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Indirect Benefits in HIV Cure Clinical Research: A Qualitative Analysis

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Abstract

Currently, much of early phase HIV cure research involves unknown and potentially serious risks, with little or no chance of direct health benefits. During informed consent, researchers emphasize this lack of personal medical benefit to minimize misconceptions that undermine genuine consent. We explored participants' and researchers' perspectives on HIV cure clinical research participation and its potential benefits. We conducted semistructured interviews with 17 HIV cure research participants and nine researchers in North Carolina, USA. We analyzed interviews to identify participant experience-related themes. We were particularly interested in indirect benefits, such as psychological support or improved care. We also assessed five consent documents for benefit/risk-related language. Research participants were male, with a median age of 50 (range: 28–62); most were non-Hispanic white (15/17) and men who have sex with men (13/17). All 17 trial participants found research participation meaningful and beneficial. Reported benefits included improved healthcare (16/17), HIV knowledge (13/17), intimate relationships (10/17), and positive behaviors (6/17). In addition, all participants described psychological benefits, including increased positive outlook, improved sense of purpose, emotional support, and enriched self-image. Participants reported risks such as quality of life concerns, uncomfortable procedures (e.g., leukapheresis), latency reversal, and HIV status disclosure. While the consent documents included discussion of these and other risks, they did not mention potential indirect benefits. Individuals involved in HIV clinical research have recognized participant psychological, social, and behavioral benefits. We recommend that researchers and institutional review boards consider these benefits for inclusion during risk/benefit assessments, consent procedures, and other discussions with prospective participants.

Keywords: HIV cure, benefits, risks, clinical research ethics, bioethics, qualitative research

Introduction

HIV research toward a cure has gained momentum,[1] but participating in these trials currently offers little or no chance of direct medical benefit.[2,3] Recent literature suggests that media announcements about cure breakthroughs[4] and use of the term ''cure'' in descriptions of these studies[3,5–8] may increase the potential for therapeutic misconception[9–14] among participants. That is, if HIV cure participants wrongly expect to receive direct medical benefits, or even cure,[7,8] they may accept risks that they would not have otherwise.[11] Emphasis on the lack of known medical benefit within consent documents is intended to mitigate therapeutic misconception and assist participant understanding of the fundamental goal of this line of research: to gain scientific knowledge needed to develop a future cure.[15] However, this approach may also obscure important indirect benefits that participants may experience and value.

These indirect benefits, also referred to as inclusion[16] or collateral benefits,[17] are often received through clinical trial participation, regardless of whether or not a direct medical benefit is realized. Examples include access to testing, improved medical care, feelings of altruistic satisfaction,[12,17–19] a sense of health-related agency, personal interest in the

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study, and support from research staff.[20] For example, an HIV prevention trial that involved people who inject drugs found multiple positive social impacts among participants, including improvements to their lives and health and valued gains in knowledge.[21]

Qualitative research may provide a window into the potential social, behavioral, and psychological dimensions of clinical trial participants' experiences and in turn may inform efforts to improve the ethical conduct of research.[22] This is especially important if researchers are unaware of or not attentive to indirect benefits. We used in-depth interviews with HIV cure research participants and researchers to examine participants' experiences of benefits and risks and perceptions among researchers regarding participants' experiences of benefits/risks related to this research.

Materials and Methods

Recruitment for this study took place from February 2015 through August 2016. During this period, research coordinators at the University of North Carolina at Chapel Hill identified 28 eligible participants among volunteers for HIV cure clinical research studies. Research coordinators did not impose any exclusion criteria on HIV cure study participants, yet due to clinic/scheduling practicalities, not all 28 participants were recruited. Nineteen HIV cure research participants 18 years or older were recruited by clinical research coordinators to take part in one semistructured, hour-long interview. Out of this convenience sample of 19 participants, 17 agreed to the interview.

Research participants were adults living with HIV who had enrolled in HIV cure research involving a study intervention. These four studies included a phase I study of HIV-1 antigen expanded specific T-Cell therapy (HXTC),[23] three phases of a histone deacetylase inhibitor (Vorinostat) HIV-latency reversal study,[24] a Phase I/II Study to Evaluate the Kinetics of the Immunologic Response and Virologic Impact of AGS-004,[25] and a study of the safety and activity of an Anti-PD-L1 antibody.[26] In addition, one participant donated cells (through leukapheresis) for a fifth study for use in laboratory studies related to HIV cure research.[27] Some participants took part in more than one of these clinical trials.

