



To report or not to report: Exploring healthy volunteers' rationales for disclosing adverse events in Phase I drug trials

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Background: Phase I trials test the safety and tolerability of investigational drugs and often use healthy volunteers as research participants. Adverse events (AEs) are collected in part through participants' self-reports of any symptoms they experience during the trial. In some cases, experiencing AEs can result in trial participation being terminated. Because of the economic incentives underlying their motivation to participate, there is concern that healthy volunteers routinely fail to report AEs and thereby jeopardize the validity of the trial results. **Methods:** We interviewed 131 U.S. healthy volunteers about their experiences with AEs, including their rationales for reporting or failing to report symptoms. **Results:** We found that participants have three primary rationales for their AE reporting behavior: economic, health-oriented, and data integrity. Participants often make decisions about whether to report AEs on a case-by-case basis, evaluating what effects reporting or not reporting might have on the compensation they receive from the trial, the risk to their health, and the results of the particular clinical trial. Participants' interpretations of clinic policies, staff behaviors, and personal or vicarious experiences with reporting AEs also shape reporting decisions. **Conclusions:** Our findings demonstrate that participants' reporting behavior is more complex than previous portraits of healthy volunteers have suggested. Rather than finding participants who were so focused on the financial compensation that they were willing to subvert trial results, our study indicates that participants are willing in most cases to forgo their full compensation if they believe not reporting their symptoms jeopardizes their own safety or the validity of the research.

KEYWORDS

clinical trials; healthy volunteers; adverse event reporting; scientific validity; financial motivation

Through their participation in Phase I clinical trials, healthy volunteers play an important role in identifying adverse effects of investigational drugs. Unlike with nonhuman animal research, safety testing on human subjects can provide information about side effects that cannot be detected through medical procedures alone. This can include volunteers' experiences of nausea, headaches, or psychological changes that may have no physiological indicators. Accurate accounting of potential side effects is particularly important because clinicians often make prescribing decisions for their patients based on a drug's side-effect profile, or "tolerability," especially when available treatments have little variation in their efficacy (Friedman, Furberg, and DeMets 2010). Inaccurate information about drug side effects is linked to misreporting at various stages of the research process, beginning with participants failing to report their symptoms during trials and continuing to the point of pharmaceutical companies excluding safety information in their published reports (Ioannidis 2009; Ioannidis et al. 2004). This is particularly concerning given mounting evidence of safety concerns emerging after drugs have been approved for the market, such as drug withdrawals or safety warnings, in approximately one-third of new drugs in the United States (Downing et al. 2017). To date, there has been a dearth of empirical research investigating how safety data about investigational drugs is collected, reported, and disseminated, and

Phase I trials provide one important window into this issue by exploring healthy volunteers' actual reporting of adverse events they experience.

Participating in a Phase I trial requires certain sacrifices from volunteers, who agree to spend extended stays at residential research clinics, observe restrictions to their diet and exercise, and expose themselves to known and unknown risks of the investigational drugs and study procedures. Unlike in later phase trials, Phase I participants are typically healthy individuals who pass health screenings and do not have identified medical conditions related to the investigational drugs. While patients affected by disease may enroll in clinical research in hopes of improving their condition or because they have limited access to health care, healthy volunteers cannot receive a medical benefit by participating. Thus, in order to incentivize study enrollment, healthy volunteers are financially compensated (Czarny et al. 2010; Iltis 2009). This has led to many becoming serial Phase I trial participants, with some even treating studies as a job and/or their primary source of income (Abadie 2010; Tishler and Bartholomae 2003).

One of the main obligations imposed on healthy volunteers is to report any symptoms they experience during a Phase I trial. Any physical or psychological changes a participant experiences while in a trial, regardless of severity, are considered adverse events (AEs) rather than effects, because these

symptoms may or may not be a direct result of the investigational drug (Edwards and Aronson 2000). Indeed, the expectation is that some AEs will occur in participants receiving the placebo, and comparisons between groups receiving the investigational drug and those receiving the placebo could help adjudicate which AEs are caused by the drug (Moore 2015). For example, some common symptoms such as headaches or gastrointestinal changes could have myriad causes, but researchers want to know about any bodily changes that occur during the trial regardless of whether the participants believe the investigational drug itself caused the symptom.

The actual side effects of a marketed drug can be misrepresented when healthy volunteers do not fulfill their obligation to the study. Specifically, when participants do not report AEs, they compromise the integrity of data being collected, as well as potentially putting themselves at higher risk of harm. Meta-analyses of Phase I trials have indicated that adverse events are common in Phase I trials, with approximately two-thirds of healthy volunteers experiencing an AE, but most of these symptoms are mild and/or resolve relatively quickly (Emanuel et al. 2015; Sibille et al. 1998; Sibille et al. 2006; Johnson et al. 2016). In spite of the documented prevalence of AEs, one study of healthy volunteers nonetheless revealed that almost 30% of participants either delayed or completely withheld AEs from study staff (Hermann et al. 1997). Explanations for participants withholding AE information include volunteers forgetting/misremembering their symptoms, having difficulty verbalizing the bodily changes they experience, or fearing dismissal from the study if they report an AE (Hermann et al. 1997; Dresser 2013; Friedman, Furberg, and DeMets 2010).

