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When a Serious Adverse Event in Research Occurs, How Do Other Volunteers React?

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Abstract

Serious adverse events in research involving healthy volunteers are rare, but their impact on other volunteers is unknown. We conducted semi-structured interviews with 60 healthy volunteers at an institution where a healthy research volunteer died. Most volunteers (85%) had heard of the event, but few said it changed their thoughts about joining research (17%), approach to studies or questions asked (25%), or future participation (4%). Despite knowing few facts, respondents created narratives about the case that served to distance them from the event and justify their continued participation in research. Downward social comparison theory, optimistic bias, and feelings of responsibility and control may help explain these narratives. Findings underscore the importance of communication and understanding of research risks and protections.

Keywords

healthy volunteers; bioethics; adverse events; narratives; downward social comparison theory; optimistic bias

In 2001, there were an estimated 10 to 19 million research volunteers in the United States (Shamoo, 2001). While many of these research participants were patients, a large number were healthy volunteers. Each year, nearly 3,500 healthy volunteers participate in studies at the National Institutes of Health (NIH) Clinical Center alone (NIH, 2008), and likely thousands more participate in research studies at other institutions.

Research with healthy volunteers is thought to be relatively safe. In one study of 1,015 volunteers across 54 research studies, the overall incidence of adverse events was 12.8% (Sibille et al., 1998). Of these, 3% were considered “severe,” such as diarrhea, vomiting, or photosensitivity, 0.8% (or one out of every 1,350 days of exposure) were considered “worrying,” such as loss of consciousness or atrial fibrillation, and there were no deaths or life-threatening events (Sibille et al., 1998). Another study found that a “clinically significant medical event” occurred once every 9,602 days of exposure (Zarafonitis et al., 1978). A survey of investigators found that among 93,399 participants in physiologic trials, fewer than 1% experienced any sort of injury, and no deaths occurred (Cardon, Dommel, & Trumble, 1976). This study concluded that the risks of participating in physiologic trials may be no greater than the risks experienced in everyday life.

Under rare circumstances, however, serious adverse events occur in research involving healthy volunteers. For example, in 1980, a volunteer did not reveal her history of cardiac arrests associated with a diagnosis of bulimia; she died of cardiac arrest during a sleep study,

and laxatives were found in her purse upon investigation (Kolata, 1980). In 1985, a volunteer participating in a study of a new antiarrhythmic agent had a sudden cardiorespiratory arrest and died; subsequently it became known that the volunteer had received an injection of flupenthixol the previous day, and a lethal drug interaction was the attributable cause of death (Darragh et al., 1985). In 1991, a healthy volunteer had a fatal reaction to a dye injected as part of a research study (Glass & Freedman, 1991). In 1996, a student at the University of Rochester was given far more anesthetic during a bronchoscopy than outlined in the study protocol, leading to her death (Rosenthal, 1996). Most recently, the safety of research with healthy volunteers was questioned after six participants in a Phase I trial of a monoclonal antibody fell severely ill and were hospitalized, in some cases with life-threatening multiple organ failure (Wood & Darbyshire, 2006).

To our knowledge, no published studies have examined the impact of serious adverse events on the attitudes and behaviors of other healthy volunteers. In June, 2001, a healthy volunteer died after participating in a study involving inhalation of the drug hexamethonium. This incident was broadly publicized and resulted in significant changes to the clinical research process at the institution where the event occurred. Internal and external inquiries in the case concluded that multiple breakdowns in processes intended to protect human subjects contributed to the circumstances surrounding this volunteer's death, including failures on the part of the investigators and the system of institutional review. Importantly, none of these investigations placed any responsibility for the death on the volunteer herself. Two years after this event, we interviewed other healthy volunteers in the same city to explore their understanding of why and how the event occurred, and to determine whether it affected their decision to participate in the future as healthy volunteers.