Nine researchers were interviewed, including three research scientists, five clinical research support staff, and one physician-researcher whose clinic patients participated in cure research. In addition, we reviewed five consent documents associated with the aforementioned cure studies and analyzed their contents for language related to discussion of potential benefits and risks.

Interviews

Interviews were conducted by one team member (A.G.) and recorded with each participant in a private office located apart from the building used to conduct the clinical trials. The interview guide included questions related to living with HIV, thoughts about HIV cure, and experiences of HIV cure research participation (e.g., researcher–participant interactions, benefits, risks, motivations, and effects on personal relationships). Informed consent was obtained before interviews or recording began. A 30 USD gift card was offered to each interviewee (participants and researchers). All research activities received ethical approval from the Institutional Review Board (IRB) at the University of North Carolina at Chapel Hill.

Data analysis

Audio-recorded interviews were transcribed and personal identifiers removed by one team member and checked for accuracy by a second. Utilizing the Framework Analysis approach,[28] a codebook was created to define and illustrate benefit and risk-related themes identified within the interview guide questions and through early analysis of interviewee responses.

The second team member used MAXQDA 12[29] to code the interview transcripts and informed consent documents. These codes were then reviewed for fidelity to the codebook by a third member. Coding inconsistencies were resolved through discussion, and illustrative quotes, including participant identification numbers, were identified to present typical responses within each theme.

Results

HIV cure trial participants

The 17 HIV cure clinical research participants were all men with a median age of 50, ranging between 28 and 62 years. Fifteen interviewees self-identified as White, one as Black, and one as Latino. Fifteen reported some college education or a professional qualification. Thirteen identified as men who have sex with men, three identified as heterosexual, and one chose not to disclose his sexual identity.

Participant perceptions of indirect HIV cure research benefits

All 17 interviewees reported personal benefits related to participation in cure research trials. Analysis of the interviews revealed six primary benefit domains. These were (1) psychological benefits, (2) indirect healthcare benefits, (3) improved understanding of HIV, (4) intimate relationship benefits, (5) positive behavioral changes, and (6) financial benefits.

Psychological benefits

All 17 participants mentioned psychological benefits. These included increased positive outlook on life, improved sense of purpose, emotional support provided by research team members, hope, improved self-image, and useful self-reflection. Exemplary statements of these psychological benefits are provided in Table 1.

Indirect healthcare benefits

Sixteen of the 17 participants made statements describing the quality of healthcare during research. Characteristics of improved care included high quality of care providers (10/16), better health professional access (3/16), more HIV-related testing (offering peace of mind; e.g., viral load, CD4 count; 2/16), and care for other medical concerns (1/16). As one person explained, ''… they do bloodwork and I know what's going on …'' (Participant 07). Another offered: ''… there's compassion, there's sincerity, there's great follow-up; [….] they're honest and their integrity is top notch …'' (Participant 17). Yet another stated, ''… yes, the standard of

Table 1. HIV Cure Study Participant Quotes Depicting Psychological Benefits of HIV Cure Research in North Carolina, 2015–2016 ($N=17$)

Psychological benefits	
Positive outlook (11/17)[a]	''So as I participate, I tend to learn more and soak things in and that helps me put a positive spin on what initially was very, very negative.'' (Participant 01)
Sense of purpose (10/17)	''I just feel that by participating I'm extending my life. I feel that by participating I'm working toward a goal, working toward finding a cure, helping the researchers.'' (Participant 16)
Emotional support (staff) (10/17)	''It's definitely made the experience a lot easier: people that seem to understand and want to help; and then put you at ease, to come up here just to help any apprehension that somebody might have.'' (Participant 15)
Hope (6/17)	''I have hope again; honestly, I really do have hope again. [….] … I want to be around for a very long time, I have a lot more to accomplish; it's given me hope that, you know, I'm doing something proactive ….'' (Participant 17)
Improved self-image (6/17)	''Being part of the study both feeling like I'm contributing to something good and learning more of the science behind it has helped me view myself in a much, much better light.'' (Participant 02)
Useful self-reflection (4/17)	''[Participation] has kind of changed the way I see myself as someone living with HIV, but still doing what I can to help prevent more people from becoming infected and sick from HIV.'' (Participant 03)

[a]The number of participants citing the benefit is in parentheses.

care … it's better than if I wasn't in the studies … I think I get a step up, I think there's a step up when you're doing this research; I just think you've got a heads up on other people'' (Participant 16).