Of these reasons for AE underreporting, scholars have primarily focused on participants intentionally subverting the clinical trial process out of their self-interested financial motivations (Dresser 2013; Resnik and McCann 2015; Devine et al. 2013). The concern is that because healthy volunteers enroll in clinical trials for the compensation, they are unlikely to report AEs if doing so could result in early discharge and only a partial payment. To contextualize this phenomenon, participants might be removed from a trial if continuing their participation would put them at increased risk. However, what constitutes an acceptable level of risk for continued participation is not standardized, and healthy volunteers often find it difficult to determine whether a decision to withdraw them for their own safety is an appropriate reaction to the AE (Hermann et al. 1997). Policies on payment upon study removal vary between clinics and studies and, in most cases, involve prorating payments based on the portion of the study completed (Dickert, Emanuel, and Grady 2002). Prorated payments and “completion bonuses” are designed to increase retention in clinical trials (Dickert and Grady 1999), but they could have the effect of discouraging AE reporting should participants fear losing the compensation for which they enrolled in the trial (Dresser 2013). Yet, not prorating payment could prompt participants to fabricate or exaggerate AEs in order to leave a study early with their full compensation (Devine et al. 2013). In both instances, scholars note how the payment system offers economic disincentives to participants for providing truthful information about their symptoms. This previous scholarship also casts healthy volunteers as either “good” or “bad” research participants, assuming

that individuals always make the same choices about AE reporting based on the degree to which they prioritize their economic motivations. This depiction creates a false dichotomy of participants, presenting them either as self-interested individuals solely concerned with the monetary compensation or as conscientious participants who understand the scientific goals of the trial and exhibit appropriate care for their own and others’ physical well-being.

Drawing upon a qualitative study of healthy volunteers’ experiences in Phase I trials, we examine participants’ rationales for reporting or withholding information about adverse events. Unlike past research that explains unreported AEs in terms of certain groups of participants withholding information because they are strictly economically motivated, we find that there is not a type of participant that accounts for nonreporting. Instead, our study indicates that reporting decisions are made by participants on a case-by-case basis. Therefore, different reporting outcomes can be explained by participants having changeable perceptions of how reporting might jeopardize their economic compensation, risk their health, and/or prevent them from being a meaningful contributor to the research process. Importantly, each of these three rationales can become the basis for the decision to report or not to report an AE.

Methods

This article draws on semistructured interviews with healthy volunteers who were recruited between May and December 2013 to participate in a 3-year longitudinal study about their experiences participating in Phase I trials (for more details about the larger project, see Edelblute and Fisher 2015). The research team gained permission to visit seven clinics across the United States to recruit and enroll healthy volunteers who were currently participating in a Phase I trial and who spoke either English or Spanish. Participants were told about the study, with emphasis on the fact that it was being conducted independently from the Phase I trial clinic, and were invited to enroll and participate in an initial interview. After the initial contact in the clinic, all follow-up, including subsequent interviews, was conducted via telephone. The study was reviewed and approved by the Biomedical Institutional Review Board at the University of North Carolina at Chapel Hill.

This article draws upon follow-up interviews conducted 1 year after enrollment in our study and includes 131 of the participants who were randomized to the “full participation” group of our larger study.¹ This was the third of five interviews with these participants in a three-year period. The first interview was conducted in person at enrollment, and four subsequent phone interviews took place approximately 6 months, 1 year,

¹In total, 180 participants were recruited to the larger study. As part of the design of this study, 20% of participants were randomized to a control group so that we could assess whether involvement in our study affected healthy volunteers’ perceptions of or participation in Phase I trials. Participants in the control group were interviewed only at recruitment and 3 years after enrollment. After randomization, 34 participants were in the control group and 146 were in the full-participation group. At the time of the 1-year interviews (the data used in this article), we had removed one participant from the study, three participants voluntarily withdrew, and 11 were lost to follow-up, leaving 131 (90% retention) in the full-participation group.

2 years, and 3 years later. We decided to focus on this single wave of interview data because participants were asked specifically about their AE experiences and were given probing questions about what they did when they had AEs and their perceptions of why those AEs occurred. Following the norms of qualitative interviewing (Patton 2002), we started with more open-ended questions about AEs and avoided survey-like questions about reporting in order to elicit more detailed information from participants (see Table 1). As is typical of semistructured interviews, not all participants were given the exact same questions or presented questions in the same order throughout the interview, as the interviewers would ask probing questions based on participants' responses. Although participants reference specific reporting events, the interview questions were directed at participants' overall experiences during their history of Phase I participation, not focused on any specific clinical trial. The interview also included a range of other topics about Phase I trials, including questions about their perceptions of the risks and benefits, their trust in the research enterprise, their health behaviors related to participation, and their plans for future trial participation.

