefits and minimize possible risks	**Assessment of risks and benefits** - The nature and scope of risks and benefits must be assessed in a systematic manner
Justice - The benefits and risks of research must be distributed fairly	**Selection of participants** - There must be fair procedures and outcomes in the selection of research participants

Informed Consent

Consent given by a competent individual who

- Has received the necessary information
- Has understood the information
- And having understood the information has arrived at a decision without having been under any coercion, undue influence or inducement or intimidation

Informed Consent

- Written informed consent
- from every subject
- before any study related procedure
- and documented on EC approved form
- adhere to GCP, based on Helsinki Declaration

Informed Consent

- Subject

  if subject unable to give consent (minor , dementia etc.) then

- Subject's legally acceptable representative

  subject should be informed to the extent compatible with his/her understanding and consent sought and documented.

Informed Consent

- Investigator or his delegate should discuss all pertinent aspects of study including the informed consent form
- Answer any queries / doubts
- Consent requested
- Consent documented if given
- Copy given to participant

Informed Consent

Signed and dated by

- Subject / subject's legally acceptable representative
- Person conducting the informed consent discussion
- If subject / subject's legally acceptable representative is illiterate, an impartial witness

Informed Consent

- Ample time for decision
- Opportunity to discuss
- Summary and consent in the vernacular
- Written translation
- Thumb impressions allowed document method of obtaining consent witness/video tape

The Common Rule

- 1981: In response to the Belmont Report, FDA revised their human subjects regulations, which became formalized as:

  Title 45 Part 46 of the Code of Federal Regulations

- Revisions in 1983 and 1991 finalized the federal policy and became known as "the common rule", establishing regulations for all relevant federal agencies.

The Common Rule

- Defines "research" and "human subjects"
- Tells what activities must be reviewed vs. what can be exempted
- Mandates the IRB and specifies its composition
- Indicates procedures for review and approval of research
- Specifies requirements for obtaining informed consent
- Defines special procedures for "vulnerable populations"

Institutional review board

- An objective review of research activities involving human subjects by a group of diverse individuals is most likely to protect human subjects and promote ethically sound research

Institutional review board

- Review, approve or disapprove all research activities involving participants.
- Review and require documentation of informed consent.
- Maintain written records of all correspondence, meetings, proposals reviewed, decision concerning reviews, progress reports from investigators and reports of injuries.

Institutional review board membership

- Chairperson : Outsider
- Member – Secretary
  - At least 1 member
  - basic medical scientist
  - clinician
  - legal expert
  - social scientist/philosopher/priest
  - lay person

Institutional review board membership

- External scientific expert
- Adequate representation : age, gender etc.
- Experts may be invited
- Patient groups may be represented

Institutional review board

- Conduct continuing review of research at least once a year.
- Suspend or terminate research that is not conducted in accord with requirements or has been associated with Serious harm to subjects.

HIPAA

- Enacted by U.S Congress in 1996
- Title I - protects health insurance coverage for workers and their families
- Title II - the Administrative Simplification (AS) provisions, requires the establishment of national standards for electronic health care transactions and national identifiers for providers, health insurance plans, and employers.

HIPAA

- Informed consent forms to be containing full details of how the participant's protected health information will be kept private.
- It establishes regulations for the use and disclosure of Protected Health Information (PHI). PHI is any information about health status, provision of health care, or payment for health care that can be linked to an individual.

HIPAA

- Disclosure of information can be made when disclosure is necessary to prevent or lessen a serious threat to a safety of a person or when it is directed at a person or persons reasonably able to prevent or lessen threat
- Covered entities must disclose PHI to the individual within 30 days upon request.

ICMR Statement

- 1980: "Policy Statement on Ethical Considerations involved in research on Human Subjects"

- ICMR: Ethical guidelines for biomedical research 2000
  - Chairperson Justice M.N. Venkatachaliah
  - Statement on general principles
  - Statement on specific principles

ICMR Statement

- Principles of essentiality
- Principles of voluntariness, informed consent and community agreement
- Principles of non-exploitation
- Principles of privacy and confidentiality
- Principles of precaution and risk minimization
- Principles of professional competence
- Principles of accountability and transparency

ICMR Statement

- Principles of maximization of public interest and of distributive justice
- Principles of institutional arrangements
- Principles of public domain
- Principles of totality of responsibility
- Principles of compliance

Forum for ethical review Committee in India

- It is the national part of FERCAP (Forum for ethical review Committee in Asia Pacific)
- Constituted in December 2002

Forum for ethical review Committee in India

Objectives :

- To establish and foster communication in India on ethical issues
- Acts as a national collaborating agency for ethics review
- Organizes meetings and symposia on ethical review process

Forum for ethical review Committee in India

- Facilitate training opportunities for members of ethical committees in the country
- Co-ordinate national communications and issues with other global bodies.
- Assist in the development and implementation of policies for ethical review in the region taking into consideration WHO guidelines

COPE Guidelines

- Founded in 1997
- To address breaches of research and publication ethics.

