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Ethical Dilemmas Encountered by Clinical Researchers

Gordon DuVal, Gary Gensler, and Marion Danis

Gordon DuVal, SJD, is a Assistant Professor at the University of Toronto Faculty of Law in Toronto, Ontario, Canada, *gordon.duval@ utoronto.ca.*
Gary Gensler, MS, is Statistical Support Staff at EMMES Corporation in Rockville, Maryland.
Marion Danis, MD, is Head of the Section on Ethics and Health Policy in the Department of Clinical Bioethics at the National Institutes of Health in Bethesda, Maryland.

INTRODUCTION

Recent research controversies, including those at Johns Hopkins,[1] the University of Pennsylvania,[2] the University of Oklahoma,[3] and elsewhere have inspired strong responses from the United States Office of Human Research Protections[4] and the broader research community.[5] Criticism of these institutions and proposals for reform have focused primarily on investigators' conflicts of interest and the quality of review of impugned protocols by institutional review boards (IRBs). Commentators and regulators have asked: Should these research projects have been allowed to proceed at all? That question is consistent with the academic literature on research ethics, which has focused almost exclusively on issues of research design and standards for review and approval by IRBs.

Yet ethical dilemmas arise in all stages of research involving human subjects. Subject recruitment, informed consent, protecting confidential research information, assessing ongoing risks to subjects, and other aspects of research commonly present difficult ethical challenges for investigators. While IRBs may be able to anticipate and make provision for some of these problems, difficulties often arise after the study design is finalized and approval from an IRB is obtained. We are aware of no systematic study of the kinds of ethical dilemmas encountered by clinical researchers, investigators' satisfaction with their resolution, or the utilization of ethics consultation in a research setting. To address these questions, we conducted a survey of physicians and nurses at the Clinical Center of the National Institutes of Health (NIH), a 267-bed hospital facility devoted exclusively to research.

METHODS

STUDY POPULATION

A random sample of research physicians and nurses was selected from lists of credentialed staff of the Clinical Center at the NIH in Bethesda, Maryland. Respondents were eligible for this study if they reported that they had been in practice for at least one year and had spent at least 20 percent of their time in clinical research activities at NIH.

STUDY SITE

The Warren G. Magnuson Clinical Center annually enrolls approximately 9,500 subjects into 1,165 research protocols, including 516 clinical trials (2001-2002 figures). Its Bioethics Consultation Service is staffed 24 hours a day by a bioethicist and a fellow from the Department of Clinical Bioethics and members of the Clinical Center Ethics Committee, which includes physicians, nurses, staff with training in social work, chaplaincy, and community representatives. Any professional or nonprofessional staff, research subjects and their families, or anyone else connected with the Clinical Center may request a consultation. The service provides approximately 90 consultations per year, ranging from telephone consultations to full committee consultations.[6]

SURVEY DEVELOPMENT

A survey instrument was developed based on a review of the research ethics and ethics consultation literature. Except for minor alterations reflecting the different context, the survey instrument is identical to that used in a parallel study of internal medicine physicians published by the authors.[7] The term "ethical dilemma" has a very specific meaning for philosophers, as a situation requiring a choice between what seem to be equally desirable or undesirable alternatives, each of which seems to be justified by a well-established moral rule or principle.[8] We intentionally did not define ethical dilemmas for respondents, because we wanted to elicit examples of ethical problems as researchers themselves perceive them.

We report results of the survey for questions in three domains: (1) the types of ethics issues faced by clinical investigators, (2) respondents' perception of the need for and effectiveness of ethics consultation services, and (3) sociodemographic, training, and practice characteristics of the physician and nurse investigators. To measure respondents' satisfaction with the resolution of ethical dilemmas and usefulness of ethics consultation, we used an 11-point scale (with 0 being "not satisfied at all" and 10 being "extremely satisfied"). To measure the usefulness of ethics consultation in reaching better ethical decisions, a similar 11-point scale was used. The survey instrument is available from the authors upon request.[9]

SURVEY ADMINISTRATION

Computer-assisted telephone interviews, lasting an average of 26 minutes, were conducted by trained interviewers from the Center for Survey Research at the University of Massachusetts in Boston. Subjects were not paid to participate.

HUMAN SUBJECTS PROTECTION

Participation did not involve the collection of personally identifiable information. Because of its anonymity and minimal risk, the Office of Human Subjects Research at NIH reviewed the study and exempted it from review by an IRB.

