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Respondent Burden in Clinical Research: *When Are We Asking Too Much of Subjects?*

BY CONNIE M. ULRICH, GWENYTH R. WALLEN, AUTUMN FEISTER, AND CHRISTINE GRADY

Case Presentation

Mrs. C. is a 32-year-old female diagnosed with melanoma and metastasis to the liver. She has been suffering from moderate, self-described annoying pain in the abdominal region almost constantly for the past several weeks and self-medicating with Ibuprofen, which provides some relief. She also reports episodes of nausea and difficulty sleeping most nights. She arrives in the late afternoon at a regional medical research facility to enroll in a clinical trial for experimental surgery and chemotherapy in the morning. She indicates to a staff nurse her sense of concern and worry about the impending surgery as well as her prognosis. Upon arrival, the attending surgeon and anesthesiologist approached her to obtain consent for participation in the clinical trial. By enrolling in the trial, she becomes eligible for participation in several other trials, including transfusion related research and health related quality of life (HRQOL) outcomes assessment. Appointments throughout the afternoon and early evening and consuming at least several hours of Mrs. C's time consist of pre-assessment lab work, a preoperative history and physical, bowel prep, and other activities related to the various clinical trial protocols. Mrs. C. verbalizes that she is physically and emotionally exhausted from the

pace of the admission and enrollment processes. That night she has difficulty sleeping and develops a severe migraine, making her eligible for a clinical trial associated with migraines. Over a period of several hours, Mrs. C. gives informed consent to participate in four different clinical trials, each with differing degrees of risk and associated burden.

Although the field of bioethics has not clearly identified or articulated the problem of respondent burden in clinical trials, the ethical concern that underlies the concept has been acknowledged periodically in health services research. For example, health care providers are sometimes reluctant to allow clinical researchers to approach their patients for inclusion in clinical trials because they perceive the research to be distressing or overly burdensome for their patients.¹ Clinicians' desire to diminish "burden" to symptom-laden patients has also been identified as a factor that contributes to recruitment barriers in palliative care and end-of-life studies.² This notion of patient "distress" or "burden" related to participation in clinical research is comparable to what social scientists and survey methodologists have previously identified as "respondent burden." This phenomenon also needs to be addressed in the area of clinical research.

The Office of Management and Budget (OMB) used the term *respondent burden* when it introduced efforts to reduce the number and fre-

quency of federal requests for information and to minimize both the time and effort required of survey respondents in order to maximize response rates or research participation.³ Bradburn further explicated this concept in health survey research, where he defined it as a subjective phenomenon that may be related to four differing factors: interview length; effort requirement on the part of the respondent; the sensitivity of the questions being asked and the stress they may engender; and the frequency of participating in interviews.⁴ Yet to date, no one has directly addressed the issue of respondent burden in cases in which the subject population is seriously ill, the subject's participation is requested in multiple, ongoing studies, and where the research is clinically based, rather than limited to survey participation. Given the nature of human subjects research in clinical medicine, there is an obvious, pressing need to explore the issue of respondent burden, to understand its frequency and severity, and to create safeguards to minimize it.

Following Bradburn, we define respondent burden in the clinical research context as a subjective phenomenon that describes the perception by the subject of the psychological, physical, and/or economic hardships associated with participation in the research process. Respondent burden may vary in intensity and degree, depending upon the risk level of the research, the procedures that the research entails, and the individual subject's condition, prognosis,

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mental state, and support systems. Returning to our case, the potential for respondent burden is easy to identify: Mrs. C., who is already suffering from pain and symptoms related to her disease, may be particularly burdened by being asked to commit limited physical and emotional energy to the demands of participating in multiple studies and clinical trials.

The Clinical Context

Clinical researchers face similar issues to those of social scientists and survey methodologists when considering respondent burden, including sample selection, methodological approaches, and the time/energy commitment required of their participants. Yet, they also face additional challenges unique to the nature of their research. First, clinical research subjects are likely to be patients with an illness, which means they are already burdened with the physical, psychological, and social challenges associated with their illness. Clinical research subjects may choose to participate in research for the explicit benefit and/or betterment of their immediate health, their families' potential future health, and/or to advance the state of the science. Like other research subjects, they commit valuable time and effort to participate in research, but at significantly increased cost given their vulnerability and compromised health status.

Given the competitive nature of the research environment, the number of related clinical trials, and the ever-increasing pressure upon investigators to recruit and retain research subjects to meet enrollment goals, it is not surprising that many individuals will be recruited to enroll in more than one clinical trial. Consequently, some individuals will end up participating in trials that are being conducted concurrently, resulting in varying degrees of intrusion and intensity.⁵ As illustrated by the case

study, the concern for respondent burden is not solely related to the burden of participation in one study, (although such participation may be demanding for seriously ill individuals such as Mrs. C), but rather about the aggregate burden of participation in multiple studies. Even if each individual study is designed well and might generate valuable and generalizable knowledge, subjects may become physically exhausted, psychologically distressed, and/or economically burdened. Little is known, however, from the subjects themselves about what they perceive to be burdensome in research.⁶ Thus, clinicians and researchers should ask themselves, "When are we asking too much of subjects in the course of clinical research?" While it is safe to assume that there is such a phenomenon as respondent burden in clinical research, we do not currently know how widespread the phenomenon is, what types of circumstances are most likely to engender it, and what types of responses are necessary to address it. We need empirical data to answer these pressing questions.

Once there is better understanding of the phenomenon of respondent burden, questions remain about who should define respondent burden and what guidelines should be followed to minimize the problem. Should seriously ill individuals recruited to participate in a clinical trial determined by an Institutional Review Board (IRB) to be greater than minimal risk and procedurally burdensome be prohibited from concurrent participation in any other type of research? How much difference should the subject's clinical status, the burdens of additional studies, or the interests of the subject make in determining whether concurrent enrollment is appropriate? Who should make this determination—the IRB, the patient, the investigator, or someone else?