Methods

Study Participants

Study methods have been described previously (Kass et al., 2007). Briefly, individuals must have served as healthy volunteers in at least one clinical study in the prior two years to be eligible. Participants were recruited through drug development and vaccine testing units, advertisements in a free weekly newspaper, and word of mouth. To reflect the demographics of healthy volunteers at the academic medical institution where the study took place, the sample was stratified to enroll approximately one-third employees and two-thirds community volunteers.

Data Collection

Interviews took place approximately two years after the death. After obtaining written informed consent, interviews were conducted in person using a semi-structured interview guide. The interview guide included four closed-ended questions related to this adverse event: (1) whether respondents had heard of the death of a healthy volunteer at the institution; (2) whether it changed their own thoughts about joining a study; (3) whether it changed how they would approach a study or what questions they would ask; and (4) whether it changed their willingness to participate in research at the same institution in the future. After each closed-ended question, respondents were asked to explain their answers in an open-ended format. Interviews lasted approximately 45 minutes. Volunteers were compensated \$25 for their time. This study received ethical approval from the local institutional review board (IRB).

Analysis

Data on demographic characteristics, history of enrollment in research studies, and effect of the volunteer death on attitudes about research participation were explored using descriptive

statistics, and bivariate analyses were conducted using Fisher's exact test. Qualitative transcripts were read in their entirety, then entered into NUD*IST qualitative data management software (N6 qualitative data analysis software; QSR International Pty Ltd. Version 6, 2002). Themes and subthemes were identified and coded. Printouts of reorganized text were read and further categorized and summarized in an iterative process. Selected quotes for different themes were re-read in their original context to ensure accuracy of interpretation.

Results

Respondent Characteristics and Quantitative Results

The study sample included 60 volunteers: 23 employees of the institution where the adverse event occurred and 37 community volunteers, a distribution roughly equal to that of healthy volunteers in the institution's Drug Development Unit. Just over half of respondents were male (57%), African American (60%), and employed full time outside of research studies (53%). The mean age of respondents was 41.8 years (range 19–65). Most respondents were single (80%) and had no college education (68%). Over half (63%) of all respondents first joined a healthy volunteer study within the previous five years, and 53% had been in at least one study requiring in-patient overnight hospital admission. Ten percent of volunteers had participated in only one study, while 27% had participated in more than 10 studies. Over half (55%) said the main reason they originally participated in research studies was the money, although when asked about the good things about participating in research, most respondents talked about a variety of things, including positive interactions with people and contributing to science.

The majority of respondents (85%) reported having heard of the death of a healthy volunteer. All employees and 76% of community volunteers had heard of the event. Of those who had heard of the death, only a small proportion (17%) said this event changed their own thoughts about joining a research study. A slightly larger proportion (25%) said it changed how they would approach a study or what questions they would ask. Only two individuals (4%) said it changed whether they would participate in research at the institution where the event occurred. There were no significant differences in these responses by volunteer demographics or enrollment history. Volunteers who had participated in multiple studies did not differ in responses from those who had participated in only one study, and responses were not correlated with age, race, educational level, or employment status. Qualitatively, responses given by employees and community volunteers were similar, so results are presented for both groups together unless otherwise stated.

Narratives about Adverse Event

The 53 respondents who said they had heard of the death, or who were not sure whether they had heard of it, were asked to describe what they knew about the situation. The level of knowledge varied widely across respondents. Some respondents gave lengthy and detailed descriptions, including the factors they believed had led to the death, and the subsequent effect on research. Other respondents said they knew very few details about the case.

Regardless of self-reported level of familiarity with the case, almost all respondents went on to construct a narrative about what they believed happened. Some described what they remembered having heard in media reports or speculated about what they thought most likely occurred. Often respondents seemed to be thinking out loud about what might have happened.

