7.3.1 Research Ethics Review

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Learning Objectives

1. To understand the rationale for prior independent review of clinical research
2. To gain some appreciation into the central issues considered by research ethics boards when they review protocols

Case

Cephalosporins are routinely administered during surgery for the prevention of post-operative wound infections. Dr. Tong has long preferred the use of a first generation cephalosporin in his surgical practice, believing that this type is as effective for infection control, and more inexpensive, than a broad spectrum cephalosporin like ceftizoxime. Other medical centres are increasingly switching to the latter type, and Dr. Tong has occasionally used ceftizoxime himself. Noting the lack of solid evidence indicating the superiority of broader spectrum cephalosporins, Dr. Tong proposes a study in which his patients will be randomized to receive either ceftizoxime or a first generation cephalosporin — cefazolin. Dr. Tong proposes to evaluate patients for infection at regular time intervals during recovery and 30 days after discharge from the hospital. The assignment of patients will be masked, as will their outcome assessment.

Dr. Tong feels that the requirement for submission to a research ethics board is a bureaucratic annoyance and an infringement on his professional autonomy. The study involves a side-by-side evaluation of two routine medical practices. There are no plausible grounds for expecting that the safety or efficacy of either treatment arm will vary significantly or that infection control will depart from the standard of care. All patients entering this trial will get closer monitoring for wound infections than typical surgical patients.

Questions

1. Why does Dr. Tong need permission to give a drug to half of his patients but does not permission when he wants to give it to all of his patients?
2. Why must this study undergo independent review through a research ethics board?
3. What general factors should a research ethics board consider in reviewing a research protocol like this?
4. Given the level of risk for Dr. Tong's proposal and the fact that both antibiotics are in routine use for surgical procedures, couldn't a patient's enrolment in the study be considered to be authorized by his or her consent to receive care?
5. How might clinicians decide when an activity requires independent review and when fully informed consent should be sought?

Discussion

Q1. Why does Dr. Tong need permission to give a drug to half of his patients but does not permission when he wants to give it to all of his patients?

One simple answer is as follows: if Dr. Tong is so confident in this drug that he would give it to all of his patients, why is he proposing to withhold it from half the patients in his protocol? As will be explained further below, denying patients access to a demonstrably advantageous drug would be an unethical breach of the physician's duty to vouch for the best interests of persons under his or her care.

Q2. Why must this study undergo independent review through a research ethics board?

The history of clinical research ethics is largely a story of scandal followed by reaction. Following
revelations of atrocities committed by Nazi doctors on concentration camp inmates, the Nuremberg Code\(^1\) (and later, the Declaration of Helsinki)\(^2\) defined the central ethical challenges of human research as informed consent and risk-benefit balance. These policies granted physician-investigators broad discretion to judge their own protocols on the basis of their risk, benefit, consent procedures and scientific rigour. Another series of scandals in the 1960s and 1970s (for example, exposés of experiments conducted at the Willowbrook State School and the Jewish Chronic Disease Hospital in Brooklyn, New York, as well as the Tuskegee syphilis observational study)\(^3\) exposed some of the limitations of self-regulation. From then on, the central ethical challenge of clinical research was recast as a problem of divided loyalty. Physicians who conduct clinical research are fiduciaries and, as such, are obligated to promote the welfare and interests of persons under their care. Yet research protocols are primarily aimed at benefiting society through the gathering of generalizable knowledge; therefore, they may involve practices that potentially compete with optimal care (e.g., randomization, masking, fixed dosing regimes). The main rationale for independent review derives from a concern that, unlike usual medical care, the physician-investigators must balance competing interests — those of their patients and those of future patients who might benefit from the knowledge gained.

Q3. What general factors should a research ethics board consider in reviewing a research protocol like this?

There are three core principles for clinical research: respect for persons, beneficence and justice.\(^4\) How these different requirements are interpreted and translated into practice will vary widely. Nevertheless, there is a broad international consensus that, for any research protocol to be ethical, it must fulfill the following six conditions:

- Valid informed consent must be obtained.
- The protocol must have a reasonable balance of risks and benefits.
- The study design must be methodologically valid, and the protocol must address a valuable question.
- Subjects must be selected in a fair manner.
- Subjects must be assured of privacy, the right to withdraw and access to information that might influence their decision to remain enrolled.
- Protocols must undergo independent review.