Study design and ethical approval

- Research protocols should seek to answer specific questions rather than just collect data.
- Formal supervision by the principal investigator, which includes quality control and long term retention of all records (for 15 years)

COPE Guidelines

Data analysis:

Action
(1) All sources and methods used to obtain and analyse data, including any electronic pre-processing, should be fully disclosed; detailed explanations should be provided for any exclusions.
(2) Methods of analysis must be explained in detail, and referenced, if they are not in common use.
(3) The post hoc analysis of subgroups is acceptable, as long as this is disclosed. Failure to disclose that the analysis was post hoc is unacceptable.
(4) The discussion section of a paper should mention any issues of bias which have been considered, and explain how they have been dealt with in the design and interpretation of the study.

COPE Guidelines

Authorship:

(1) The award of authorship should balance intellectual contributions to the conception, design, analysis and writing of the study against the collection of data and other routine work. If there is no task that can reasonably be attributed to a particular individual, then that individual should not be credited with authorship.

(2) To avoid disputes over attribution of academic credit, it is helpful to decide early on in the planning of a research project who will be credited as authors, as contributors, and who will be acknowledged.

(3) If professional writers employed by pharmaceutical companies, medical agencies, or other parties have written the paper, then their names should be included, and any conflicts of interest declared.

COPE Guidelines

Conflict of interest:

(1) Such interests, where relevant, must be declared to editors by researchers, authors, and reviewers.
(2) Editors should also disclose relevant conflicts of interest to their readers. If in doubt, disclose.
(3) Editors should also consider disclosing to readers their own conflicts of interest and those of their teams, editorial boards, managers, and owners.
(4) Sometimes conflicts of interest may be so extreme that publication will not be possible or people (for example, reviewers or editors) may have to be excluded from decisions on publication.

COPE Guidelines

Peer review:

The submitted manuscript should not be retained or copied.

Reviewers and editors should not make any use of the data, arguments, or interpretations, unless they have the authors' permission.

Reviewers should provide speedy, accurate, courteous, unbiased and justifiable reports.

If reviewers suspect misconduct, they should write in confidence to the editor.

Journals should publish accurate descriptions of their peer review, selection, and appeals processes.

Journals should also provide regular audits of their acceptance rates and publication times.

COPE Guidelines

Redundant publication:

(1) Published studies do not need to be repeated unless further confirmation is required.

(2) Previous publication of an abstract during the proceedings of meetings does not preclude subsequent submission for publication, but full disclosure should be made at the time of submission.

(3) Re-publication of a paper in another language is acceptable, provided that there is full and prominent disclosure of its original source at the time of submission.

(4) At the time of submission, authors should disclose details of related papers, even if in a different language, and similar papers in press.

COPE Guidelines

Plagiarism:

Plagiarism ranges from the unreferenced use of others' published and unpublished ideas, including research grant applications to submission under "new" authorship of a complete paper, sometimes in a different language.

It may occur at any stage of planning, research, writing, or publication: it applies to print and electronic versions.

Action

(1) All sources should be disclosed, and if large amounts of other people's written or illustrative material is to be used, permission must be sought.

Ethics in research involving animals

- Alternatives should be used such as cell cultures.

Research should be so designed that :

- The objective is feasible and clearly defined
- Species with most appropriate physiology for the work are used.
- Number of animals should be minimum
- Severity of procedures kept to minimum
- Experiment should be as short as possible and analgesia should be used to minimize pain.

Ethical considerations for special classes of subject

Women:

- Special emphasis should be placed on the need for inclusion of minorities and women in studies of diseases, disorders and conditions which disproportionately affect them.
- If one gender/ minority excluded – rational explanation should be given.

Ethical considerations for special classes of subject

Women:

Pregnant women or fetus may be involved in research if all of the following conditions are met:

- Appropriate, pre clinical studies on pregnant animal, clinical studies on non pregnant women conducted.
- Risk minimal, No other means of conducting study.
- Prospect of benefit to the woman – Her consent

Ethical considerations for special classes of subject

Women:

- Prospect of benefit to the fetus – Her consent and father's consent
- No inducement , monetary or otherwise will be offered to terminate pregnancy.

Ethical considerations for special classes of subject

Vulnerable groups:

- Burden and benefits should be equally distributed.
- Research on genetics should not lead to racial inequalities
- Persons who are socially and economically disadvantaged should not be used to benefit those who are better off than them.

Ethical considerations for special classes of subject

Vulnerable groups:

- Rights and welfare of mentally challenged and mentally differently able persons who are incapable of giving informed consent or those with behavioral disorders must be protected.