I wasn't really following it religiously, but from what I heard she was doing an asthma study and he [the investigator] had put something in an inhaler, I think, that

wasn't IRB approved. And that's what caused—whatever happened to her. See, I don't even really know what happened to her, I just know she died. I don't remember if she got a reaction, she got sick, or if it was something else that maybe just coincided with it. (Male, employee)

These narratives included descriptions of what factors participants thought were involved in the death, what might have caused the event, how it could have been avoided, and, in many cases, judgment about who was at fault.

Specifically, about a third of respondents (15/53), both employees and community volunteers, felt that the study investigators were somehow responsible for the volunteer's death. Many of these individuals believed the healthy volunteer must have had a medical history that should have excluded her from study participation, and study investigators should have identified that during the screening process or should have more carefully monitored the volunteer during participation.

What I heard was that a research doctor made a bad call in allowing this woman in ... He should have had a closer eye on what was going on. (Male, community volunteer)

A few individuals also suggested that the IRB might have been partly responsible.

I believe it had to do with the IRB not catching something on a consent form ... and one of the doctors involved in the study not catching something having to do with her medical history. I think her medical history did play a part in her death. (Male, employee)

Another third of respondents (17/53) suggested through their narratives that the healthy volunteer herself was somehow responsible for the circumstances leading to her death. Some believed the volunteer hid information about her medical or drug history from the research team. While both employees and community volunteers voiced this view, it came more often from community volunteers. Two respondents went further, saying that although they did not know the details of what had happened in this case, they speculated that perhaps the volunteer had done something to violate the rules of research participation.

Finally, about a third of respondents (22/53) did not specifically blame anyone for the death. Some of these individuals also believed that the volunteer might have been sick or had a preexisting condition, but they felt that this could not have been identified in advance.

There was something physically wrong with her that I think that made her die, that she [the volunteer] didn't realize and that they [the investigators] didn't pick up on. She probably never really should have done the study. She probably was not healthy enough for some reason, had some kind of problem that may not have surfaced until she had done the study. (Male, community volunteer)

Others felt that the event was just a chance occurrence or did not specifically blame anyone for the circumstances leading to the volunteer's death.

It's unfortunate that it happened. A major devastating effect on research, but I think the whole purpose of doing research is to find out things that help people and occasionally sometimes bad things happen when you are doing research. So, unfortunate, but it's just those things happen. (Male, community volunteer)

Effect of Adverse Event on Research Participation

The majority (75%) of respondents who had heard about the death said that it did not change their thoughts on joining a study. These respondents gave a variety of reasons for their answers.

THAT'S JUST THE RISK YOU TAKE—A few respondents said that while the death of a healthy volunteer was a tragedy, it was also a very rare event and all research participation involves a certain level of risk.

[W]hen you sign up to do volunteer studies you know there's a risk. Everybody knows there is a risk. (Female, employee)

[Y]ou do research, it happens. You know, that's why you take the risk and they pay you for it, and, you know, you hope it comes out in your favor [laugh]. I hate to think of it like that, like you throw dice up in the air and hope that you get the right number, but you know, but when you do research ... you can't predict everything. (Male, community volunteer)

Of the people who speculated that the volunteer had a medical problem that related to the cause of death, a few expressed that this, too, might be a risk of study participation.

[It's] a risk you have to take. I mean, what happened with her is like maybe a one in a million thing. You know, she didn't know she had an allergy to the medication that they gave her, otherwise she probably wouldn't have done the study. So, people don't know what they're allergic to, you never know until you get it. (Male, employee)

TRUST IN THE SAFETY AND QUALITY OF RESEARCH—Several respondents said they had not changed their views on research participation because they trusted the safety and quality of research at the institution where the event occurred. For employees, this trust was often based on their reported familiarity with researchers and with the quality of research that they had experienced.

No, I think because I see a lot that goes on here with the research. And they're pretty good with it. You know, with all the questions they ask us, yeah. I think that was just a fluke thing that really happened. (Female, employee)

Some community volunteers also described developing personal relationships with researchers through their years of participation which led them to trust research staff. One likened investigators to "a second family." Only one respondent noted that studies undergo review by an IRB and that this might be a reason to trust the safety of research.

