Research in Children: challenges

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outline

- Need for research in children
- Consent by minors
- Clinical trials
- Recruitment

Research in Children

Until the end of last century, children were precluded from entering clinical trials,

Intention: to shield particularly vulnerable individuals from the unanticipated risks inherent to experimental drug exposure

Consequences: greater risk of suboptimal treatment efficacy or of adverse effects, often caused by dosage errors due the use of drug formulation unsuitable for a specific patient's age, leading to poor therapeutic adherence

Unethical medical experiments

Tuskegee syphilis study (1932-1972)

- Curran WJ. NEJM 1973;289:730-1

US government funded studies of human exposure to radiation (1944-1974)

- Vulnerable groups deemed expendable for research purposes
  - McCarthy M. Lancet 1994;344:1498

Nazi experiment on prisoners (1939-1945)

Nuremberg code

- Voluntary informed consent from all research subjects
- Excluded minors, mentally handicapped and unconscious individuals
  - Muremberg Military Triburnal. The Nuremberg Code. JAMA 1996;276:1691

Easier to say ‘no’ to research with children as it is difficult

Is it acceptable to continue to offer health care to children without seeking to improve the evidence base for many of the treatments provided?

Research in children

FDA

European Commission

Regulation to encourage high quality research on drug effects in children through adequate and well controlled clinical trials, with the aim of introducing more efficacious and safer medicines into paediatric clinical practice

Protect children and young people through research and not from research

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

JAMA November 27, 2013 Volume 310, Numb

erable Groups and Individuals

ome groups and individuals are particularly vulnerable and may ave an increased likelihood of being wronged or of incurring ad- itional harm.

ll vulnerable groups and individuals should receive specifi- ally considered protection.

20. Medical research with a vulnerable group is only justified research is responsive to the health needs or priorities o group and the research cannot be carried out in a vulnerable group. In addition, this group should stand to efit from the knowledge, practices or interventions that r from the research.

Definitions of childhood

Vary by geography, culture and legislation

Some countries: anyone younger than 19 years

16th birthday marks the beginning of adulthood

Singapore: 21st birthday

Consent by minors

Complex

Ability to grasp all relevant consequences of participating in research

Decision making:

- Understanding the disclosed information about the nature and procedures of the research
- Reasoning in the process of deciding about participation
- Appreciation of the effects of research participation
- Expressing a choice about participation

Concept of research: risks and benefits uncertain

Children's capacity to consent to research

Hepatitis B vaccine trial

123 children age 12-17 years (mean 15y)

Read a consent form

Comprehension test: only 56% absolute comprehension (100% correct answers)

Conclusion: almost half of the study subjects made a decision on information they did not fully understand

- Lee et al. J Med Ethics 2013;39:410-2

Empirical examination of the ability of children to consent to clinical research

Nancy Ondrusek, Rona Abramovitch, Paul Pencharz and Gideon Koren *The Hospital for Sick Children, Toronto and the University of Toronto*

Journal of Medical Ethics 1998;**24**:158-

18 children, 5-18y old

Nutrition study, included in consent study

Understanding of several aspects o the study: purpose, potential harms, right to withdraw, potential benefits definite age related

Majority of those <9y did not understand those elements of the study

Those >9y did appear to understand

Implication

Consent process

- Approach the consent process in a stepwise fashion without rushing
- Address any risk concerns right away and encourage questions
- Always communicate in lay person's language – avoid medical and research jargon
- Discuss the qualifications and experience of the investigators and staf members
- Reassure parent or caregiver that the child's safety and well being is paramount
- Establish trust with parent or care giver by building a good relationship with the family

Obtaining consent and assent

- Provide clear education about the disease or condition being studied
- Relay interest in improving care or outcomes for those with the disease or condition
- Explain how the parent or child can be part of finding better ways to treat the condition
- Explain the randomization process if applicable or the right to withdraw at any time
- Demonstrate key procedures in the study protocol as applicable
- Create easy to understand print material to keep and use as reference

Accuracy of the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) for Measuring Children's Competence to Consent to Clinical Research

JAMA Pediatrics December 2014 Volume 16

RESULTS Of 209 eligible patients, we included 161 (mean age, 10.6 years; 47.2% male). Good reproducibility of MacCAT-CR total and subscale scores was observed (intraclass correlation coefficient range, 0.68-0.92). We confirmed unidimensionality of the MacCAT-CR. By the reference standard, we judged 54 children (33.5%) to be incompetent; by the MacCAT-CR, 61 children (37.9%). Criterion-related validity of MacCAT-CR scores was supported by high overall accuracy in correctly classifying children as competent against the reference standard (area under the receiver operating characteristics curve, 0.78). Age was a good predictor of competence on the MacCAT-CR (area under the receiver operating characteristics curve, 0.90). In children younger than 9.6 years, competence was unlikely (sensitivity, 90%); in those older than 11.2 years, competence was probable (specificity, 90%). The optimal cutoff age was 10.4 years (sensitivity, 81%; specificity, 84%).

