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Science at the heart of medicine

Grey Areas in Research Involving Human Subjects

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Uncertainties and dilemmas

- Many unresolved difficulties remain in the domain of human subjects research
 - > How to improve the process and documents for obtaining informed consent
 - > How to determine when risks to research subjects are “reasonable”
 - > Which research subjects are vulnerable and in what ways
 - > What constitutes an “undue inducement” to participate in research
- These are among many traditional, ongoing concerns in research ethics

More fundamental issues

- A series of broader issues comprises a number of “grey areas”
 - > When is an activity research and when is it something else
 - that resembles research
 - but is not (or need not be) subjected to the ethical requirements for research
 - > How to determine when a medical practice has become the “standard of care”
 - This has implications for the design and review of research

Activities that resemble research

- Two activities that blur the line between activities that are research and non-research
 - > Public health practice
 - > Quality improvement (QI) in clinical settings
- Methodology of these activities may be identical to research methodology
- Publication of results may follow the conclusion of the activity
- Informed consent may be needed for both types of activities

Why make a distinction?

- Why is it necessary or important to make a distinction between research and these other activities?
 - > If an activity is considered research
 - A protocol must be submitted to a research ethics committee (REB, IRB)
 - It is usually necessary to obtain informed consent
 - Research subjects have the right to refuse to participate and to withdraw at any time
 - Research is subjected to governmental oversight
 - > These ethical requirements for research are often absent in public health practice and QI

Definition of 'research'

- Widely accepted definition of 'research'
 - > “Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”
 - Key element is “designed to contribute to knowledge that is generalizable”
 - > Definition does not mention publication of results of the activity
 - Yet some maintain that publication is a *de facto* determinant of research

Activities in public health practice

- Surveillance

- > The collection, analysis, and interpretation of data in a systematic and continuous manner. This activity is integrated with the timely diffusion of information to people and agencies responsible for preventing and controlling diseases or injuries
 - Typically conducted by governmental agencies with authority to carry out investigations
 - Surveillance may involve taking blood or other biological samples from people
 - Consent would then be necessary for this type of public health surveillance

Activities in public health practice

- Response to emergencies
 - > An activity carried out in an urgent situation or an emergency, usually caused by a suspected or identified threat to health or safety
 - Purpose is to document the existence and the magnitude of a public health problem in a community and implement appropriate measures to deal with the problem
 - What is learned in the course of the investigation may lead to generalizable knowledge
 - Even if not the initial intent of the activity

Emergency response as research

- Would require preparation of a detailed research protocol
 - > Research ethics committee would have to review the protocol and possibly request revisions
 - > This would delay initiation of response to emergency resulting in greater harm
- Could require obtaining informed consent from individuals studied in the emergency situation
 - > This would take time and take resources away from dealing directly with the emergency situation
 - > May be stressful for people affected by the emergency

Emergency response as research

- Even if distinction cannot be made clearly between data gathered for responding to emergency situations and data gathered for research
 - > REBs could establish a policy for disease outbreak investigations, in which a full, detailed protocol need not be submitted
 - > A duly constituted oversight body could decide to waive the requirement for signed consent forms in favor of oral consent or no consent for gathering data in which individuals cannot be identified

Evaluation as public health practice

- Evaluation

- > The systematic evaluation of scientific and statistical procedures to arrive at the conceptualization, design, implementation, and usefulness of public health programs. This includes making comparisons based on measurements and the use of this information to optimize the results of such programs
 - These appear to be identical methods used in the conduct of research
 - Is “operations research” research? Or program evaluation?

The debate

- Some people argue that there should be a narrow definition of public health research
 - > If it were necessary to submit all proposals to a research ethics committee, there would be long delays before a public health project could be carried out
 - > If it were necessary to obtain informed consent from each person before gathering personal information for surveillance, some people would refuse and therefore, the results would not be valid

The debate

- Other people argue that there should be a broad definition of public health research
 - > Research ethics committees could then better ensure that privacy and confidentiality will be protected
 - > People would be given the right to decide what should happen to their personal information

The debate

- Some people argue that it is not really possible to make a clear distinction between public health research and practice
 - > Because there is an irreducible overlap in the activities in both situations
- Other people contend that it is necessary to clarify the distinction
 - > Because it is very confusing, and different groups and agencies accept different definitions

Distinction adopted by US CDC

- The CDC distinction between public health research and practice is based on the intention of the activity
 - > If the primary intent is to prevent or control disease or injury or to improve a public health program, and no research is intended at the present time, the project is non-research. If the primary intent changes to generating generalizable knowledge, then the project becomes research.

Objections to the CDC guide

- Officials in state governments in the US made strong objections to the guide
 - > “We don’t consider these activity to be research when the state carries them out. However, if another entity carries out the same activities, that would be research and would require review by a research ethics committee”
 - > It is not the *intent* that determines whether an activity is research
 - It is the organization or sponsor of the activity

One suggestion

- Public health surveillance is at the same time research and practice
 - > Although an emphasis can be on one or the other
- What is required in either case is the articulation of ethical principles that justify and limit the collection of data
 - > And to develop a mechanism to oversee ethical aspects of public health practice

A different suggestion

- It is necessary to clarify the line between research and practice in the field of public health
- In addition, it is necessary to reform the current systems of oversight
 - > In order to ensure that reviews of research are commensurate with the level of risk
 - > To appropriately situate the regulation of human subjects protections relative to public health more broadly