ANALYSIS

Respondents were asked to give narrative responses to identify the types of ethical dilemmas they face. These responses were coded using a consensus process. The investigators reviewed a 20 percent random sample of responses to identify major themes and to establish a coding scheme. The coding scheme identified broad categories of dilemmas (described below), such as informed consent, recruitment, and termination of research participation (see table 1). This coding scheme was used to identify: (1) the most difficult type of ethical problems encountered, (2) the most recent ethical problems encountered, and (3) the most recent ethical dilemma for which ethics consultation was sought. Two investigators assigned up to three codes to each response. Multiple codes were required when complex situations gave rise to different kinds of ethical issues. Three investigators discussed coding disagreements until consensus was reached.

We developed a seven-point index to measure respondents' training and experience with medical ethics. This training/experience index was scored as follows:

- Attendance at six or more bioethics rounds (1 point),

- Participation in a bioethics conference or bioethics course (1 point),
- Participation in an intensive bioethics course (1 point),
- Completion of a bioethics fellowship (1 point),
- A report of general confidence about knowledge of current standards of ethics (1 point),
- Past or current participation on a clinical ethics committee (2 points).

Possible scores ranged from 0 points for no experience to 7 points for the most experience.

Descriptive statistics were used to summarize the frequencies of responses. Univariate and multivariate logistic regression analyses were performed to determine factors associated with the likelihood of a researcher requesting an ethics consultation. Linear regression was performed to determine factors associated with physician satisfaction with their own efforts to resolve dilemmas and with ethics consultation.

RESULTS

STUDY PARTICIPANTS

Among 600 randomly selected physicians, 325 were ineligible, primarily because they spent less than 20 percent of their time in clinical activity at the Clinical Center. Among the 275 eligible physicians, 89

Table 1
Categories of research ethics dilemmas

	Most difficult dilemma		Most recent dilemma		Dilemma leading to ethics consult	
	Physicians (*n* = 160) %	Nurses (*n* = 159) %	Physicians (*n* = 130) %	Nurses (*n* = 137) %	Physicians (*n* = 175) %	Nurses (*n* = 85) %
Dilemmas not directly related to research						
End-of-life care	18*	29*	18	26	19	25
Informed consent	4	9	5**	18**	15	24
Confidentiality/truth-telling	5	9	8	16	7	7
Religious or cultural difference	2	3	5	4	9*	1*
Beneficence	2	2	2	3	3	0
Dilemmas related to research						
Informed consent	31	29	37**	15**	31	18
Conflicting clinical obligations	15	12	11	15	1*	9*
Children in research	8	9	8	11	12	12
Study design	9	7	4	7	4	
Termination of research participation	4	8	7	10	47	
Justice and the uninsured	5	4	13	10	8	10
Professional conduct	3	4	12	10	5	2

Notes: The table presents the percentage of responses that were assigned to each code category. The results add up to more than 100 percent because up to three codes were assigned to each response. Responses of "don't know," "no," and uninterpretable responses were omitted.

* Indicates statistically significant difference in the responses of the groups of subjects at the .01 level.

** Indicates statistically significant difference in the responses of the groups of subjects at the .05 level.

refused to participate and 19 could not be located or interviewed before the end of the field period; 167 completed an interview (61 percent response). Among the 260 randomly selected nurses, 58 were ineligible. Of 202 eligible nurses, 27 refused to participate and 12 could not be located or interviewed before the end of the field period; 163 nurses completed an interview (81 percent response). A larger number of physicians were sampled to ensure roughly equal numbers of eligible respondents.

The majority of physician respondents were male and White, and the majority of nurse respondents were female and White. The primary religious affiliation for both groups were Protestant and Roman Catholic (see table 2). Respondents had varied exposure to the field of bioethics: 25 percent reported attendance at six or more bioethics rounds, 51 percent reported attendance at a bioethics conference, and 4 percent had served on an ethics committee. The mean ethics training and experience score was 2.0 (out of 7.0) for physicians and 1.9 for nurses.

KINDS OF ETHICAL PROBLEMS

Researchers at the NIH reported ethical dilemmas that involved both research issues and clinical-care issues that arose independently of the conduct of research, but which involved enrolled subjects. Of the respondents, 95 percent could identify their most difficult kind of ethical problem and 76 percent could recall a specific recent ethical dilemma (71 percent of physicians; 81 percent of nurses). The frequency of responses identifying each kind of ethical problem is reported in table 1. These classes of dilemmas are described below, with a brief description of a representative case.