For both employees and community volunteers who expressed trust in the safety and quality of research, the fact that the death happened at this institution did not affect their views of the institution, but instead was seen as an unfortunate, chance occurrence.

The fact that it happened at [that institution] was unfortunate, but it could have happened anywhere. I think all the studies that I got involved in here were always well thought out, they were always well explained and I knew what I was getting involved in when I got involved. (Male, community volunteer)

ONE ISOLATED CASE—A few respondents explained that the death did not change their approach to research participation because they believed it was an isolated case or a single investigator who acted improperly, and as such it did not affect their overall experiences with research. Some explicitly mentioned the high quality of the research staff responsible for the studies in which they had participated.

From what I heard, that was one individual [investigator] who made a very, very huge mistake. My personal relationship with research units [is] long standing, [so] I am very comfortable. The doctors, the nursing staff, on a five scale they're rated five. They know their business. (Male, community volunteer)

PERSONAL RESPONSIBILITY FOR SAFETY—Respondents frequently cited the individual responsibility they took for their safety in explaining why the death did not impact their decisions regarding future research participation. For example, several respondents said they always made sure to have all the information they needed to understand the study and said they asked questions of investigators when necessary. Other respondents explicitly said that they made sure to fully understand the risks involved in a study before joining.

I always listen to what they say or give me information. Some laugh. I've had people laugh a little bit because I was still reading. I was taking my time. I'm not rushing when it comes to reading the risks. (Male, community volunteer)

Some respondents linked their willingness to continue to volunteer to reading the consent form or other study documents. One volunteer suggested that she would have been able to recognize the dangers of this particular study and would not have agreed to participate.

No, because I realized ... the way that that study was done [was] so below par that had I been approached about that study, I probably would never have done it, after having read the consent. (Female, employee)

Other respondents who said they continued to participate in research studies because they took personal responsibility for their own health and safety expressed this as a general inquisitiveness and desire to learn as much as possible about studies they joined. Two respondents, one employee and one community volunteer, linked personal responsibility for their health with the fact that they had advanced degrees or more knowledge about the science of research studies than an average person, and used this to justify their decision to continue to participate in research.

I have a master's in kinesiology, master's of science in physical education, so I know enough about my body that I can ask very intelligent questions. I know enough to be dangerous. That's the best way to put it. (Male, community volunteer)

One respondent described her commitment to making sure safety measures were in place before she joined any research study in describing why the death did not affect her decision to continue to participate in studies. She emphasized that although she trusted research staff, she ultimately placed responsibility for her health in her own hands.

I came in knowing that I want everything there ready to go should something happen, should this bad side effect be there. I want a beeper number, I want an ER address, I want the ambulance to know where I live, I want all this stuff. So for me, I went in taking a lot of responsibility on my end as opposed to, gee, I'm going to join this study and everything is going to be fine ... you walk into everything with a very critical view and you say hey, is everything safe, am I set up, are these people reliable? And like I said before, trust is a huge factor when it comes to people who are staffing it and are these people capable of helping you, should the worst of the worst happen ... I think there is a lot of personal responsibility on your half. You can trust people as much as you want, but don't be stupid. (Female, community volunteer)

Other respondents alluded to the differences they believed to exist between the behavior of the volunteer who died and their own behavior as justification for their continued participation. Respondents who felt that the volunteer hid important information about her medical history often used this opportunity to emphasize that they themselves always told the truth about their medical histories and followed the rules for participation outlined in study documents.

You can't control the person that's trying to get into the study. [Researchers emphasize the importance of] being honest. Well okay, how can you control for whether the person [is] going to manipulate the questions? ... It's my responsibility to let the doctors or whoever is interviewing me know any type of medical anything I've ever had in my life. That's my responsibility. (Female, community volunteer)

NOTHING TO DO WITH ME—A small number of respondents said that the death, while tragic, was not related to their own situation, and therefore had not affected their decision to participate in research studies.