Improved understanding of HIV

Thirteen participants mentioned newly gained or improved understanding of HIV, or the state of HIV treatment or cure research specifically, as benefits of participation. One told us: ''I've gained a lot of knowledge just from being involved in the studies and getting to talk to the researchers'' (Participant 03). Increased knowledge was also linked to hope, as illustrated in this statement: ''… just knowing that there are people behind the scenes … trying out new things and exploring different avenues and ideas. And you know, just trying to fight the battle and kind of keep hope alive …'' (Participant 04).

Intimate relationship benefits

Potential benefits to intimate relationships were cited by ten participants. For an interviewee, who was in a long-term relationship with another participant, this benefit was especially poignant: ''If anything, I feel like it's brought us closer together. Being able to participate … in the same studies and you know, both being in the same situation, and we've both been able to kind of help each other out in coming to study visits …'' (Participant 03). Another participant who did not have a partner in research offered a similar sentiment: ''I think it's definitely brought a relative closeness, a different level … a general understanding for … what somebody else is going through. An emotional connection …'' (Participant 15).

Positive behavioral changes

Six participants described positive behavioral changes related to being in the research. Four of these participants cited improvements in diet and/or exercise habits; two mentioned safer sexual practices; and two cited a reduction in tobacco, alcohol, or drug use. As one explained: ''I don't want there to be a question asked as to whether, well, is the drug [Vorinostat] not working because th[is] guy's not eating right, not exercising, not doing the right things. So I made it a goal to eliminate everything … [as] far as a processed food'' (Participant 05).

Financial benefits

Money provided to compensate participants for time/travel across the four HIV cure clinical studies averaged 25 USD per hour. The length and total number of research visits varied by study (between 1 and 10 h and 5 and 32 visits). However, only three of our participant-interviewees seemed to see this money as a notable benefit. When asked if he benefited personally from taking part in research, one explained: ''… just believing that I'm doing the right thing is emotionally good for me. And they do provide money … to compensate for these visits, but the emotional part of it is much greater … if they didn't offer any money at all, I'd still come …'' (Participant 05).

Benefits in proximity to cure

Four of the 17 trial participants made statements with a tenor that suggested their participation included the potential for cure, but not outright cure as a benefit. For instance, one said: ''I'd be lying if I didn't say that … I'm closer than somebody else [who is] sitting on their hands just taking their antiretrovirals and getting their blood checked every three months, right. I'm closer to a cure if I'm involved in the research …'' (Participant 06). Another interviewee, following a statement that referenced his own potential for cure, elaborated: ''I would say the elements of me being cured are inside my body right now. [….] I do believe what they've done, has at least stepped it up to the point of, if not cured, then probably pretty close to that point of saying … we've brought this research this much further and now we can take it a little bit more'' (Participant 17).

Nevertheless, most participants seemed to have a realistic understanding and tended to focus on contributions to science.

For instance, one told us: ''… hopefully, something I provide may lead to a cure or some type of breakthrough that is able to at least begin to forward the research and cure process'' (Participant 15). When asked what he might say to someone thinking about joining a similar study, another said: ''… are you going to be part of a cure or something? Not really. This is investigational research on a variety of different things. I'd honestly say, 'if … you see some value in [the] benefit to society, do it''' (Participant 06).

How participants described benefits as motivating factors

Sixteen interviews with participants suggested how perceived benefits served as motivators for participation in HIV cure research. The most commonly cited reason was altruism (13/16). For instance, when asked about the reasons why they wanted to take part in research, interviewees responded with the following statements: ''I feel like I'm contributing to a global effort to do something really good for everyone'' (Participant 02) and ''… it makes me feel better as a person … that I'm trying to help'' (Participant 07). Besides altruism, participants cited hope for a cure (6/16) and financial incentives (4/16).