NON-RESEARCH-RELATED DILEMMAS INVOLVING SUBJECTS

Investigators identified the following types of ethical dilemmas involving the care of patient/subjects, encountered in the research relationship but not directly related to study participation.

End-of-Life Care

These were issues involving decision making at the end of life, such as withdrawing and withholding treatment, do-not-resuscitate (DNR) orders, and palliative care. For example, one respondent described a pediatric patient/subject in a cancer trial who was given a bone marrow transplant. She became neutropenic and developed a fungal sinusitis. The family strongly urged that everything be done to keep her alive, but the research team felt there was very little hope that she could be saved and that continued treatment would be burdensome.

Table 2
Demographic characteristics

	% Physicians (*n* = 167)	% Nurses (*n* = 163)
Gender		
Male	71.9	7.4
Female	28.1	92.6
Race*		
White	74.3	81.0
Non-White	25.7	19.0
Religion		
Protestant	28.1	42.3
Roman Catholic	23.4	39.9
Jewish	18.0	3.7
Other	7.8	0.6
No affiliation	17.4	13.5
Country of birth		
U.S.	67.7	89.6
Other	32.3	10.4
Medical training outside U.S.		
None	61.1	84.1
All or part	24.6	7.4
Ethics training and experience**		
Low (0 - 1)	35.3	38.7
Medium (2 - 3)	55.7	50.9
High (4 - 7)	9.0	10.4
Years at NIH		
< 5	24.0	14.1
5 - 10	39.5	38.0
> 10	36.5	47.9

Note: % ≠ 100% because nonresponses were excluded.
* The categories reflect U.S. Census Bureau standards for reporting race/ethnicity; *http:/factfinder.census.gov/home/en/epss/race_ethnic.html,* accessed 9 September 2005.
** On a 7-point scale, 1 point was given for attending 6 or more ethics rounds; 1 point for participating in a bioethics conference or course; 1 for feeling knowledgeable about current standards of ethics; 1 for taking an intensive bioethics course; 1 for completing a one-year bioethics fellowship; 2 for past or current participation in a clinical ethics committee.

Informed Consent

These were ethical concerns about the validity of the informed consent obtained from a patient/subject or when decision-making capacity was questioned. The range of issues included those relating to advance directives and surrogate decision making. For example, one researcher described a 21-year-old seizure patient with developmental delay who was judged to require brain surgery that was not a part of the research protocol. Although the patient's mother was anxious for the surgery to proceed, the patient seemed hesitant, and the team was unsure whether he understood the procedure and could give capable informed consent.

Conflict between Parties

In these cases, there was a strong difference of opinion regarding the clinical management of a research subject. The conflict could be between research team members, patients, or family members. For example, a patient/subject insisted on continuing smoking despite advanced lung disease and the unsafe proximity to oxygen, which he needed. This created an ongoing conflict with staff who believed that his behavior created a danger to himself, to his family, and to others.

Confidentiality and Truth-Telling

Questions about whether to divulge information were identified as raising ethical problems for respondents. One respondent told of an adult subject in a brain radiation study who lacked decision-making capacity and who had unexplained bruising and other injuries. The research team was worried that there may have been an unsafe environment at home, and wondered whether it was ethically permissible or obligatory to report these injuries, and, if so, to whom.

Religious or Cultural Issues

Beliefs and attitudes of persons from different religious or cultural traditions gave rise to ethical dilemmas. One researcher described the mother of a 13-year-old boy from a Middle Eastern country who did not want the child to be informed of his diagnoses of HIV and cancer, because she considered it would be unnecessarily distressing to him. Some research team members felt it was incumbent upon them to disclose.

Beneficence

In these situations, the researcher was striving to determine what course of action would best promote the welfare of the patient/subject. For example, a subject was suffering from a painful but nonterminal illness, and the research team believed that giving adequate doses of pain medication would likely result in addiction. The team was uncertain whether to moderate the medication to ensure adequate pain control without creating addiction.

RESEARCH-RELATED ETHICAL DILEMMAS

Respondents reported the following ethical dilemmas that were directly related to the conduct of research (see table 1).

Informed-Consent Issues

Physician and nurse researchers described situations in which the competence or voluntariness of an individual research participant's decision making, or the appropriateness of his or her informed consent to research participation, were in doubt. In one case, screening revealed that a proposed subject had a low IQ, was illiterate, and had a history of psychotic illness. The research team was uncertain whether she was capable of giving informed consent to participate in the study.