I don't know ... it was just her time to go ... I felt sorry for her, but I mean, it didn't affect me. (Female, community volunteer)

WOULD NOT HAPPEN TO ME—A few respondents explicitly said that what happened to the healthy volunteer could not or would not happen to them.

Well me personally, I don't think that it would ever happen to me, and that's the reason. And like I said it's a major part of my income. So that's the risk you take. That's why we sign the consent form. (Male, community volunteer)

Others said that the types of research they participated in or the format in which investigational agents were administered were different from the study in which the volunteer death occurred. These respondents implied that what happened to the volunteer who died could not happen to them.

Well, you know [the] study she was in [was] an investigational type study ... It wasn't a normal type of medication, it was something experimental. With something like that, you definitely want to be more concerned about it, and ask questions about it, and so on and so forth. But most of the ones I've done here, they're not investigational. (Male, employee)

A small minority of respondents said that the death had affected whether or how they would participate in future trials. Notably, one of these respondents still did not think what had happened to the volunteer would have happened to him, even if he had been enrolled in the same study.

I realized I could have been in the same position as she. Although, I felt even if I had [been in the same study], I didn't think I would have that reaction. I think she had some allergy or something, as I recall. But it made me more aware, more cognizant of... um, of... um, the procedures and the protocols and stuff. (Male, employee)

MORE CAUTIOUS/ASK MORE QUESTIONS NOW—Only nine respondents said that the death changed their thoughts about joining other studies. Most of these respondents said that the death had simply made them more thoughtful about their participation in research. One called it “a huge wake-up call” (Female, employee), while another said, “it reinforced my beliefs that I'm not taking an investigation too lightly” (Male, employee). Only two respondents said that they felt personally at risk of an adverse event or being “in the same position” as the volunteer who died.

Thirteen respondents said that the death changed how they approached a research study or what questions they asked. All of these respondents said that they would ask more questions of researchers and learn more about the research study, particularly regarding the anticipated risks and side effects. Many other respondents, however, said they already asked a lot of questions and were as informed as they needed to be. Only one person said he would not ask

more questions because doing so would not be an effective way of preventing an adverse event.

The kind of thing that was involved [in that case] was the kind of thing where no questions that I would ask would have found the answers to. You need a district attorney with subpoena powers and a staff of investigators to get the answers.
(Male, community volunteer)

PERCEPTIONS OF THE INSTITUTION—Only two respondents said that the death changed whether they would return to the same institution where the event occurred to participate in future studies. One male employee said it would change “a little bit, but not a whole lot,” since the studies he participated in were generally less risky than the study in which the healthy volunteer had died. One female community volunteer vaguely expressed some distrust of the institution. No strongly negative views of the institution were expressed; in contrast, numerous respondents repeated how positively they felt about the institution and said that their confidence in the institution was one of the reasons why they continued to participate in research studies there.

Discussion

To our knowledge, there have been no previous examinations of the effect of a serious adverse event in research on other healthy volunteers. Although our interview questions concerned the death of a healthy volunteer, these responses may be relevant to other rare but serious adverse events in research as well.

While all employees and three-quarters of community volunteers had heard of the death, only a small proportion said that this event changed their own thoughts about joining a research study, how they would approach a study or what questions they would ask, or whether they would participate in research at the same institution in the future. In quantitative analyses, there were no differences in these responses by any participant characteristics, including age, race, educational status, employment, institutional affiliation, and history of participation in research studies, although numbers for these stratified comparisons were small and likely underpowered to detect any significant differences. Similarly, in qualitative analyses, we did not find strong response trends by participant characteristics; men and women, employees and community volunteers, and individuals of different ethnic backgrounds all expressed similar thoughts.

