7.3.3 Physicians' Obligations to Patients in Clinical Research

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Educational Objectives

1. To review the availability of guidelines and policies for the conduct of human research, including the role of the research ethics board (REB) in human research.
2. To examine the specific responsibilities that physicians have to patients who are participating in research, including issues of informed consent, conflict of interest (COI), confidentiality and disclosure of research results.

Case

Jordan is a 10-year-old, grade 4 student who presents with a 3-month history of back pain. His pain is exacerbated by playing hockey and is associated with progressive difficulty in sleeping at night. He has been well prior to this, but there is a strong family history of breast cancer and sarcoma in young adults. A pelvic MRI demonstrates a probable Ewing's sarcoma arising from the ilium, with invasion of his lumbar plexus.

The Kid's Cancer Group is a multinational, cooperative clinical trials group. A randomized clinical trial for Ewing's sarcoma is available. This trial is examining the use of standard chemotherapy versus standard chemotherapy plus an antiangiogenesis agent (SloVenGrow). The local REB in Halifax has approved the study after institutional review board approval in the USA. There is an understanding that an independent data safety monitoring board (DSMB) has been established. A secondary aim of the study is to collect biology specimens for gene testing to look for potential cancer-susceptibility syndromes.

Jordan is told of his cancer diagnosis. With guidance from his parents, the concept of the research study is presented to him in a way that he can understand. His parents provide consent and he is randomized to the new antiangiogenesis arm. As the trial proceeds, and while Jordan is still receiving therapy, evidence arises from a separate study that SloVenGrow is associated with an increased risk of learning difficulties in children and adolescents. The DSMB recommends continuing this trial pending further information, and this is discussed with the parents. They elect to continue on the research protocol.

The biology specimens are banked with linked but confidential patient identifiers. Two years after the close of the therapeutic study, these samples are analyzed for known cancer susceptibility syndromes (BRC1 and Li-Fraumeni) by a separate clinical laboratory. Following this, a planned search is conducted for novel genes that may be involved in cancer susceptibility. Jordan's specimen is found to contain the Li-Fraumeni mutation of the p53 gene. Jordan and his parents have a careful discussion with the oncologist as to how to notify them of their elevated breast cancer risk as a consequence of the diagnosis of the Li Fraumeni syndrome.

Questions

1. What Canadian and international guidelines govern the conduct of human research?
2. What obligations do physicians have with regard to research ethics review?
3. What responsibilities do physicians have to patients with respect to obtaining consent for research? How does this apply to those without the capacity to consent? When should assent be sought?
4. What types of COI may arise in research with patients?
5. What responsibilities do physicians have with respect to the confidentiality of results that may affect other family members?

Discussion

Physicians have a moral duty to support human research in order to assist in maintaining evidence-based practice and the advancement of the care of their patients. They may participate in this duty in a number of ways, including serving on REBs, designing and conducting research studies or playing a role in the recruitment of patients or in the routine care of a patient who is participating or has participated in human research.
Obligations that arise in these contexts in the conduct of research stem from an over-arching principle of respect for persons and avoiding the treatment of individuals as a means to an end.1

Q1. What Canadian and international guidelines govern the conduct of human research?

Historically, the ethical conduct of research has been raised at a number of levels over many years, but most succinctly following the Nazi atrocities, as was articulated in the Nuremberg code.2 Subsequently, the Declaration of Helsinki and its revisions have been the guiding documents that describe international standards of conduct of human research, including specific obligations in medical research.3

In Canada, the TriCouncil Policy Statement (TCPS) is the policy document for the conduct of all human research affiliated with academic institutions that receive funding from the three major funding agencies in Canada (Canadian Institutes of Health Research, Social Sciences and Humanities Research Council and Natural Sciences and Engineering Research Council).4 In practice, this has been adopted as the standard for human research in Canada at all levels. Health Canada clinical trials regulations apply to clinical trials.5

Human research policy statements from the Council for International Organizations of Medical Sciences6 and the International Conference on Harmonization—Good Clinical Practice guidelines,7 of which Canada is a signatory, may also apply, depending upon the nature of the research being conducted. Researchers should also be attentive to local provincial legislation, which may provide additional requirements related to, for example, age of consent or specific articles addressing research in children (for example, Article 21 of the Québec Civil Code8).