All interviews were transcribed in full by an independent transcription company and verified and corrected for accuracy by a member of the project team. All transcripts were then uploaded to Dedoose qualitative analysis software and coded by two members of the research team. The goal of having a second coder was to ensure completeness of code applications and the second coding was not performed independently (i.e., the second coder could see and edit the first coder's work). Codes relevant to this inquiry include the parent code "Adverse Events/Side Effects." We also developed the additional subcodes "Not the Drug" for statements in which participants claimed that an AE was not caused by the investigational drug, "Never had Side Effects" for statements in which they asserted they had never had an AE in the course of their trial participation, "Reporting" for all statements about their own or others' reporting behavior, and "Leads to Self-Change" for statements in which they indicated the experience of an AE made them reevaluate how they participate in studies (e.g., avoid studies similar to ones in which they had AEs or stop participating in trials altogether). Data for this article consist of any portion of the participants' 1-year interviews coded as "Adverse Events/Side Effects" in order to capture their or others' AE reporting behavior or feelings about reporting adverse events, not just answers to specific interview questions. We applied abductive reasoning (Tavory and Timmermans 2014) to this data to explore the ways participants approach reporting. Unlike grounded theory, this methodology allowed for analysis of the data in light of preexisting explanations of reporting behavior.

Table 1. Interview guide questions pertaining to adverse events.

1. How common is it for you to experience side effects during a study?
2. How common is it for others to experience side effects?
3. What do you do when you experience some side effects during a study?
 - a. [If tell staff] How does the staff respond?
 - b. [If don't tell staff] How do you think the staff would respond?
4. [Depending on response to #3] Who do you talk to about experiencing these side effects? How often do you tell staff? [Follow with #3a or #3b probe as relevant]
5. Why do you think some people experience more side effects than others?

The demographic representation of our sample reflected the broader population of Phase I volunteers found in previous studies (Fisher 2015; Fisher and Kalbaugh 2011). Specifically, our sample was predominantly men (75.6%) and racial and ethnic minorities (65.6%) (see Table 2). Our sample had the following age (years) demographic representation: 18–29 (19.1%), 30–39 (35.9%), 40–49 (29.8%), 50 and older (15.3%). Less than half of our sample had full-time employment, with 35.9% employed full-time, 16.8% employed part-time, 25.2% self-employed, and 22.1% not employed or retired at the time of the interview. The annual household income of our participants ranged from less than \$10,000 to over \$100,000, with 84% of interviewees claiming a household income of less than \$50,000 and 4.6% claiming a household income of over \$100,000.² These income data do not lend themselves to categorizing directly participants' dependency on clinical trial compensation, but the variation in participants' employment statuses and household income provides insight into a wide range of reliance that healthy volunteers have on clinical trial income.

Healthy volunteers in our sample also varied in terms of their rate of Phase I trial participation, both at the point of recruitment and since enrolling in this longitudinal study (Table 3). At the time of the 1-year follow-up interview, participants self-reported having completed a total number of studies ranging from one to 204. Fifteen percent had completed only one clinical trial, which was the one during which we recruited them to our study the year prior, and 64.9% of participants had completed five or more clinical trials. During their first year in our study, participants on average screened for Phase I trials 3.13 times, ranging from no new screenings to 16 new screenings. Participants completed an average of 1.7 new studies during this same time frame, ranging from enrolling in no new studies to having completed 9. This indicates that participants in our sample collectively had significant exposure to Phase I trials, suggesting that they had the opportunity to experience personally or witness adverse events during their trial participation.

Findings

Most participants recalled having reported an AE or suggested they would report an AE if they were to experience one. Still, a quarter of participants recalled at least one instance of not reporting an AE or presented hypothetical scenarios in which they would not report an AE. We found, however, that differences in reporting behavior were context dependent and shaped by divergent beliefs about the consequences of disclosing or failing to disclose any symptoms experienced. In general, we found that participants described three primary rationales to justify their reporting behavior: economic, health-oriented, and data integrity. While each of these rationales can be examined as a discrete narrative, individual participants might subscribe to multiple rationales, deploying different ones and

²Based on the qualitative data obtained through the semistructured interviews, it became apparent that participants appeared to vary in how they accounted for household income, with some participants only accounting for their personal income (regardless of household configuration) while others included income of spouses/partners, roommates, or parents.

Table 2. Demographics of study participants ($N = 131$).