The main function of research ethics board review is to ensure that a research protocol meets each of these conditions. This includes the last requirement, which research ethics boards fulfill by ensuring that their membership has sufficient medical, ethical and legal expertise to review a protocol. In addition, research ethics boards also manage conflicts of interest.

Q4. Given the level of risk for Dr. Tong’s proposal and the fact that both antibiotics are in routine use for surgical procedures, couldn’t a patient’s enrolment in the study be considered to be authorized by his or her consent to receive care?

Obtaining and documenting informed consent imposes additional administrative and resource demands for investigators. Some clinicians also feel that the legalism of the process disrupts the relationship of trust between the caregiver and the patient. The question might be reframed as follows: “Might Dr. Tong ethically waive informed consent?” On the one hand, there’s a plausible case that he could. Apart from the 30-day follow-up phone call, surgeons in this study will not be departing from standard of care. As well, surgeons do not generally describe in detail which particular antibiotic they will be administering preoperatively. So why should they do so here? The response to this question is that ethical codes stipulate criteria that must be fulfilled for a waiver of informed consent. According to the Canadian “Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans,”\(^5\) consent waivers are granted only in the event that

- the research involves minimal risk,
- the waiver is unlikely to adversely affect subjects,
- obtaining consent would be impractical,
- if possible, subjects will be debriefed following the study, and
- the study does not involve a therapeutic intervention.
Clearly, Dr. Tong's study would fail the third condition (impractical is not the same as burdensome) and the fifth condition. From an ethical standpoint, it seems a mistake to consider risk as the only reason to obtain informed consent. As stated above, the core ethical tension is that clinical research is primarily aimed at serving the interests of future patients. As a society, we agree that people are generally entitled to determine what activities they involve themselves in as well as to understand the nature of relationships they enter into with others. In response to a very similar research proposal, one group of ethicists put it this way: if consent is waived, "everyone knows [the subjects are entered into a research protocol] but the subjects. How can this be justifiable?" Nevertheless, given the low risk and given that the study drugs are not a major departure from standard medical practice, an abbreviated consent document mainly aimed at explaining the fact of the research, rather than its specific details, might be more appropriate than the lengthy forms used in higher-risk research.

Q5. How might clinicians decide when an activity requires independent review and when fully informed consent should be sought?

In a sense, a clinician is conducting an experiment every time he or she administers a drug. For example, physicians often prescribe medications off-label on a hunch that doing so might help their patients. Dr. Tong's proposal provides an example of a study that closely resembles quality improvement rather than clinical research. Some activities, like a randomized controlled trial involving a new medication, clearly qualify as research and must undergo independent review. Other activities — say, innovative surgery — are much more ambiguous and will generally not undergo research ethics board review. Dr. Tong's proposal borders on a third category of research — quality improvement — aimed at helping health care providers optimize care and minimize expenses. The Tri-Council Policy Statement actually states that quality assurance studies need not undergo research ethics board review.

There are no simple rules for deciding which studies are "research" such that they require independent review and which are innovative care or quality assurance protocols. Nevertheless, here are a few of the central considerations. First, to what degree does the protocol interfere with normal clinical practice? In Dr. Tong's proposal, the caregiver (Dr. Tong) will be prevented from learning the identity of the antibiotic, and, through randomization, he will avoid using his own medical judgment to decide which antibiotic to use. These validity requirements seem to pull Dr. Tong away from his normal way of practising medicine. Second, to what degree is the information in a given protocol likely to benefit the subject in the future? In Dr. Tong's study, his patients are not likely to require another identical surgical procedure; they — unlike future patients — are therefore less likely to benefit from the knowledge gained by his study. In contrast, quality improvement studies often provide information that can be used to optimize care for the subject in addition to future patients. Research ethics boards have limited resources and personnel; were benign quality assurance studies always put before research ethics boards, they might draw resources away from more ethically contentious studies. Nevertheless, when uncertain, the investigator should always contact a research ethics board administrator to decide whether to submit a protocol for consideration or to seek expedited review.

References


Resources

- Appelbaum PS, Roth LH, Lidz CW, Benson P, Winslade W. False hopes and best data: consent to research and