Quality improvement: a case example

- Quality improvement project in US hospital aimed to improve dialysis measures of adequate blood cleaning through better compliance with dialysis prescriptions
- Project not submitted for review by IRB
- Two scholarly papers were published in journals
 - > Faculty member reported the published papers to the institution's IRB in compliance with the committee's rules
 - > Committee determined that the project was research and should have been reviewed
 - > Two federal agencies disagreed with each other about whether the project was research

Another example

- Leading US medical school developed QI program with a checklist designed to prevent hospital infections
- Checklist was initiated in 108 intensive care units
 - > Rates of infection lowered
 - > Lives and money saved
- Results of program published in NEJM
- US Federal oversight agency wrote to medical school claiming that these activities were human subjects research but were done without IRB approval
 - > Agency ordered activities to halt immediately

QI case example

- Medical school replied that they considered the activity exempt from review by the research ethics committee at the school
 - > But admitted that IRB should have made that decision
- The hospitals replied that their involvement was QI, not human subjects research
- Case caused a furor and public outcry when reported in the popular press
 - > A program that succeeded in reducing infections, saving lives and money, was shut down arbitrarily by the agency

QI in clinical settings

- Requirements for protection of human subjects of research appear to apply to many quality improvement projects
 - > Privacy concerns exist in QI as well as in research
 - > Trying a new mode of care or treatment in a hospital may place patients at risk or be worse than the current mode
 - > Projects that compare a new mode of care with an existing one have a “control group,” just like research
 - > If something “new” is being tried out on patients, shouldn’t they have to provide their consent?

Barriers to improving quality of care

- But, it is argued, if all QI projects were treated as research
 - > QI projects would be much slower to get off the ground
 - > Proposed projects would have to undergo prospective review by a research ethics committee
 - Would increase the work load of existing committees
 - Would place burdens on those doing the QI by requiring detailed reports
 - > Need to obtain individual informed consent would make projects logistically impossible to carry out

Investigators prefer to classify as QI

- QI does not require preparation of a detailed protocol, or review and approval of the protocol by a committee
 - > Therefore, QI activities can be designed and implemented more quickly and without the need for changes that may be required by an REB
- QI does not require
 - > preparation of informed consent documents
 - > a time-consuming consent process
 - > problems that could occur in the need to maintain sample size if individuals wish to withdraw from the activity

On the other hand...

- Even when a proposed project appears clearly to be QI and not research, practitioners may wish to present it as research if they think the results may warrant eventual publication
 - > Based on the questionable belief that if publication is intended, it must therefore be research
 - > Journal editors will question whether IRB/REB approval has been obtained
 - > Existing cases indicate the trouble may ensue from IRB/REB or governmental oversight agencies

Determining what is “standard of care”

- New drugs and devices must be approved by a regulatory agency before crossing the line between research and accepted medical practice
- However, other medical interventions lack the “bright line” provided by regulatory agency approval
 - > New surgical procedures
 - > New routines introduced into an ICU or other unit of a hospital
 - > Newly developed procedures for treatment that do not involve new drugs or devices

Case example 1

- Early goal directed therapy (EGDT) to deal with sepsis in the emergency room
 - Intensive care protocol demonstrated a dramatic mortality benefit
 - Reported in one paper published by NEJM
 - Degree of uncertainty remained about the efficacy and in some cases appropriateness of this highly intensive medical management
 - One ICU sought to study implementation of the protocol
 - » Should that be considered research?
 - Question arises: at what point can it be considered “standard of care”?

Case example 2

- Freezing oocytes for future use
 - > Procedure is done by about half of US infertility centers
 - > Long term consequences unstudied and remain unknown
- Practice Committee of ASRM considers it to be experimental
 - > Available outcomes data insufficient to consider it established medical practice
 - > Says it therefore merits IRB review
- Critics argue there is no bright line, but use in 50% of centers qualifies as “standard practice”

Standard of care

- How much evidence is needed before a new medical or surgical procedure can be considered “standard of care”?
 - > Does evidence always have to be a result of randomized, controlled clinical trials?
 - > Does endorsement of a treatment protocol by a professional medical or surgical society determine that it has become standard of care?
 - > How many papers validating the procedure must be published in reputable journals in the field?

Studying implementation

- If a protocol for medical intervention can be considered the “standard of care”
 - > Then studying its implementation in a new setting may be considered QI rather than research
 - Protocol may not (or need not) be submitted to ERC for review
 - Need not be compared with the existing intervention in that hospital or unit
 - Would not require informed consent from seriously ill patients or their representatives

Studying implementation

- Questions to be answered in studying implementation of a newly developed procedure may differ sharply from studying the safety and efficacy of the procedure itself
 - > Study may look at time to implement
 - > Skill of practitioners in implementing a complex new routine may be object of study
 - > Monetary cost of the implementation
- Even if such investigations do undergo REB review, the risks would be assessed differently from a study in which outcomes include the safety of the procedure in patients

Some (tentative) conclusions

- Attempts to sharply distinguish research from public health practice or quality improvement may be futile
 - > When genuine uncertainty or overlap exists, it is dogmatic to seek a definition that makes a clear distinction
- What is needed is ethical oversight of such activities whether they are determined to be research or non-research
 - > Human beings may be placed at risk
 - > Their privacy may be intruded upon

Conclusions

- The rules and procedures for REB prospective review of research are probably ill-suited to ethical review of public health activities and QI
- Participation in research is optional, whereas patients and health care providers have a responsibility to participate in QI
 - > A mechanism should be established for ethical review
- Governments have a mandate and authority to take steps to ensure the health of the public
 - > Here also ethical guidance is necessary as well as a mechanism for review