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When the Subject Is More than Just the Subject: Two Case Studies of Family Involvement in Human Subjects Research

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Abstract

Institutional review boards (IRBs) protect human research subjects by reviewing research to ensure compliance with federal regulations and institutional policies. One of the most important functions of IRBs is to ensure that investigators anticipate, plan for, and minimize risks to subjects. Under certain circumstances, however, participation in research may pose risks to nonsubject family members or other members of a subject's social network. In the context of a research protocol designed to test an intervention to prevent depression among a population of culturally diverse, urban mothers, we present two case studies of unanticipated problems, which demonstrate how nonsubject family members can either impact, or be impacted by, an individual's participation in research. The case studies illustrate the incongruence between federal regulations addressing IRB approval of research—which focus specifically on risks to subjects—and regulations on reporting incidents that occur during the conduct of the research, which extend to risks involving “others” as well. The cases also illustrate how risks to “others” can be accentuated in certain cultures where codependent family structures may increase the role that family members play in an individual's decision to participate in research. The question is raised as to whether this incongruence can inadvertently result in investigators and IRBs under-appreciating the risks that participation in research can pose to nonsubjects.

Keywords

maternal depression; secondary subjects; family involvement in research

The United States Department of Health and Human Services' Office for Human Research Protections (OHRP) defines a human subject as a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual, or identifiable private information (DHHS, 2010). Institutional review boards (IRBs) exist to protect subjects, in part by reviewing research protocols to ensure respect for subjects' autonomy, their self-determination regarding research participation, and their right to privacy. In studies that collect detailed family histories or genetic information, family members of research subjects can become subjects themselves. In such cases, family members may be formally considered “secondary subjects,” and thus be afforded similar protections as the principal subjects themselves (Botkin, 2001).

It is perhaps even more common, however, that subjects' family members and social contacts, as true nonsubjects, may incur risk through others' participation in research. For

example, a subject's participation in a diet study could unfavorably alter a family's eating patterns; or an experimental drug could substantially affect a spouse's quality of life through side effects such as impotence or behavior changes. Based on the regulatory definition of human subjects, however, IRBs often limit their focus to those persons who are the direct recipients of research interventions or data collection, or who meet the definition of a secondary research subject.

The federal regulations that outline the criteria that IRBs use to evaluate risk to research subjects (45 CFR 46.111) are sometimes referred to as the "one-eleven criteria" (DHHS, 2010). These criteria mandate, in part, that IRBs ensure that risks to subjects are minimized and that risks are reasonable in relation to anticipated benefits. None of the one-eleven (45 CFR 46.111) criteria, however, addresses risks to nonsubjects—who, as members of a research subject's family or social network, may be substantially impacted by research activities. In conducting a randomized pilot study of a depression prevention intervention among urban, low-income women with hospitalized preterm infants, we encountered two cases in which either inadvertent involvement of family members in the project or unanticipated repercussions of the research on family members arose as unanticipated problems. We present these two cases, followed by an analysis of their significance.

Context

Between September 2008 and January 2010, we conducted a randomized controlled pilot trial of a behavioral intervention to prevent depression among urban, low-income mothers of preterm infants. Our study population included 50 mothers with newborn infants ≤ 33 weeks gestational age, who were admitted to one of two Level III neonatal intensive care units (NICUs). Unlike most depression treatment studies—which enroll subjects on the basis of symptoms or diagnosis—our prevention study enrolled subjects on the basis of risk: specifically, being low-income and having recently given birth to a preterm infant. Among this population, the risk of developing clinically significant depressive symptomatology has been estimated to be around 30% in the infant's first year of life (Singer et al., 1999). For safety and ethical reasons, we purposefully excluded from the study mothers in danger of losing custody of their infants, as well as those with suicidal ideation, obvious cognitive limitation, or psychosis.

As part of an IRB-approved protocol, information about the study was included in standard NICU informational packets, and research assistants approached potentially eligible mothers during preassigned times on the postpartum unit. As is common in clinical research, subjects were asked to supply primary and alternate contact telephone numbers, and were informed that the reason for this was to give study staff multiple mechanisms to reach them. Mothers were randomized either to an intervention arm—which entailed four one-on-one sessions geared toward solving one's daily life problems—or to usual care. Intervention sessions took place either on hospital premises or in subjects' homes. All subjects were followed for six months with monthly assessments of depression symptoms and social functioning. Clinical and research staff were blinded to one another's assessments.