Ethical considerations for special classes of subject

Vulnerable groups:

- Adequate justification is required for the involvement of subjects such as prisoner, students, subordinates employees, service personnel etc who have reduced autonomy as research subjects.

Ethical considerations for special classes of subject

Research can involve prisoners only if:

- Study of possible causes, effects and processes of incarceration and of criminal behavior, provided that the study presents no more that inconvenience to the subjects.
- Minimal risk
- Only after consultation with appropriate experts
- Resulting in improvement of health.

Ethical considerations in research involving children

- Relevant knowledge cannot be obtained by research in adults.
- Purpose is to obtained knowledge relevant to the health, well-being or healthcare needs of children.
- If informed consent obtained.
- A child's refusal to participate or continue in research should always be respected.

Ethical considerations in research involving children

- If a child becomes upset by a procedure, researcher must accept this as a valid refusal.
- Researcher should involve parents/guardians in the decision to participate wherever possible and in all cases where the child is not yet competent.

Ethical considerations in research involving children

- Researcher should avoid any pressures that might lead the child to volunteer for research or that might lead parents to volunteer their children in the expectation of benefit.
- Researcher must take account of the cumulative, medical, emotional social and pschycological consequence of the children being involved in research.

Principles in research using people s information

- Personal information of any sort – confidential
- All personal information must be coded or anonymised.
- At the outset researchers must decide what information about the results should be available to the people involved in the study once it is complete and agree these plans with research ethics committee

Principles in research using people s information

- Legality of using personal confidential information without consent could be judged by taking into account :
  - Necessity
  - Sensitivity
  - Importance
  - Safeguard
  - Independent review
  - Expectations

Principles governing research using information without consent

- Hospital and practices involved in research must develop procedures for making patient aware that their information sometimes be used for research and explaining the reason and safeguards.

Principles governing research using information without consent

- When consent is impracticable confidential information can only be disclosed without consent only if :

Principles governing research using information without consent

- The likely benefits outweigh the implication of loss of confidentiality.
- No intention to feed information back to the individuals involved or to take decision that affect them.
- There were no practicable act of equal effectiveness