Conflicting Clinical Obligations

These were dilemmas in which the clinical well-being of subjects conflicted with the requirements of research. In one study, patients/subjects who were diagnosed with schizophrenia were to have their antipsy-

chotic medication discontinued to test the efficacy of an experimental memory-enhancing drug. Because of this medication "washout," a member of the research team became concerned about the well-being of some of the subjects in this study.

Children in Research

The special problems attending the involvement of minor children in research were identified as creating a number of dilemmas. In one case, a young child was proposed for participation in a bone marrow transplant under a research protocol. The parents, who were divorced and had a very inharmonious relationship, disagreed on whether the child should be given the transplant.

Study Design Issues

Investigators identified ethical problems relating to study design. For example, in the early stages of a phase I trial of an experimental HIV medication, infected subjects were to receive a dose that was not expected to be effective in reducing infection, and some staff feared it could cause drug resistance.

Termination of Research Participation

Some respondents described cases in which they were unsure whether to discontinue a subject's participation in the study. In one, a patient/subject who received an investigational treatment was having difficulty complying with the requirements of the study protocol. The team was uncertain whether it would be ethical to discharge him from the study, since he had no medical coverage and might have no access to treatment as a result.

Justice in Research

In these cases, researchers were concerned about whether the social obligations of justice or equality were afforded to research subjects. For example, a patient/subject with an illness for which an effective standard treatment was available, but who could not afford the cost of the standard treatment and who was uninsured, sought to be enrolled in a study of an experimental drug. The team was frustrated that this person felt obliged to enter a risky study to obtain treatment for his condition.

Professional Conduct

These were cases in which the professional conduct of a member of the research team was called into question. One researcher described a minor child, who was not a good candidate for surgery and who was otherwise not appropriate for the study, on whom surgery was performed solely to give the appearance that "something was being done."

The profile of the ethical issues encountered by physicians differed somewhat from those of the nurses. Nurses were more likely to identify dilemmas involving end-of-life care, and physicians were more likely to identify informed-consent issues. Informed-consent issues and those involving conflict between involved parties tended to be referred more often for ethics consultation, and issues involving conflicting clinical obligations tended to be referred less (see table 1).

On a scale of 1 to 10, with 10 the most satisfied with the decisions that got made in the most recent ethical dilemma, respondents gave a mean score of 6.9 (physicians 7.0; nurses 6.8). Gender was the only variable for which there was a statistically significant difference — male respondents were more satisfied (7.3 *v.* 6.6, $p < .05$).

USE AND EFFECTIVENESS OF ETHICS CONSULTATION

Of the research physicians and nurses who participated in the survey, 44 percent reported that they had personally initiated an ethics consultation. Overall, 68 percent of the respondents had participated in an ethics consult. Multivariate analysis of the likelihood of requesting a consult revealed no significant differ-

ences between male and female respondents, or between physicians and nurses. However, those researchers with greater knowledge in ethics, as indicated by a higher score on the ethics training/experience index, were more likely to request an ethics consultation compared with those who had less knowledge and experience (odds ratio = 4.73, 95 percent confidence interval = 1.98-11.30).

Respondents' satisfaction with their most recent ethics consultation averaged 8.0 on a scale of 10. Only those who reported participation in ethics consult were asked. The level of satisfaction was similar for physicians and nurses and for male and female respondents. No other statistically significant differences were found based on race, years of experience at NIH, or level of ethics training and experience; 23 percent reported that the consultation had changed the existing plan of treatment; 78 percent reported that they gained something from the consultation that might prove helpful in a similar situation in the future; 93 percent claimed that they were somewhat or very likely to request another consultation in the future.

DISCUSSION

To our knowledge, this is the first survey to systematically examine the ethical dilemmas encountered by clinical researchers. Three implications of these findings are noted.

First, the majority of researchers report encountering ethical dilemmas in the conduct of research; 95 percent could identify their most difficult type of ethical problem and 76 percent could recall a recent ethical dilemma. These dilemmas arise at all stages of the research process, from design through all aspects of the conduct of clinical studies. They can arise either prior to or following the traditional protocol review process of the IRB, but most of the dilemmas described by respondents in this study arose after IRB approval, while subjects were being enrolled or cared for as part of a study. The spectrum of issues reported by the clinical investigators surveyed here differ from those reported by clinicians.[10] At times the issues were exclusively focused on matters pertaining to research ethics, at times they related to clinical obligations, or to the competing demands of the two. While there are established bodies of literature on the ethics of the research in clinical domains, the resolution of ethical dilemmas at the intersection remains less well-explored and warrants further ethical analysis.