What was most striking about our study was not that respondents had heard of the death, or the degree to which it influenced their approach to research participation, but rather the narratives they created to interpret the event. Volunteers commonly began responding to our questions by saying that they had almost no information about the circumstances of the volunteer death, but continued with a process of “thinking out loud,” creating a story or narrative to make sense of the situation. Importantly, many of these narratives served to justify participants’ continued involvement as healthy volunteers.

The phenomenon of creating narratives, or “filling in the blanks” when facts or accurate understanding are missing, has been observed previously in the research setting. Prior studies have found that when research participants did not fully understand informed consent information, they created narratives to make sense of what they had heard or experienced (Featherstone & Donovan, 2002; Kass, Maman, & Atkinson, 2005). While these narratives may have been reasonable and understandable, they were often inaccurate representations of the studies in which the individuals had enrolled.

The narratives created by the healthy volunteers in this study were striking not only because participants “filled in the blanks” when they did not actually know what had happened, but also because the narratives almost always served to distance volunteers from the death. Respondents speculated that perhaps the adverse event occurred because the volunteer failed to disclose critical information about her medical history, that she violated the study protocol, or that she failed to ask sufficient questions of the investigators. A surprising one-third of respondents suggested that the healthy volunteer was responsible, at least to some degree, for her death. This came despite strong evidence from multiple investigations that this research subject in no way contributed to the circumstances surrounding her death.

Distancing oneself from others who have experienced negative life events is a feature of downward social comparison. Building on social comparison theory (Festinger, 1954), Willis (1981) proposed the concept of downward social comparison in which individuals enhance their own sense of well-being by comparing themselves with others who are less fortunate. Such comparisons may reduce threats and serve as a coping strategy. There is concern, however, that individuals may fail to take adequate precautions if they underestimate their own risk (Klein & Weinstein, 1997). In our study, by presenting the case of a healthy volunteer who died, we gave participants a social comparison against which they seemed to compare themselves in a relatively positive light.

Social comparison is hypothesized to be one mechanism behind the well-documented psychological phenomenon of unrealistic optimism about personal risk, also known as optimistic bias. Optimistic bias describes how individuals often judge their own risk of negative events to be smaller than the risks faced by others (Weinstein, 1989). In general, such optimism is greatest for risks that are rare, controllable, and not previously experienced by the individual (Helweg-Larsen & Shepperd, 2001; Weinstein, 1987). Serious adverse events in healthy volunteer research are indeed rare (Sibille et al., 1998) and generally not previously experienced by individuals. However, they are only somewhat controllable by individual research participants beyond the original decision to participate. What was striking regarding participant responses in this study was the common belief that serious adverse events in research are controllable. Many of the narratives about the death of a healthy volunteer attributed some degree of control to either the investigators or the healthy volunteer herself. These narratives suggest that participants attributed a level of control to this particular event in order to be able to distance themselves from it, feel comfortable with their decision to continue to volunteer, and retain their optimistic bias about their own risk of future adverse events while participating in research.

This study raises important questions for the informed consent process and for IRB oversight. Research into risk assessment has shown that individuals, in general, are consistently inaccurate when making risk assessments or situating their own risk amidst population-based statistics (Kahneman, Slovic, & Tversky, 1982; Slovic, 1987). If research volunteers consistently display these cognitive biases and inaccurately assess research risks, this could affect the validity of informed consent, or the procedures used for obtaining it. Existing literature suggests that volunteers often do not fully understand the studies in which they participate (Appelbaum et al., 1987; Edwards et al., 1998), and attention has focused on strategies to increase the likelihood that consent is truly informed (Flory & Emanuel, 2004; Jefford & Moore, 2008; Woodsong & Karim, 2005).