In terms of hope for a cure, it was not always clear whether interviewees meant for themselves or for future generations, but most statements suggested hope for both. They also clarified that trust and relationships with researchers affected their participation decisions and motivations. Speaking about his involvement in what he understood to be a ''shock and kill'' strategy study (HIV latency reversal paired with interventions that aim to eliminate the virus from the body),[30] one explained: ''I've already agreed to doing another study, cause if I'm in the kill part, and [cure researcher] wants to do the shock, and it involved the Vorinostat, you know, I'll trust his judgment to do that'' (Participant 17).

Some participants described changing motivations over time as they learned more about the research, as for example: ''… when I first heard 'cure study,' my first thought is like: 'I could be cured of this? What?' That would be awesome. But then … once I learned more about it, and really started thinking about it … I saw it as an opportunity to make some money and possibly help me cope with having the condition'' (Participant 02). Similarly, another told us: ''… initially I was thinking [that] I want to beat this. [….] But after a while, it became: 'hey I just want to further what research is out there and see if I can maybe contribute in any way, shape, or form''' (Participant 15).

Risks and barriers

Sixteen participants talked about potential risks of being in the trial. Potential negative impacts on their day-to-day quality of life were the most common concerns (13/16), while a smaller number mentioned cancer-related risks (5/16), drug side effects (4/15), and disclosure of HIV status during research clinic attendance (3/16). Interestingly, one participant worried about the potential for participants to accept greater risks for money.

Barriers to research participation were described by most of the participants (15/17). Time commitments (9/15) and transportation issues were most commonly mentioned (8/15). Two participants recognized instability or other social factors in participants' lives as an important potential barrier as well.

Negative experiences

Most trial participants cited few or no negative experiences associated with HIV cure research. However, six did recall uncomfortable and/or painful experiences associated with study-related leukapheresis procedures. One participant described the need to lie to friends and family regarding his reasons for travel for study visits, since he preferred that they not know about his participation. Another participant mentioned experiencing some degree of conflict with an intimate partner regarding participation decisions. Still another expressed concerns about latency reversal. In a statement that revealed both his understanding of the study, as well as his concern about perceived risks to others, this participant explained: ''… knowing that … it amps up the viral load in my body potentially, … it's a little bit scarier [….] [It] feels a little weird with this study, knowing that it's trying to push it [HIV] out of hiding and into my blood stream …'' (Participant 10).

Researchers' perceptions of participant experiences

As noted above, we interviewed nine research investigators and study staff members. Researcher interviews echoed participants' statements regarding psychological benefits from HIV cure research. They described these benefits in terms of emotional support provided by research staff, sense of purpose, hope, and improved self-image. Most also mentioned improved medical care for participants, including personal relationships with staff, increased access to care providers, testing access, and increased quality of care.

Researchers saw participants as altruistic and as dealing with their personal HIV issues through giving to this new area of science. For instance, one HIV physician-researcher explained: ''I think there just has to be this other motivating factor, which is being part of something bigger than them, that this is how they can give back to their community … people feel like they're really doing something for science'' (Researcher 01). In addition, research staff acknowledged the risks of the experimental interventions and the potential for future issues that may develop from participating in these studies, such as infertility or cancer.

Informed consent document benefit statements

We reviewed five informed consent documents associated with the HIV cure studies that participants reported joining. All of the consent documents included a short section on potential benefits for study participants. One stated that participants would not receive any direct benefit; three stated that direct benefit may not exist for participants. None mentioned individual psychological or social benefits. All indicated that potential benefits would be for science, future research/patients, and/or society. One mentioned the indirect benefit of improved healthcare due to close monitoring while on study. Although our focus was on benefit statements, we examined the risks listed in the consent forms, which detailed potential risks of harm associated with the experimental intervention (e.g., side effects, cancer, and fertility issues), and

research activities such as leukapheresis. Other possible risks were listed, including an inadvertent HIV status disclosure.