	<i>n</i>	%
Women	32	24.4%
Men	99	75.6%
Race/ethnicity		
Non-Hispanic white	45	34.4%
Black	51	38.9%
American Indian	2	1.5%
Asian	1	0.8%
Native Hawaiian/Pacific Islander	2	1.5%
More than one race	10	7.6%
Hispanic ¹	29	22.1%
Age (years)		
18–21	3	2.3%
22–29	22	16.8%
30–39	47	35.9%
40–49	39	29.8%
50+	20	15.3%
Employment status		
Employed full-time	47	35.9%
Employed part-time	22	16.8%
Not employed	28	21.4%
Retired	1	0.8%
Self-employed	33	25.2%
Household income		
Less than \$10,000	15	11.5%
\$10,000 to \$24,999	37	28.2%
\$25,000 to \$49,999	58	44.3%
\$50,000 to \$74,999	11	8.4%
\$75,000 to \$99,999	4	3.1%
\$100,000 or more	6	4.6%
Educational attainment		
Less than high school	9	6.9%
High school or GED	26	19.8%
Some college	38	29.0%
Trade/technical/vocational training	17	13.0%
Associate's degree	11	8.4%
Bachelor's degree	27	20.6%
Graduate degree	3	2.3%

¹ The category Hispanic includes all racial groups, of which we have those that identify as white, black, American Indian, Native Hawaiian, and more than one race in our sample.

making disparate decisions about reporting depending on the specific clinical trial context. We explore each of these themes to illustrate how healthy volunteers make sense of the risks of reporting and not reporting AEs.

Economic rationale for reporting behavior

AE reporting can be an economic calculation for healthy volunteers because it occurs in the context of a larger financial

Table 3. Study participant clinical trial experience ($N = 131$).

	<i>n</i>	%
Clinical trial history		
1 study	20	15.3%
2–4 studies	26	19.8%
5–10 studies	36	27.5%
11–25 studies	31	23.7%
26–50 studies	10	7.6%
51–204 studies	8	6.1%
Past year clinical trial activity		
No new screenings	18	13.7%
Screened but did not participate	23	17.6%
Participated in 1 new trial	32	24.4%
Participated in 2–3 new trials	36	27.5%
Participated in 4–9 new trials	22	16.8%

decision regarding their participation in Phase I trials. As we previously noted, AE reporting involves the risk of losing some portion of the study compensation if the research team deems it in the best interest of the participants to remove them from the trial before it is complete. Among healthy volunteers, there was a shared narrative about the importance of the economic compensation for their participation, underscoring that few, if any, of our interviewees would enroll in studies without the financial incentive. There was, however, significant variation in volunteers' reliance on clinical trial income. Some volunteers used the money they made in trials as a supplement to their main source of income, while it accounted for the entirety of others' income. If reporting behavior were dependent on economic rationale alone, we might expect that those volunteers most financially dependent on clinical trials would be the most cautious to report AEs. Instead, it appeared that even when participants provided an economic rationale underlying their reporting behavior, the variation in reporting could be attributed to volunteers' perception of how likely AE reporting was to jeopardize their chance of receiving the full compensation.

The following two healthy volunteers provide examples of how economic reasoning influenced their reporting behavior. Edgar³ was a Hispanic man who had participated in 7 clinical trials, and Sylvester was an African American man who had participated in 24 trials. Both had a relatively similar financial profile: Neither maintained full-time employment and both used clinical trial earnings to help support household expenses. Despite the similarities in their financial profiles, they did not exhibit the same reporting behavior. On one hand, Edgar believed reporting AEs would lead to his dismissal from a study, so the decision not to report became the most logical choice:

Interviewer: Have you ever experienced a side effect during a study when you were in the clinic?

Edgar: Yeah, I think so. Like everybody wanted to throw up. Your stomach was all messed up, headache.

Interviewer: Yeah? What do you do when you experience something like that?

Edgar: Well, you can't do nothing 'cause if you tell 'em, they kick you out. [laughs]

On the other hand, Sylvester held the opposing belief that reporting AEs would not affect his continued trial participation:

When I first started [enrolling in Phase I trials], it was around 2008 [or] 2009, I didn't report anything because I thought it would-. I thought they would cancel me out of future studies. See, that was a lack of knowledge. Now ... I know that [AE reporting] that's the whole point of doing it [the study]; it has nothing to do with your next study. ... I used to just keep it to myself as long as it wasn't something, you know, extreme, but if it was a stomachache or headache, I would keep it to myself. Now I tell everything.

When comparing Edgar's and Sylvester's decisions, it is clear that the difference in their reporting behavior was due to how they understood the economic consequences of reporting. As Sylvester recounted a shift in his reporting behavior, he pointed to a transformation in his understanding of what would happen

³All participant names used in this article are pseudonyms.

if he reported AEs, not changes in his desire to earn income through clinical trials.