Q2. What obligations do physicians have with regard to research ethics review?

Physicians should recognize their responsibilities with respect to approval, conduct and reporting of research, and to individual patients in the conduct of research. REB approval of human research protocols is required before the recruitment of patients, even if the research project has received grant funding.

The ethical conduct of research in international settings is also an important obligation of Canadian researchers.9 Canadian researchers must receive approval from their home institutional REB and adhere to international regulations in the country where the research is being conducted, such as the Code of Federal Regulations in the USA.6,10–12 Researchers should plan to provide ongoing care for participants with therapies that are found to be effective through clinical trials in that jurisdiction.13,14 All guidelines and policies require an assessment of the balance of risk and benefit to the participant, with a minimization of risk and maximization of benefit in the design and conduct of the research. Physicians involved with the design and conduct of research must structure the research to achieve these aims.

Those involved with an REB at a reviewer level are charged with determining if the scientific rationale is appropriate and the methods sufficient to achieve the aims with the least exposure to risk as possible. REBs are also responsible for reviewing consent and assent procedures, privacy and confidentiality plans, risk determinations, COI issues and—increasingly—plans for the dissemination of results.4

Q3. What responsibilities do physicians have to patients with respect to obtaining consent for research? How does this apply to those without the capacity to consent? When should assent be sought?

Respect for persons is manifest by seeking their consent to research. This should include an assessment of participants with respect to their capacity to consent, provision of sufficient information about the research in such a manner that participants can make an informed decision and ensuring that consent is given voluntarily.15–17 Physicians must never conduct research with an individual without their expressed consent or that of an appropriate surrogate. Exceptions are allowed by policy in very limited circumstances, and only after approval by a REB (see Sections 2.1.c and 2.8 of the TCPS4).
The TCPS and other similar documents recognize that vulnerable populations (including children, elderly patients with diminished capacity, prisoners and others) may have special risks when participating in research.\textsuperscript{15,18–21} If they lack the capacity to consent then a surrogate decision-maker may be appropriate. Assent is the affirmative agreement by the participant to participate in a research project in the absence of the full capacity to provide informed consent.\textsuperscript{22} It is generally accepted that children aged less than 7 years usually do not have the capacity to understand research participation. Every effort should be made to support the development of autonomous decision-making as children mature.

The ability to provide full consent to research is related to a complex interaction of the complexity of the research, the cognitive development of the child and an understanding of the potential consequences of participation (or non-participation). While ethically there is no fixed age at which full consent may be sought, some jurisdictions do have legal statutes that address this issue and with which researchers must be compliant. Physicians should design research to ensure the inclusion of vulnerable populations with appropriate allowance for the assessment of capacity to consent or to participate in the assent process. They should also encourage opportunities for assessment and respectful consideration of dissent.

Once consent has been obtained, it is important to recognize that this is never static. Patient or surrogate understanding of the risks and benefits may evolve during the conduct of the research, new information may arise either directly within the study or in other studies, or the clinical context of the patient may change. Researchers have an obligation to confirm the ongoing validity of the consent based on these factors. The TCPS and other regulations\textsuperscript{10} specifically state that individuals should be provided with “continuing and meaningful opportunities to withdraw” (TCPS article 2.4.e.).\textsuperscript{4}

Similarly, assent and dissent to research participation should be regularly assessed. Points of increased burden are natural junctures at which to conduct this assessment. It should be remembered that individuals may mature during or after the conduct of the study, and will thus have the ability to fully consent or withdraw use of their data or samples. The latter issue is particularly relevant to biological tissue banking, where research on samples may be conducted after the point of collection.\textsuperscript{23,24} There are increasing calls to confirm consent for samples collected from minors who have now reached maturity.

**Q4. What types of conflict of interest may arise in research with patients?**

Physicians should be aware that they have a duty of care to the patient that must be at the forefront in decision-making around research participation. Physicians should be cognizant of potential COIs in research conduct. These are classically thought of as financial COIs, but more subtle COIs may relate to academic promotion, increased stature and other enticements.\textsuperscript{15,25–28} These COIs are inherent in life and do not necessarily reflect malevolent intent. However, COIs may damage the individual physician–patient relationship or global trust of physicians in a number of ways. A few of these are demonstrated in these following examples.