Discussion

Few previous studies[22,31] have focused on the experiences of individuals taking part in HIV cure research. This study expands the limited knowledge base on participants' perceptions about HIV cure research[3,32–35] and adds to research[36] on HIV cure researchers' perspectives on participant benefit. Consistent with the broader literature on indirect benefits,[17–21,37,38] and one study of four HIV cure research participants,[31] our study revealed that participants perceive substantial benefits associated with HIV cure research, despite clear understanding that the research offered to them has no direct medical benefit. Few of our interviewees mentioned risks or negative experiences related to the research, even when strongly encouraged to do so by the interviewer. Rather, they focused upon perceptions and experiences of the various benefits they received as HIV cure clinical trial participants.

The 17 participants reported that taking part in these studies had a profound impact on their lives. All described psychological benefits, including increased positive outlook on life, as well as improved sense of purpose, emotional support, hope, and enriched self-image. Other reported benefits included improved healthcare, HIV knowledge, intimate relationship benefits, and positive changes in health-related behaviors. While the researcher respondents reported knowledge of indirect benefits associated with research participation, individually they seemed less aware of the full range of potential benefits their participants reported experiencing.

None of the informed consent documents we analyzed mentioned the potential for direct medical benefits. This finding is consistent with a previous analysis of HIV cure research consent forms, for varying types of research designs, which found that direct medical benefits tended to be framed as future goals, and immediate benefits framed only in terms of scientific progress or value to society.[39] Despite this, and researchers' best efforts to ensure participants understood that there were no direct medical benefits related to participation in HIV cure research, statements by three trial participants raised concerns about possible misunderstanding. Of these, two thought that they were ''closer'' to a cure than nonparticipants or that their participation would move them to the front of the queue once a cure is discovered. Ironically, a history of participation might actually make them ineligible for inclusion in future HIV cure studies[5]—information not mentioned in any of the informed consent documents we analyzed, although noted in others.[39]

Nevertheless, the majority of our participants had realistic expectations and reflections on the potential for benefit from continued participation in HIV cure research. Hope for future benefits, described in the literature as therapeutic optimism, should not be equated with misunderstanding or therapeutic misconception.[10]

Concerns about undue or inappropriate inducements to enroll in early phase HIV cure clinical trials that offer little or no direct medical benefit may lead researchers and IRBs to omit most indirect benefits from consent forms and discussions. Given the perceived importance of nonmedical indirect benefits associated with the HIV cure research studies reported in this article, we wonder whether researchers should consider such benefits in risk/benefit evaluations and indeed in informed consent discussions. This argument is supported by the Belmont Report[40]—an established set of ethical principles for human subjects research that encourages taking more than just medical benefits into account—as well as increasing discussion in the ethics literature about the importance of indirect or inclusion benefits.[38,41–43]

Our data suggest that psychological, social, behavioral, and healthcare-related benefits are commonly reported and valued by the HIV-cure research participants at the University of North Carolina at Chapel Hill. Supportive trusting relationships with study staff or access to healthcare may be just as important to participants as the altruistic motivations that they also mention. If these benefits are found to feature commonly among participants in other HIV cure clinical studies around the world, then failure to mention them during consent may frame participation as all risk with no gain.

Some have suggested that portraying the balance of uncertain and possibly significant risks against no direct benefit in HIV cure trials makes participation a ''bad deal.''[44] This striking contrast between the risk/benefit relationship as seen by third parties and by research participants is at least worth exploring. If these benefits are real, what justifies them being inadmissible from an ethical point of view? We suggest that appropriately forecasting the potential for indirect benefits may facilitate more accurate risk/benefit calculations for potential participants. The fact that researchers cannot guarantee that some or all of these benefits will be experienced by every participant does not, we argue, justify ignoring them.

In short, one might argue that the reasons in favor of mentioning such benefits (at least as possibilities) during the consent process and of making them part of ethical assessments of risks and benefits are stronger than the reasons to exclude them. However, even if radical exclusion of such benefits is hard to justify, inclusion of such benefits in the consent process remains ethically challenging. There is tension between denying the reality of indirect benefits on the one hand and creating added risks by communicating them to prospective participants on the other.