Many healthy volunteers recognized that reporting any AE was not likely to get them discharged from the study, but assessing which symptoms in which studies could do so became the focal point for their determination to report. Jason, a biracial man in his 30s, traveled extensively to pursue clinical trials as his full-time job and had enrolled in more than 30 studies. He claimed to report AEs 90% of the time, and he noted that most other participants were overly concerned that they could be sent home for minor symptoms. He felt quite confident that he was not at risk of losing his compensation for reporting a headache or a stomachache. For more severe symptoms, however, it became more difficult to assess what the clinic staff might do. Because of his frequent participation in studies, Jason had a robust network of healthy volunteers with whom he exchanged information, including about adverse events. Part of his decision making about reporting depended on what he had heard happened to other participants with similar symptoms at the same clinic. To illustrate, he described a study in which he expected to experience sickness but had been forewarned that it was safe to report AEs:

In a case like that there [at that clinic], we weren't the first group of [healthy volunteers for] that study. In the first group of that study, they had bad side effects. ... I had a friend in that group, and he told me before, you know, hey, that the side effects are gonna be bad and that they weren't gonna send people home, you know, just because of, oh, you're having, you know, vomiting or diarrhea or, you know, nausea or whatever. ... So, I pretty much knew going in that it's okay to report my side effects [because] they're not gonna send me home from this study.

Jason highlighted that the decision to report AEs was subject to revision based on what information he might receive about how it could affect his compensation. While he understood that AE reporting was not automatically going to lead to his study participation being truncated, he also protected himself from the risk of losing some of his compensation by choosing not to report 10% of his symptoms.

These economic rationales underlying reporting can be troubling to healthy volunteers. They feel as though they need to protect their compensation by hiding their symptoms from research staff, but they can resent that the system of research disincentivizes them to be honest. For example, Oscar, a Hispanic man who had participated in nine trials, encapsulated the problem in this way:

In a lot of ways, [AE reporting] it's kind of based on the honor system. I mean, it's kind of like an urban legend as far as studies go that they're gonna send you home if you feel kind of down in the dumps, but I mean, they do tell you straight out that they could take you out of the study if the doctor determines that it's unsafe for you to continue. ... They just kind of discourage ... people from being honest, you know, with like results and stuff. ... I can't necessarily blame them [healthy volunteers] for thinking that way 'cause, you know, they're always under the constant threat that they may starve to death if they don't make it through this thing. I don't know.

Oscar was a bit vague about his own reporting behavior, but when asked later in the interview how studies could be improved to make the experience better for healthy volunteers, he returned to the reporting problem: "Like, even if you give them [healthy

volunteers] the illusion of control, just tell them like, you know, if something happens to you [and] you still want to continue to be in the study, you can still do that." Oscar's qualms suggest that even when participants have an economic rationale for their reporting behavior, they can feel conflicted about their decision not to disclose AEs to the research staff.

Health-risk rationale for reporting behaviors

Healthy volunteers have vastly different perceptions regarding the level of harm they are exposing themselves to during the clinical trial process. Some believe there is virtually no risk, whereas others see Phase I trials as extremely risky (Cottingham and Fisher 2016). As has been shown in previous studies of healthy volunteers, the experience of adverse events is not taken as a sign of risk or harm (Fisher 2015), and our participants similarly varied in their interpretation of what symptoms during a trial might mean for their health more broadly. We did not find evidence that AE reporters were more concerned with prioritizing their health compared to nonreporters. In fact, our findings do not provide any indication that participants are willing to withhold AEs in order to protect their compensation when they feel their health may be in immediate danger. Instead, reporting in this context was reliant on two interrelated criteria: participants' assessment of the severity of the AE and their belief about the potential for minor AEs to be precursors of greater harm.

Representing the view that not all AEs pose equal threats to participants' health was Charlie. He was a white man who was a highly experienced healthy volunteer, as evinced by his record of completing more than 60 Phase I trials over the span of two decades. He discussed making individual determinations about when it was necessary to report AEs:

Interviewer: What do you do when you experience side effects in a study?

Charlie: [jokingly] Pray. No. [laughs] Depends on the side effect. I mean, if it's a bad side effect, you know, I gotta go tell them. I mean, there are times I don't say anything because it's not that big of a deal, and they're not going to do anything other than open up their little report and constantly pester you with questions. It's not really gonna be significant ... There are definitely a lot of guys who have a policy of unless it's bad, they don't say anything. I sometimes do that just 'cause it's annoying, 'cause it's such a minor side effect. You're like, "Oh Jesus, whatever."

Considering that Charlie was a serial participant who relied on clinical trial income to support himself, the risk of being kicked out of a study could sway his decision. Here, he focused instead on whether reporting the AE was important to his health or would simply lead to an unwelcome level of surveillance by research staff. Charlie, like many other participants in our study, did not feel as though he was endangering himself when he chose not to report what he saw as minor symptoms.