IRBs at both study sites approved identical protocols for how to handle moderate to severe depressive symptomatology, suicidal ideation, unmet social needs, and the mandatory reporting of suspicion for child abuse or neglect. When subjects reported suicidal ideation, research assistants immediately alerted study investigators, who made clinical assessments; and when necessary, investigators sought the opinion of a consultant psychiatrist. Algorithms for referral to urgent and emergent psychiatric services were detailed in the IRB protocol. A Certificate of Confidentiality was obtained from the National Institute of Child Health and Human Development.

Case #1

Ms. A, a single, 22-year-old woman, was enrolled in the trial and randomized to the control group, after giving birth to her first child at 32 weeks gestation. Ms. A was unemployed, did not attend school, and shared a room with her high school-aged sister in their uncle's home—a housing situation she described as unstable. During the study's baseline interview, Ms. A's depression symptoms were in the moderate range. She endorsed no family history of depression; nor had she been diagnosed with, or treated for, depression in the past. She expressed no thoughts of suicidal ideation or intent. She disclosed a history of abuse by her father; and was offered, but declined, a mental health referral.

Because Ms. A was assigned to the control arm, she had no contact with clinical project staff (whom we term "clinicians"). However, for follow-up assessments, Ms. A was contacted by research staff three times over the next three months. Each time, it took research staff several attempts to reach Ms. A because the only way to contact her was through her younger sister's cell phone (Ms. A did not have her own phone). Since the younger sister was in school from early morning to late afternoon, Ms. A was only reachable at the extremes of the day. As the holder of the cell phone, Ms. A's sister communicated with study staff and relayed phone messages to Ms. A.

During one of Ms. A's monthly research assessments, she revealed thoughts of suicidal ideation, including a specific plan of action. Per protocol, the research assistant notified the principal investigator (PI), while in the presence of the subject. The PI contacted Ms. A through her sister's cell phone. Ms. A's sister confirmed that Ms. A had a plan for suicide, and shared that the two slept in the same room so that the sister could protect Ms. A from hurting herself. At this time, both sisters disclosed that they were afraid of the uncle in whose home they resided. Although he was not physically abusive, they feared his strict rules, anger, and verbal hostility.

The PI contacted the consulting psychiatrist, who recommended that a local crisis intervention team be contacted. The PI informed the subject and her sister that he would be contacting a crisis intervention team and that the team would be phoning the family shortly. Ms. A and her sister refused to give the crisis team the address of their uncle's home, fearful of negative repercussions. After considerable time on the phone with the crisis team, Ms. A contracted for safety and agreed to come to the hospital for an evaluation the following day at a walk-in mental health center.

The following day, Ms. A came to the hospital while her sister was in school and underwent a mental health assessment, during which she expressed homicidal thoughts toward her child. Child protective services was called, and opted to remove the child from Ms. A's care. Upon learning that she would temporarily lose custody of her child, Ms. A attempted suicide on hospital grounds. She was restrained and admitted to the hospital.

When Ms. A's sister returned home from school and found Ms. A and the infant absent, she became fearful that their uncle would blame her for what had happened. Fearing for her own safety, Ms. A's sister, angry, phoned the PI and demanded that he phone the uncle to explain that she was not responsible for Ms. A's absence. This request contradicted a specific request made by Ms. A that the uncle not be contacted about what had happened. At this point, Ms. A was removed from the study, and all of the information regarding her clinical care was treated as confidential and thus not shared with the researchers. The research staff notified the IRB of the incident.

Case #2

Ms. B, a single, 19-year-old woman who immigrated to the U.S. while pregnant with her first child, enrolled in the study after giving birth at 27 weeks gestation. She was randomized to the intervention arm. Ms. B's assigned clinician had trouble reaching her on the phone, and per protocol, phoned an alternate contact, Ms. B's older sister. Ms. B scheduled her first session with the clinician, but did not keep the appointment.

The next day, Ms. B's sister phoned the clinician to express concern that her younger sister was inappropriate for the study: her (Ms. B's) English was poor; she was overwhelmed with having an ill newborn in a new country; and she was "young for her age." The sister explained that for Ms. B, moving to the U.S. upon discovering she was pregnant had caused her great distress; and compounding the physical and emotional difficulties of being pregnant, Ms. B was struggling to adapt to a new culture. In her native country, women did not receive prenatal care; but while in the U.S., she was expected to take vitamins, undergo tests, and visit her doctor every other week. The sister explained that these stresses had caused the baby's premature birth, and that her younger sister had taken to saying "yes" to everyone, only so that hospital personnel would leave her alone. The clinician tried to explain the processes and goals of the study, explicitly mentioning that the intervention was designed to help individuals manage the stress brought about by life circumstances. Thus, Ms. B was actually an appropriate subject for the research.