Physicians should avoid situations in which recruitment is influenced by monetary gain that may impair an impartial assessment of risk to the patient. They should avoid situations where ongoing research is not independently monitored and where participants are potentially at substantial risk. They should retain the ability to publish their data, even if these are negative or unfavourable to the sponsor of the research. COIs may also arise if the goals or conduct of the study are not in the patient’s best interest. Physicians with the dual role of caregiver and researcher must, in particular, be aware of a power imbalance between themselves and their patients (amplified with pediatric patients) that may influence their patients’ freedom of choice to participate in research. Management of COIs may be as simple as open disclosure or may require complete abstinence from participation in the research project.\textsuperscript{29}

**Q5. What responsibilities do physicians have with respect to the confidentiality of results that may affect other family members?**

Respect for persons includes respect for the need to retain privacy of personal information. Physicians are already familiar with the essential practice obligation to keep personal information confidential, and this extends to information collected in a research context. As part of the study design, mechanisms
should be in place as to how data will be maintained, if there are linkages to coded data and under what circumstances, if any, confidential data may be released (e.g., the identification of a child at risk, mandating appropriate agency notification).

Genetic data may hold particular risks to both the individual and to populations.30–32 There has been considerable debate within the genetics community as to whether there is an obligation to notify relatives of patients who have been identified with specific genes that confer risk to others.33,34 A detailed discussion is beyond the scope of this summary. However, when the obligation to confidentiality potentially clashes with an obligation to prevent harms in others, physicians should be prepared to encourage the sharing of relevant information, seek assistance from experts in genetic counselling and, on occasion, obtain legal advice.

Case Discussion

The case presented here illustrates a number of issues, including the importance of complying with national and international research ethics review. It also brings up the matter that assent to research should be considered in children who do not have the capacity to fully consent. The case demonstrates that correlative studies, especially genetic research, may have implications beyond the participant. Issues of confidentiality and privacy need to be discussed prior to the research, and plans made in anticipation of potential significant results that need disclosure.

In summary, physicians have a fiduciary responsibility to the individual patient as their primary duty that supersedes any potential benefit to others from the research being conducted. Physicians may play a number of roles in research. Each of these comes with different responsibilities, but all are linked to the primacy of the principle of respect for persons. The autonomy of the individual must be respected in seeking informed and continuing consent or assent for research participation. Physicians must be aware of potential COIs in the context of their duty of care, and their responsibility to disclose these COIs. Maintenance of the confidentiality of patient data and care in reporting is an essential obligation. Physicians must be aware of the potential limits to this promise of confidentiality, including in situations of risk to the participant and to others. Detailed guidance for these issues is available in a number of policies and regulations that physicians engaged in research must be aware of.

Pragmatic suggestions for residents

1. Physicians should be aware of local and national requirements in complying with physician responsibilities in the conduct of human research. In Canada, compliance with the TCPS is mandatory. International research endeavours require compliance with both the Canadian regulations and those of the international site.

2. The Declaration of Helsinki and other similar policy statements require that consent from participants must be received before the research is conducted. In the case of potential participants in which the capacity to consent is uncertain (e.g., children, adolescents, the elderly with dementia), the appropriate assessment of the capacity to assent to research is required. Assent should be obtained where possible. If a potential participant is unable to fully consent then a surrogate decision-maker is required.

3. In designing research studies, physicians should be aware of their obligation to confirm consent to participation on a regular basis—in particular if relevant, new information arises that may impact upon the continuing consent of the participant. Some studies may require a formal DSMB and a protocol design with pre-set stopping rules based on toxicity and efficacy outcomes.

4. It is important that research protocols prospectively establish mechanisms to deal with anticipated and (as far as possible) unanticipated relevant individual results that may have medical clinical relevance to the participant. A plan should be in place as to how to maintain the confidentiality of biological samples, while maintaining the ability to link these to the participant for disclosure.

5. Physicians should be aware of their legal obligations to others if important information arises from a patient that is known to potentially compromise others' safety. They should be aware of the debate that is occurring in the genetics community with respect to notifying kin of potentially relevant results.

6. Physicians should be aware of their moral responsibility to offer a summary of results to participants.35 (See case Ethical Issues Arising in the Return of Research Results to Research Participants.)

Suggested readings and references cited

1. Beach MC, Duggan PS, Cassel CK, Geller G. What does ‘respect’ mean? Exploring the moral obligation of