We found a similar pattern with a first-time participant who decided to report an AE only after the symptoms had been exacerbated. Timothy, a white man in his 40s with a graduate degree, was a particularly interesting case because he was financially stable, worked in a professional job, and claimed a household income of over six figures. Although he would not have enrolled in the trial except for the \$1,500 payment, he did so,

after learning about it from his mother who worked in a Phase I clinic, on more of a whim than from any immediate economic need. Timothy experienced severe gastrointestinal symptoms and weight loss that ultimately led to him fainting at work and winding up in the emergency room. He had initially been reluctant to report his symptoms to the research staff, and the interviewer explored why this might have been the case:

Interviewer: So some people say that they're nervous about reporting side effects.

Timothy: Yeah.

Interviewer: Have you heard of this in your experience?

Timothy: No, you know, [but] I can understand that though 'cause they, you know, maybe fear getting kicked out of the study and losing the financial incentive. For me, at first, I was pretty ambivalent about it [the symptoms], that it probably wasn't a big deal, and so I didn't feel the need to call, you know. It wasn't until after I, you know, ended up in the emergency room that I did call. But I had been kind of gritting my way through it for a couple of weeks.

In other words, while acknowledging the potential financial risk of reporting AEs, Timothy dismissed this as irrelevant to his decision making, noting that for him, reporting hinged on him recognizing the AE as a true health risk.

In general, participants who perceived AEs as a sign of harm from a trial were all the more apt to report all of their symptoms regardless of their severity and expressed the belief that reporting would reduce their risk. Barry, an African American man who had participated in seven studies, explicitly articulated this view: "If you do feel a headache or something that's going on, let them [the research staff] know, ... or if you feel the nausea or anything. That take[s] away a lot of the-, it prevents the risk." Barry illustrates that some participants were adamant about the importance of reporting even minor symptoms. Felix, a Hispanic participant, took the point further and advocated for active monitoring of one's body to be aware of any changes that might occur. During his first and only study, he experienced tingling in one of his toes, which he promptly reported to the research staff members and was impressed by the attention he received as they examined and questioned him about it. Felix explained his reporting behavior by saying,

Most people know their bodies, and you know when they're [sic—you're] feeling a little, you know, woozy or a little different, a little dizzy. You know what I mean? So, when you do a study, you gotta-, you know, you gotta be conscious of your body and what it's doing.

The responsibility to protect oneself by reporting AEs becomes all the more imperative when participants perceive that minor symptoms always have the potential to develop into a serious medical problem. Victor, a black Nigerian man who had completed more than 70 studies and used to think of his participation as his full-time job, elaborated on this reason to report all symptoms:

It's not something you want to keep to yourself ... My health is way more important than the money, the amount of money that I'm making. So, I think there's a good chance you'd get kicked out of the study, but also, at the same time, that's a good thing for you [to get kicked out]. You might hide it and it balloons into something other than what it was supposed to be, you know? Like you start with a headache and before you know what's happening, you have a fever, and right after the fever, you go into some kind of shock, septic shock or whatever, and you don't know why that is. So I

always think it's better off if you tackle it in the beginning before it becomes worse.

By focusing on the inability of participants to evaluate the potential risks that AEs signal, Victor demonstrates that the decision to report can be a strategy to reduce potential danger. In this way, these participants mobilized a health-risk rationale over an economic one in their reporting behavior.

Data-integrity rationale for reporting behavior

A primary goal of drug development is to create drugs with improved efficacy while also minimizing their deleterious side effects. In order to achieve such a goal, clinical research must be designed to collect accurate information about a drug's effects on the body. Some participants expressed beliefs that pharmaceutical companies are more interested in maximizing profits than in developing more effective treatments. This tension between the scientific and capitalistic goals of testing investigational drugs was also present in healthy volunteers' perceptions of Phase I trials, and it inflected their decision making about AE reporting. Indeed, those who reported AEs tended to explain their behavior in terms of concern about data integrity, whereas those who did not report AEs often questioned the overall value of the data being collected in Phase I trials.

Some participants who recognized clinical research as potentially beneficial to society demonstrated a commitment to providing accurate data about adverse events. In one of the five studies in which he had participated, Gavin, an unemployed white man, experienced severe burning in his stomach each time he received a dose of the investigational drug. He immediately reported this symptom to the research staff, recalling,

I went to the doctor and said, "Hey, that stuff hurts, it burns," and they made a note and all that good stuff, you know. [I was] hoping the suggestion is, "Eat this, take this with food, not on an empty stomach," you know? "[Otherwise,] It's gonna burn a hole through your stomach."

In talking with the other participants in the trial, Gavin realized that many of the others had the same AE but did not report it to the staff. In reflecting on AE reporting, he contrasted volunteers' personal, economic motivations with the broader societal benefits that are part of participation in Phase I trials:

They [the other participants] don't wanna be kicked out of studies, point blank. They think they're gonna get kicked out for reporting a side effect ... so they just keep quiet and suffer through whatever the side effect is, rather than saying, "Hey, look, you know, this hurts." How are you helping a drug industry or anyone if you're not telling them what the side effects are? That's why they're doing a human trial.