Second, nearly half of the clinical investigators in the study reported requesting an ethics consultation. Those who had used the service were generally satisfied, with a mean satisfaction score of 8.0 out of 10. This suggests that researchers value the presence of a resource to provide advice and consultation regarding ethical issues arising during human subjects research. It would be useful, then, for existing ethics support services to be sufficiently trained in research dilemmas to offer this kind of more-flexible consultation. A resource of this kind would be a helpful complement to IRBs in addressing clinical research dilemmas that arise in the conduct of research.[11]

Singer and colleagues have proposed a model of research ethics consultation for innovative therapies that involves collaboration between investigators and clinical ethicists.[12] At the NIH, the Bioethics Consultation Service functions in a similar way. For a number of reasons, this model has promise for use at other medical research centers. Ethics consultants generally have knowledge of ethics standards and expertise in facilitating the resolution of ethical problems. In addition, ethics consultants are in a position to respond promptly to ethics problems that require a relatively urgent response, such as the validity of informed consent, the release of information, the eligibility of a proposed research subject, or a request for advice on the completion of research advance directives.[13] IRBs are generally not structured to respond in this way, and typically do not have adequate resources to do so.[14] Consequently, an ethics consultation service may be better able than an IRB to handle the additional responsibility of consulting on research ethics issues. Another possibility would be for IRBs to establish consultation facilities to help investigators resolve difficult ethical dilemmas. Because of their more formalized committee structure and processes, IRBs may be more intimidating to research subjects and health professionals, especially nonphysicians, than a more informal ethics consultation service would be.

Since investigators commonly encounter the types of ethical dilemmas that are associated with provid-

ing regular clinical care, such as end-of-life issues, determinations of decision-making capacity, and cultural/religious differences, some of the fundamental bioethical values at stake are similar to those routinely addressed by clinicians and ethics consultants. This indicates that existing ethics consultation services, which offer consults by individuals or committees, might already be reasonably well-equipped to provide advice and guidance with respect to research ethics dilemmas. The involvement of IRBs in such consultations may be desirable because of their particular expertise in issues regarding the human subjects of research, methods and regulations, and their obligation to ensure the protection of human subjects and to monitor ongoing research.[15]

Third, the extent of self-assessed training and experience in ethics plays some role in researchers' attitudes toward ethics consultation. Those respondents who have higher levels of training and experience were more likely to request an ethics consult, although they did not report higher levels of satisfaction with the consult they received than other respondents did. In light of the frequency with which clinical researchers encounter ethical dilemmas and address them on their own, it is important that institutions and their ethicists focus efforts on teaching ethics and training investigators to resolve ethical dilemmas.

This study is limited in that it reports the experiences of investigators from only one site, a site that only conducts research. It remains to examine whether the experiences of clinical researchers reported here are similar to that at other medical research facilities. Further, these data were collected through self-report. There was no validation of the reports, which may have differed from actual behavior. In particular, the frequency with which researchers reported requesting and participating in ethics consultations was not verified. While the response rate in the study is similar or better than that reported for other physician surveys, we cannot exclude the possibility of response bias.[16] The exploratory nature of the analysis warrants conservative interpretation of its significance.

Although published and anecdotal data indicate that ethics consultation services do not typically provide consultation in the research context,[17] this study was not designed to determine the extent to which IRBs do so. The IRB structure does not lend itself to answering consultation requests, particularly those requiring a prompt response, nor do IRBs typically have the resources to do so effectively.[18] While investigators sometimes approach IRB members informally with ethical problems, there is little evidence that IRBs generally address these problems in a systematic or formal way.

In summary, IRBs are mandated to decrease the risk of ethical transgression in clinical research. Results of this study indicate that there is a range of ethical issues in research that are logistically out of the scope of IRBs. These results suggest that an ethics consultation service could have a role at the side of IRBs in assisting researchers to conduct ethical research.

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DISCLAIMER

The opinions expressed here are those of the authors and do not necessarily reflect the policies of the National Institutes of Health or the U.S. Department of Health and Human Services.

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