CONCLUSIONS AND RELEVANCE The MacCAT-CR demonstrated strong psychometric properties. In children aged 9.6 to 11.2 years, consent may be justified when competence can be demonstrated in individual cases by the MacCAT-CR. The results contribute to a scientific underpinning of regulations for clinical research directed toward children.

Clinical trials

Therapy or product performs as expected?

- Drugs
- Treatment procedures
- Device
- Behavior intervention
- Other forms of treatment

Prospectively evaluates the risks and benefits

Research question

Designed to answer one or more specific questions

- Clinically relevant to the community
- Size of the problem

Reason for multi-center trials

- Need different resources from different centers
- Inadequate subjects in one center

Forming a network

Know people in the region

- Travel / training institution
- Professional meetings
- Professional society / organization

Let people know you

- Professional organization
- Scientific publications

Mass media

- Institutional website

National research focus

Aging

Obesity

Cancer

Diabetes

Cardiovascular disease

……..

Funding is aimed to support clinician scientists

Public perception – research on children

- Has improved over the years
- Reluctance to subject healthy children for ‘experimental treatment’
- Venipuncture
- Phase 1 or 2 trials rare in children in Singapore

Recruitment

Health care personnel

- Reasons for not participating:
  - Do not see the need for research in children
  - Extra work

Parents or guardians

Prenatal recruitment of participants for a birth cohort study

Ernst et al.

GMS German Medical Science 201

- Conducted in Germany
- Jan 2012-Mar 2013
- 22 gynecologists with offices
- n the vicinity of participating
- ospitals invited
- Eligible mothers recruited
- 8 gynecologists took part
- Reasons for not taking part:
  - Lack of time (9)
  - No reason given (5)

Table 1: Data collection, variables and source of information

Data type (time interval)	Section	Variables concerning
Self-administered questionnaire (prenatal)	Influencing factors on childhood leukemia	Birth order; weight gain during pregnancy; hospitalization; hormonal treatment; x-ray and CT examinations during pregnancy; usage of drugs, vitamins, minerals*; folate and vitami supplementation; type of conception; infections and other diseases during pregnancy**; family history of specific diseases; hair dyeing; use of pesticides and chemicals; smoking habits*; alcohol and drug intake*; dietary habits/nutrition; use of electric household appliances; living in mold infested rooms
	General and socio-economic information	Date of birth*; age*; weight*; length*; family size of household; school and professional education; current type of profession; financial situation
Physician records: pregnancy record books and newborn documentation sheet (prenatal/at birth)	Medical information and data on biological samples	Number of pregnancies: live/stillbirth, miscarriages; APGAR; ultrasound examinations; infections and other diseases during pregnancy ; date of birth; sex; gestational age at birth; birth weight, length, head circumference; mode of delivery; complications at birth; date and time of collection of biological samples; weight of cord blood sample
Biological samples (at birth)	Genetic and biochemical information	Maternal blood: DNA stored at –80°C Umbilical cord blood sample: Plasma, serum, whole blood, red blood cells stored at –80°C Living cells/mono-nuclear cells stored in nitrogen tanks at –196°

Prenatal recruitment of participants for a birth cohort study

Ernst et al.

GMS German Medical Science 201

Conducted in Germany

Jan 2012-Mar 2013

200 eligible mothers

48 (24%) agreed

34 enrolled by their gynecologists

12 recruited by study staff

Reasons for not taking part:

- Uncertainty
- Not willing to decide for their children

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/hy do children decide not to participate in clinical research: a uantitative and qualitative study

Volume 78 | Number 1 | July 2015 Pediatric Rl

Prospective study among 161 paediatric patients, aged 6-18y, who are eligible for clinical research

Reason for not participating:

- Expected burden for themselves directly deriving from the research procedures, such as extra time investment,
- possible adverse effects of trial medication,
- inconvenience
- Participating would impact on their time schedule
- Did not want to miss school
- Did not feel like participating

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Reason for participating:

- Participation would benefit others
- Help to advance knowledge
- ‘mistook as individualized treatment’
- Helping others
- Because the doctor told me….

Recruitment and retention

- Build trust by communicating research goals to the community
- Select a research question perceived to be important to the community
- Characterize the target population that will benefit from the research
- Design trials with practicality and minimizing risk
- Involve the community with the design and implementation process
- Incorporate a detailed recruitment plan
- Use focus groups
- Avoid or minimize blood draws or other invasive and uncomfortable procedures

Adolescent engagement

- Expect higher that anticipated dropout rate
- Hectic lifestyle of most adolescents
- Busy schedules, sports, enrichment activities after school or on weekends
- Messaging reminders