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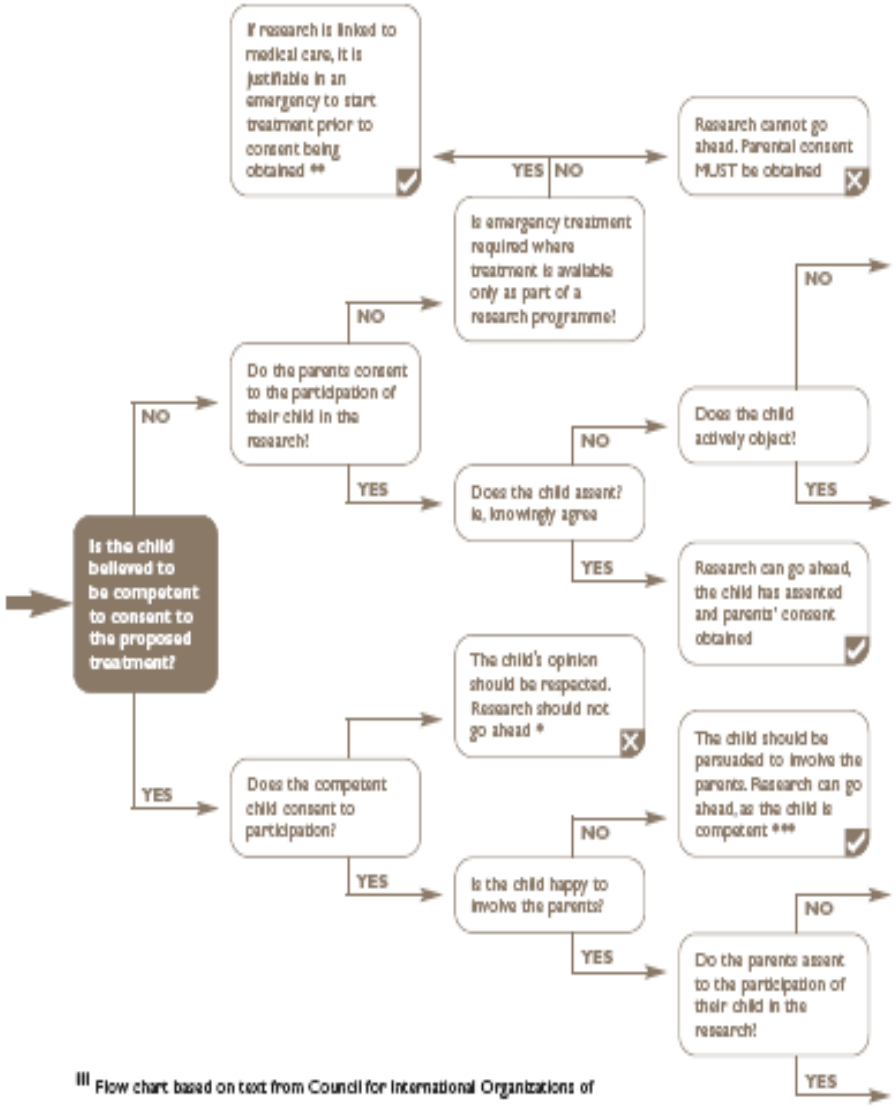
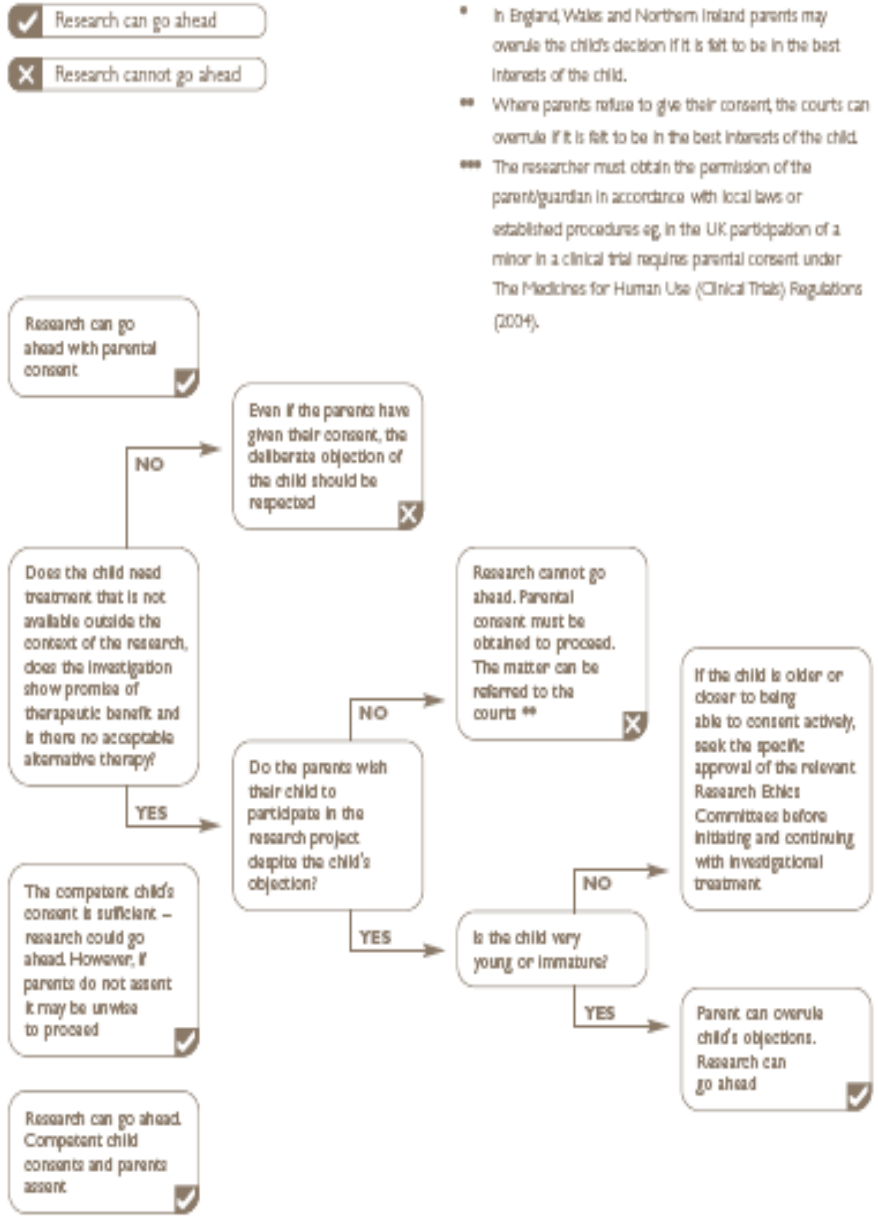
Thank You

5.1.6 Seeking consent – a summary[iii]



[iii] Flow chart based on text from Council for International Organizations of Medical Sciences International ethical guidelines for biomedical research involving human subjects.[5]



* In England, Wales and Northern Ireland parents may overrule the child's decision if it is felt to be in the best interests of the child.

** Where parents refuse to give their consent, the courts can overrule if it is felt to be in the best interests of the child.

*** The researcher must obtain the permission of the parent/guardian in accordance with local laws or established procedures eg, in the UK participation of a minor in a clinical trial requires parental consent under The Medicines for Human Use (Clinical Trials) Regulations (2004).

Central concepts of common rule

- IRB review—need not be local IRB
- Exempt research—e.g., educational tests, unlinked biomaterials from public sources
- Expedited review—e.g., minimal risk
- Informed consent
- Parent or legal guardian