In the absence of guidelines and professional consensus about what constitutes too much respondent

burden, IRBs might be the appropriate body to make such a determination. However, investigators and patient-subjects might also be appropriate judges in determining whether clinical trial participation reflects patient-subject values, goals, and priorities. Given the lack of empirical data, conceptual clarity, and ethical discourse on what constitutes respondent burden, we are limited in our ability to answer these questions.

Reducing Burden

Several strategies for reducing burden in clinical research may include integrating multiple ancillary studies into one package for the IRB to review rather than limiting the number of research protocols in which subjects can concurrently enroll; periodically revisiting consent for patients involved in multiple studies;⁷ establishing and reviewing a central registry of studies; and using research participant advocates.

■ **Integrating Multiple Ancillary Studies.** One possible strategy for reducing respondent burden would be to integrate multiple ancillary studies into one package for the IRB to review and potential subjects to consider rather than limiting the number of clinical trials in which individuals can concurrently enroll. This would be important for two reasons. First, restricting concurrent participation may be objectionable because this option would not only potentially violate an individual's right to choose research studies that are consonant with her values and goals but also hamper recruitment targets and possibly the validity of data derived from underpowered trials.⁸ Second, demands on IRB members to accomplish protective oversight of human subjects and to ensure compliance with institutional and other research rules and regulations continue to increase in number, scope, and complexity. More often than not, these demands must be met with limited resources.⁹ Thus,

integrating studies may help IRBs balance the demands of efficiency in protocol review with ethical oversight of human subjects.

■ **Revisiting Consent.** Clinical scientists have begun to examine the importance of addressing each individual's unique experience as a participant in clinical trials, particularly the experience of critically ill and terminally ill patient-subjects. When individuals are faced with personal crises, we assume they will need to conserve their inner or external resources. At these times, they deserve to be self-protective, self-concerned, and self-focused; others should be supporting them and not requesting their help. Yet, some patients may only find satisfaction and meaning during trying times through the knowledge that they are helping others. Limiting their ability to participate in research could ultimately inhibit their ability to care for themselves.

In a recent survey by Burnet and colleagues of breast cancer patients' views on enrollment in clinical trials, the majority of respondents said they would consider enrolling in more than one study if the study were adequately explained to them.¹⁰ More than half of the respondents questioned 6-12 months following completion of their primary treatment said there should be no limit on the number of clinical studies offered to patients. However, the survey did not ask individuals about the type of research they would consider joining. Respondents' concerns about participation in multiple studies included demands on their personal time, transportation issues, and attending to one's normal life processes.

More studies of this kind would help determine subjects' perception of burdens and under what circumstances it is appropriate to approach similarly situated ill subjects for enrollment in additional research. Some subjects, for example, may

welcome participation in an additional study, particularly if the research questions are pertinent or salient in some way to their life. For example, subjects enrolled in a Phase I clinical trial that involves an invasive surgical intervention may find the opportunity to discuss their associated tumor or surgical pain—as it pertains to an additional clinical trial—important and potentially cathartic, psychologically beneficial, and contributing to the well-being of future patients. Moreover, subjects may view additional studies as inter-related rather than separate. It may be important to distinguish when respondents say “yes” to additional research fully understanding what the additional research will mean in terms of associated risk(s), benefits, and added respondent burden, from when they simply find it difficult to say “no” in some situations. With each additional study they enroll in, the aggregate burden may be greater on the individual. In cases where research subjects appear ambivalent and are hesitant to say “no” to additional research, Wendler and Rackoff suggest that researchers conduct an independent assessment of subjects' willingness to participate and reaffirm their right to withdraw.¹¹

■ **Central Registration.** A third possible strategy is to establish a central registry of every clinical study and research subject. IRBs could use the registry to periodically conduct a targeted form of research protocol review for those studies where burden and unnecessary duplication may be implicated.¹² Levine and colleagues propose “special scrutiny” for protocols they describe as “outliers,” i.e., research that involves innovative translational research and risk of significant harm or death to subjects, and research that raises serious ethical questions for which there is no consensus about whether it should go forward. Research involving respondent burden as we

define it could also fall under the “special scrutiny” umbrella. Different levels of review or the use of an independent research monitor could be used for clinical trials that involve greater than minimal risk and that are procedurally burdensome to research subjects.

■ **Research Participant Advocates.** Finally, advocates in clinical research settings could be used to help research participants better understand research studies offered to them, to monitor the amount of burden individual participants are experiencing, and to help research participants negotiate decisionmaking, including the decision to decline to participate in studies that are perceived as too burdensome.¹³

Future Research Needs

Research is needed to determine how frequently seriously ill individuals participate in multiple clinical trials, and the extent to which respondent burden varies by the subject's disease severity, the type of research they enroll in (qualitative versus quantitative, experimental versus nonexperimental), the number of studies in which they are enrolled, and the prospect of financial compensation for enrollment. Studies that identify the extent to which people feel free to decline research participation, especially when they are patients of the clinician-researcher or of her colleagues in the same institution, are also needed. So too are studies that examine what subjects, IRBs, and investigators perceive as burdensome, what factors and/or characteristics might minimize, mitigate, and/or intensify respondent burden in clinical research, and that explore the extent to which participants perceive interviews or quality of life assessments as more beneficial than burdensome. Understanding research subjects' perception of respondent burden—whether the burden is psychological, physical,



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and/or economical—will better inform the design of research studies, as well as guide ethical judgment in conducting those studies.

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