The clinician discussed the situation with investigators, who decided that Ms. B would have to communicate herself that she no longer wanted to participate in the study; but that she should be proactively offered the option to withdraw. The clinician contacted Ms. B, who disclosed that despite her desire to be involved in the study, she would no longer be able to participate because her older sister was very upset and vehemently disapproved. She further elaborated that her sister would yell at her if she continued to participate, and that this conflict was causing substantial friction within the family.

Before the clinician had the opportunity to report the subject's decision to withdraw to the research team, one of the research assistants, blinded to the subjects' study allocation, called Ms. B to complete her first monthly follow-up assessment. Ms. B cooperated and expressed her desire to participate in the study. The project coordinator, who was the only unblinded member of the research team, called Ms. B to confirm her decision. Ms. B made it clear to the project coordinator that her prior hesitancy to participate was based solely on inappropriate pressure from her older sister, and that she would like to continue as an intervention participant. Ms. B and her clinician then began to meet weekly.

Analysis

According to the one-eleven (45 CFR 46.111) criteria, before IRBs approve research studies, they must ensure that risks to subjects are minimized; that risks are reasonable relative to anticipated benefits or knowledge gained; that the study is appropriately monitored for safety; and that there are adequate provisions to protect subjects' privacy (DHHS, 2010). Each of these criteria applies explicitly to research subjects only; none, however, applies to family members or other social contacts, who may incur risk by virtue of another's participation in research. By contrast, federal regulations (45 CFR 46.103(b)(4)) governing the reporting of unanticipated problems that occur during the conduct of research apply not only to subjects, but to "others" as well (DHHS, 2010).

There are many possible interpretations of our case studies. One way to look at them is from the perspective of how family issues can amplify risks to subjects. However, the somewhat more novel—and potentially remediable—perspective we wish to explore is the

incongruence between the one-eleven criteria and the regulations governing the reporting of unanticipated problems. In adhering to the one-eleven criteria, the investigators presiding over our reported studies and the IRB appropriately focused on potential risks to prospective study subjects. In drafting the IRB protocol, investigators assessed risk to subjects, including the likelihood of having a subject disclose suicidal ideation; they minimized risks; and they justified why the proposed research was worth incurring any risk at all. However, prior to enrolling subjects, the researchers and the IRB focused exclusively on the risks to actual subjects and did not prospectively consider potential risks to “others.” Thus, when the two events described in case studies occurred, they became—by definition—unanticipated problems.

In the first case, Ms. A’s sister experienced substantial emotional distress and possibly genuine risk from her uncle. The research team thus had to balance the need to maintain the confidentiality of information collected from Ms. A, the study subject, with the desire to protect Ms. A’s sister from potential harm. Specifically, the events that unfolded after Ms. A expressed suicidal ideation left the PI to choose between contacting the uncle, in the interest of protecting the younger sister, but potentially violating the subject’s confidentiality; or honoring the subject’s explicit request not to contact the uncle, but feeling a sense of responsibility for the safety of the teenage sister. Whereas the investigators had planned for suicidality among subjects, the investigators had not anticipated this level of involvement, stress, or risk to befall a family member.

In the second case, the study team felt a responsibility to explore Ms. B’s sister’s requests to withdraw Ms. B from the study, but worried that the subject’s participation was causing so much discord in the sister’s relationship that continuing to contact Ms. B—through her sister’s cell phone—would be irresponsible and might escalate the conflict. At the same time, however, they also wished to respect Ms. B’s autonomy and her right to decide for herself whether to participate in the study. The research team felt that Ms. B’s sister put undo burden on Ms. B around her desire to participate in research (specifically, pressure to withdraw from the study), and thus had to balance causing friction within the family with honoring what they felt was the subject’s well-informed desire to participate in research. Although the subject was comfortable participating in the research, her sister saw participation as a final “insult” in a string of culturally aberrant gestures made by the healthcare system against the subject and her family.

Our case studies raise the issue of whether IRBs should consider broadening their interpretation of the one-eleven criteria, and compel investigators to think about potential risk to nonsubjects. Although this may be seen as beyond the IRB’s purview, it may also be seen as particularly salient when research involves subjects whose cultural or social backgrounds may make them highly dependent on others. While both subjects in our cases were autonomous—as they had the ability to make decisions and to act on those decisions—they both relied heavily on their sisters. In fact, it could be argued that without their sisters, they could not have been fully functioning in society: the first, without an independent means of telephone communication; the second, as a new immigrant with an ill newborn, who relied on her sister to help navigate new systems and cultures.