Gavin confessed that he was unsure whether reporting AEs could get someone kicked out of a trial, but he seemed to believe it was a risk. Nonetheless, he demonstrates that some healthy volunteers were willing to put data integrity or the public's health before their own economic compensation. This was also true of Elena, who was one of the more passionate healthy volunteers about the societal benefits of reporting AEs. She was a Hispanic woman who was also unemployed and had participated in five trials, during which she had observed how pervasive nonreporting can be. She described herself as quite

confrontational in her interactions with those other participants when she saw this happening:

I put them on blast when I started talking to them on [sic] our dorms. I said, “Do you think that it’s fair for other people to take this medicine when you didn’t even give your accurate side effects? I mean, the pharmaceutical [company] is giving you money for your time and for your information, but yet all you’re giving is time, but no information. ... Do you think it’s fair for the other people that are gonna depend some day on this medicine? Do you not think that one day your child is gonna be the one to be on this medicine?”

Elena made her argument personal, that even if those participants did not care about their responsibility to the trial itself, they might be endangering their own children by failing to report AEs today. This emphasis on the importance of data integrity might not have convinced her fellow participants to report their AEs, but for Elena, it fully justified her duty to report symptoms she experienced during trials.

On the other end of the spectrum, some healthy volunteers perceived that the pharmaceutical companies sponsoring the trials as well as the research staff conducting them would prefer for participants to withhold information about their AEs. Thinking of the industry itself as motivated by economic factors, these participants positioned themselves as unwilling to sacrifice their economic compensation because they doubted the possibility of data integrity regardless of their actions. For example, Myra, an African American woman who had participated in nine studies, imputed,

The pharmaceutical companies, yeah, I wouldn’t say I trust them as much. ... I’m saying the nature of the beast ... their objective is to make money. And I did see people who had side effects [that] when they told about their side effects, they [the research staff] came up with all kinds of issues as to why they [the participants] could not get into another study with them.

In a context of pharmaceutical companies actively eschewing AE reports, the risk of losing out on one’s compensation or the ability to enroll in future studies is not worth the risk. Tina, a white woman who had participated in more than 30 trials, had also experienced similar situations in which she felt certain that based on how badly the staff treated participants who reported symptoms, the staff did not want participants to give accounts of AEs. When Tina generally felt unwell during one study, she calibrated her reporting behavior accordingly:

It was a place [that] they pay a lot of money, but they didn’t really want you to come clean [about AEs], so I didn’t. I looked at that particular study as a study that I was doing and that we were being paid to be quiet, so I did. I’m not proud of it, but I did it.

While Tina also confessed to how badly she needed the money at the time, thereby aligning herself with the profile of the self-interested volunteer, her feeling of discomfort about not reporting her symptoms indicates that the immediate need for financial compensation alone cannot explain her decision not to report. Rather, her disillusionment with the research being conducted at that time undoubtedly influenced her decision to withhold information from the staff about her symptoms. Ironically, while not prioritizing data integrity, Tina responded in a similar way to other participants who discussed data integrity as a factor in their decision to report AEs. In both types of

cases, participants described providing the information they believed the company was looking for, whether that be full accounts of adverse events or no adverse events at all.

Additionally, Tina’s example of deciding not to report her AE in that particular study also illustrates how healthy volunteers make judgments about the importance of data integrity on a case-by-case basis and make decisions about reporting adverse events accordingly. Rather than seeing a trial as tainted, as Tina did, most participants instead felt as though they needed to interpret the cause of their symptoms in order to add value to the research process by reporting. For example, Renee, a biracial woman who had participated in 14 studies, contrasted herself with other participants declaring that she is someone who will always report AEs:

I’ve seen people actually have side effects. They won’t say anything because they’re afraid of getting kicked out. Because, I mean, they’re there to get money, so they’ll sit there and suffer and not say anything. And I’m not-, I’m just not that type of person. If I’m feeling something, you know, *I’m going to make sure it’s definitely a side effect*, and I’m going to say something because ... it could mess up something. You know, and at the same time, you know, the people [i.e., researchers] that are interested enough to do these studies—’cause there are actually sick people that’s gonna take this medicine—they need to know. (emphasis added)

At first glance, it appears that Renee was describing herself as someone who reports any symptoms she might experience during the course of a clinical trial. However, she indicated that she did not see all symptoms as AEs and wanted to report only those she believed were caused by the drug. Because she saw herself as a reliable volunteer who understood the goals of the science, she wanted to filter out any symptoms that might sabotage the trial’s findings. Despite Renee’s good intentions, the results of her actions nevertheless undermine the accuracy of the data.