We observed important discrepancies between the perspectives of the participants in this study and those of the internal and external committees that reviewed the case. Committee reports concluded that the death resulted from failures on the part of the investigators, the system of scientific and ethical review, and outside factors. No responsibility was attributed to the healthy volunteer herself. In contrast, participants in this study focused on the

volunteer's behavior and the investigator's behavior, and contrasted the volunteer's behavior with their own perceived ability to identify and guard against unsafe research. Only one participant suggested that the system of IRB oversight provided a reason to trust the safety of research studies. Instead of focusing on institutional systems, participants relied on confidence in their own savvy and, to a lesser extent, trust in investigators to protect them from adverse events. This may suggest a lack of awareness of the system of human subjects protections. Alternatively, it may indicate that research participants place a much higher value on their relationships with investigators than on any other level of protection. This confidence is not entirely misplaced. The quality and integrity of study investigators is extremely important to the extent that they make every effort to ensure the safety of their studies and adherence to protocols designed to minimize risk. However, there is also a system of human subjects protections beyond the investigators, and some adverse events may not be under investigator control.

Limitations

Findings from this study must be examined in light of several contextual factors. First, interviews took place approximately two years after the event occurred, and it is possible that the impact of a highly publicized event would fade over time. Second, the circumstances surrounding the death were unique, and therefore participants' reactions to this case may not be representative of their reactions to other research-related adverse events. Therefore, the results of this study may not be generalizable to other events. Third, the small sample size gave us low statistical power to detect differences in quantitative analyses. Fourth, we recruited healthy volunteers who had agreed to be re-contacted for future studies, or who responded to newspaper advertisements. This sampling strategy may have selected individuals with a positive bias toward research, as volunteers who no longer want to participate in clinical studies were likely to have refused further contact and stopped seeking research opportunities. Further, many participants were repeat research subjects or health professionals who were themselves involved in the research enterprise. The limited geographical and institutional demographics of participants may have limited response diversity, and many participants were volunteers at the institution in question, so they may have been reluctant to criticize the institution. However, interviewing volunteers from the same institution or region where a death occurred was important in addressing our study aims. We also felt that we achieved response saturation within this sample, meaning that there was redundancy across responses and we were hearing similar themes from different participants. Finally, while demographics of this sample broadly reflect those of healthy volunteers who generally participate in research at this institution, they will not mimic demographic backgrounds of other institutions or communities.

Best Practices and Educational Implications

The research community has an existing responsibility to minimize risks to research participants where possible, to safeguard participants from avoidable risks, and to ensure that volunteers understand both the uncertainties and protections that exist in clinical research. Investigators, IRBs, and research sponsors must appreciate that many volunteers enter research studies assuming not only that adverse events will not happen to them, but also that they have significant degrees of control over these events. Many research participants may also lack awareness of the system of human subjects protections. The research community should be aware of these issues and continue to be attentive to how volunteers understand the risks of research, strategies to minimize these risks, institutional safeguards, and the remaining possibility of adverse events that are outside the control of either volunteers or the research community. Researchers should remember that informed consent is a process that may require creative means of communication and education to

ensure the best possible understanding of participants. Finally, when adverse events and deaths in research tragically do occur, these events may provide an opportunity to remind other volunteers—as well as members of the research community—about the risks of research and existing safeguards.

Research Agenda

To our knowledge, downward social comparison theory and optimistic bias have not been studied in relation to risk assessment by research volunteers. Further research incorporating relevant theories and concepts from the social sciences will help provide a more nuanced understanding of the risk-assessment and decision-making processes of healthy research volunteers. Applied research evaluating different strategies for communication with research participants, including alternative informed consent procedures, could answer questions about how to best address downward social comparison theory and optimistic bias in the context of healthy volunteer studies.

Conclusions

Serious adverse events and deaths in research with healthy volunteers are tragic. They are also extraordinarily rare. Statistically, the volunteers in our sample correctly assessed that they are unlikely to personally experience an adverse event of this magnitude, even if they participate in dozens of studies. Generally, such a response is an appropriate way of coping with the low level of risk that exists in most activities of daily life. However, many respondents also believed that their own careful approach to research participation helped to explain why their future risk was so small. Findings from this study underscore the existing responsibility of the research community to protect and educate research volunteers to ensure that they understand both the uncertainties and protections that exist in clinical research.

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