Codependent family structures are common in low-income, immigrant, and minority populations (Pyke, 2004). Families of such cultures have also been reported to have a strong sense of collectivism—characterized by a deep commitment to family and community, and shared decision making (Phinney, Ong, & Madden, 2000). Codependence and collectivism may be functions of one’s native culture; or they may stem from language barriers, social marginalization, or financial insecurity, and thus may be viewed as coping strategies common among highly vulnerable populations. In either case, this type of family structure

may challenge the notion of individualism that defines traditional American culture (Phinney et al., 2000; Pyke, 2004). Low-income, immigrant, and minority families may thus have a conception of autonomy that incorporates familial codependence, and which may vary from the concept of autonomy, as described in the federal regulations.

While it would violate the basic ethical principle of autonomy to require additional informed consent from family members (National Institutes of Health, 1979), it could be argued that investigators and IRBs should recognize that in certain research paradigms, among certain populations, it may be prudent (and culturally appropriate) to formally recognize that family members are likely to be intimately involved in the research being conducted. This issue becomes even more controversial when considering the under-representation of minority populations in research, and the widespread desire to make research participation more accessible to such populations (Noah, 2003). Proactively involving family members in research—if done thoughtfully—may also be seen as providing greater protection for subjects and their families, and in the end may result in improved long-term retention of study subjects.

One way to address the issue of codependence would be to screen potential subjects upon enrollment in a study, and to offer specific protections based on the results of this screening. In our case studies, for example, one common thread was that investigators relied on family members as conduits for communication with study subjects. It could be, therefore, that asking potential subjects if they had their own telephones would have been an appropriate screening question; and that for those who did not, investigators could have offered either a project-supported cell phone or asked the subject to name a “research partner,” as is common in Alzheimer’s research (though for different reasons), to support the study subject as she proceeds through the different phases of the research. Providing cell phones to subjects, in our case examples, would have cut the sisters out of the communication loop, and could have minimized their risk on that basis; enlisting a research partner, on the other hand, would have guaranteed that an informed and supportive individual had “bought into” the subjects’ participation in the research from the onset. Another way to explore possible family-oriented influences on research participation might be to explicitly inform subjects, during the informed consent process, that sometimes participation in research creates differences of opinion among family members, and to ask potential subjects how they would like study staff to manage any potential future conflicts.

Resolution

In the first case of Ms. A and her sister, the PI did not have the opportunity to discuss a course of action with an IRB representative, as the dialog between him and the subject’s sister occurred at night—with the uncle actively waiting to be informed why Ms. A (the subject) was not at home. The PI decided that in the interest of both protecting the nonsubject sister and maintaining confidentiality for Ms. A, he would inform the uncle only that the Ms. A had required medical care; that both she and her baby were safe; that the sister had not been involved in any events of the day (which were not disclosed); and that rules of confidentiality prohibited him from disclosing anything further. The PI notified the IRB of an unanticipated problem, and proposed to distribute cell phones to all study subjects without a reliable means of independent communication. In the second case of Ms. B, because the study team strongly felt that the subject’s sister was pressuring her to withdraw from the study against her will, the PI requested assistance from the IRB regarding whether to enroll Ms. B in the study. The PI was referred to a hospital attorney who provides legal counsel to the IRB, and on her advice, a plan was made collaboratively to assess the subject’s interest in participation in the study. The subject and her clinician developed a dependable means of communication that did not involve the sister.

Conclusion

Like any health or healthcare-related endeavor, human subjects research takes place in a context. For individuals with highly codependent family structures, the possibility that participation in research will impact—or be impacted by—nonparticipant family members is likely to increase. While the one-eleven criteria compel researchers and IRBs to anticipate and plan for risk to subjects, it may be important, in certain studies, among certain populations, to proactively plan for risk to family members and other members of a subject's social network.

Best Practices

Those practicing human subjects research should carefully consider the impact of their research on subjects' family members, even if those family members do not meet the technical definition of secondary subjects.

Research Agenda

Just as IRBs ask investigators to speculate on the potential benefits and harms of their research to subjects, it would be important to explore the IRB's role in asking investigators to do the same with regard to subjects' family members—and whether doing so results in any benefit or helps to minimize risks.

Educational Implications

As many IRBs have continuing education that they provide to investigators as the basis for certification in human subjects research, modules on family involvement in research may be important as well.

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