The idea that healthy volunteers can and should determine which adverse events can be attributed to the drug also appears to be reinforced by clinic staff. When healthy volunteers believe that they should interpret the cause of their symptoms, their reporting behavior is motivated by a data-integrity rationale and illustrates why individuals would vary in their decision to report. Roman, an African American man who had participated in more than 200 studies, provides an example of how participants can learn selective reporting from research staff:

See, a lot of times I don’t report my AEs because ... anything will give me a headache, and most of the places that I go, they basically know this [about me]. So, a lot of times they’ll say, “How are you feeling?” I’ll say, “Well, I have a slight headache.” They’ll be like, “Well, do you think it’s ’cause of the drug, or?” And most of the time, I’m like, “No, it’s the [clinic] environment. I mean, I got a guy inside my room that’s snoring [and] keeping me up, so I’m not getting any sleep.” Or, “The diet that y’all have us on is affecting me ’cause now I gotta wait till 2:00 [p.m.] to eat breakfast, you know, and I don’t normally fast that long.”

Roman then elucidated how he recognizes a real AE from a symptom caused by the environment: “I have a three-day process. ... If it keeps happening for three days, then at that point, to me, it’s a side effect.” While Roman acknowledged other participants’ fear of getting dismissed from a study for reporting AEs, he did not seem to believe or worry about this. Instead, he was trying not to skew the data by providing extraneous

symptoms, and his interactions with staff confirmed for him that he was acting as a responsible participant.

Discussion

Previous research provides interpretations of why healthy volunteers fail to report adverse events without incorporating perspectives from healthy volunteers. These reports have mainly depicted the healthy volunteers who fail to report adverse events as subversive and threatening individuals, assuming they are profit maximizers who disregard their own safety as well as the health of future users of prescription drugs (Dresser 2013; Devine et al. 2013; Resnik and McCann 2015). We advance existing literature by using qualitative data to give voice to healthy volunteers who narrate multiple rationales for reporting behavior.

Our findings demonstrate that the decision to report or not report AEs is far less a reflection of volunteers' character and more indicative of their knowledge of clinical trial processes. While most participants want to protect their economic interests in the trial, they are willing in most cases to forgo their full compensation if they believe not reporting their symptoms jeopardizes their own safety or the validity of the research. Importantly, while we treated each of these rationales as discrete, healthy volunteers likely deploy combinations of these ways of thinking about AE reporting when determining their own actions. It is apparent that the economic rationale for not reporting can become dominant when participants have less concern about their own safety or doubt that detailing their symptoms to research staff will contribute meaningfully to the integrity of the trial. Likewise, even participants with strong economic motivations to avoid reporting AEs are likely to risk losing part of their compensation when they are truly worried about their health or safety in a trial. Finally, depending on their interpretation of the value of the information they can provide about an investigational drug to the research team, AE reporting might become an imperative regardless of their own economic need.

Our study has important limitations. First, we collected data only on healthy volunteers' perceptions of AE reporting and examples of times when they opted to disclose and not to disclose their symptoms to staff. As a result, it is difficult to assess what healthy volunteers actually do each time they enroll in Phase I trials. Additionally, these three rationales cannot encapsulate all the nuanced and varied reasons that determine individuals' reporting behavior, considering the wide range of symptoms they might experience as well as differences in how research staff might affect participants' reporting. In spite of these limitations, our participants, perhaps due in part to being interviewed as part of a larger longitudinal study, exhibited much candidness in describing their past experiences, including times when they failed to report.

The value of research on healthy volunteers' experiences is that it illustrates the otherwise invisible institutional structures that shape their behavior. Our findings point to opportunities to intervene and incentivize AE reporting. Currently, healthy volunteers' perceptions of the importance of reporting AEs stem from a variety of sources. Specifically, beliefs about how AE reporting could affect study compensation, its importance

for participants' safety in trials, and the value of this information for data integrity could be shaped by the informed consent process, as well as by participants' personal or vicarious experiences with reporting. For example, when explaining their beliefs that AE reporting leads to study dismissal, healthy volunteers provided explanations derived from secondhand stories more than from any other source. This suggests that providing more clarity about what types of AEs would be grounds for study withdrawal could reduce participants' hesitation to withhold information about AEs they perceive as nonthreatening. Additionally, participants need clearer information about how all bodily changes are important to report regardless of whether participants believe the change is due to the investigational drug or due to some other factor. Healthy volunteers need to understand that their role is not to adjudicate symptoms but to report them. Finally, participants should not feel discouraged from reporting AEs because research staff members give the impression that "bad news" about an investigational drug is unwelcome information. Instead, research staff members need to communicate unambiguously how valuable AE reporting is to the drug development process, for volunteers' own safety, as well as for the safety of patients who may be prescribed these drugs in the future.

Conflicts of interest

None.

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Ethical approval

This study was approved by the Biomedical Institutional Review Board at the University of North Carolina at Chapel Hill.

Author contributions

JAF conceived of and designed the larger longitudinal study. JAF (and other non-author research team members) conducted the interviews. JAF and LM (and other non-author research team members) coded the transcripts. JAF and LM conceived of article topic. LM analyzed the data. LM wrote the first draft of the article. Both authors contributed to article editing and revision.

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