As our study suggests, many participants are motivated by altruism, and mention of these benefits might crowd out some positive motivations, by directing participants' focus toward their potential for personal gain. In certain contexts, such as low-resource settings, telling prospective participants about potential indirect benefits might lead to ''undue inducement''—that is, disproportionate prospects of benefit that may inappropriately lead participants to discount risks.[45] Therefore, there exists a possibility that mentioning indirect benefits during informed consent could reduce the quality of consent, if decisions to participate are based on expectations of indirect benefit that never materialize for a given participant.

In addition, since informed consent does not involve disclosing all possible information related to a study, the inclusion of indirect benefits needs to be justified, presumably on a contextual, selective, study-by-study basis, informed by prior experiences observed in methodically similar studies. Guidelines should be developed to help determine whether and how to take indirect benefits into account in ethical review, research communications, and study documents. While

this may be a real concern, since indirect risks are infrequently mentioned in research practice, it is difficult to know. These are important and neglected issues and should be the focus of future empirical and conceptual research.

Limitations

Our research has at least three major limitations. First, this was a small, qualitative study of participants and researchers at one research site. The majority of the cure study participants were White and male with a median age of 50, thus lacking diversity and limiting the generalizability of our findings. Lack of success in recruiting women for interviews, despite focused efforts by the study team, is especially unfortunate.[46]

Second, few interviewees recalled any negative experiences. This suggests a possible selection bias for participants with overall positive research experiences, since those with negative experiences might have declined the interviews. Alternatively, interviewees could have emphasized positive experiences in attempts to please researchers. This research was conducted at the researchers' own university. While interviews were conducted outside the context of the clinical trials, and the interviewer was not associated with the clinical studies, interviewees nevertheless may have been reluctant to report negative experiences associated with clinical research participation.

An additional factor might be retrospective bias: interviewees might be uncomfortable recalling or mentioning negative experiences, since doing so might call into question their own motivations or original decisions to participate in the research. Although we tried to build rapport, make respondents comfortable, and reassure them about the confidentiality of the interviews, these potential biases cannot be ruled out. Furthermore, it could be that perceptions of trial benefits were heightened due to the novelty and potential specialness of research efforts to cure HIV. While the similarities in benefit perception between study participants and investigators suggest that participants were not subject to misunderstandings or social desirability bias, future research should be designed to confirm this finding in a quantifiable way.

Third, descriptions provided by participants may reflect total research experiences, including other, previous non-HIV cure studies. For instance, for approximately half of our respondents, study-related emotional support for living with HIV emerged from participating in previous treatment trials rather than the HIV cure trials that were the subject of our study. For serial trial participants, the impact of cumulative research experience is unsurprising, but sometimes challenging to parse.

Conclusion

Analyses of informed consent,[39,47,48] participant motivations,[3,49] and understandings of risks versus benefits[2,37,50,51] are essential to improving the ethical conduct of HIV cure research.[22] Through a qualitative analysis of participant interviews, we identified substantial unanticipated benefits associated with HIV cure research. While this study was exploratory, our data show that indirect benefits are important to HIV cure clinical research participants and may contribute to their motivations to take part in future studies. In addition, our data reveal how participants' perceptions of benefits and motivations may change over time. For instance, while the initial excitement of taking part in HIV cure research seems to fade with time, it may be replaced by a genuine sense of ''doing good'' and of taking part in something greater and more important than oneself.

Given the limitations of this small qualitative study, much more research is needed from multiple sites, including larger, more diverse, cross-cultural representative samples. This further work will be necessary to determine how these benefits might affect participant enrolment and retention, especially across multiple and/or serial studies. Moreover, future research should address participants' decision-making processes over time,[3] especially their assessments of risks versus benefits,[2,37,50,51] when given the opportunity to join a cure trial.

While not generalizable, our data suggest at the very least that some participants in HIV cure clinical trials experience indirect psychological, social, and behavioral benefits that they find to be meaningful and valuable within the context of studies in which they are instructed not to expect benefits. Certainly, experiences of nonmedical inclusion benefits are subjective, often contingent on factors beyond researchers' control, and would need to be communicated with care; however, coupled with continued ethical evaluation, our study suggests that researchers might contemplate discussing these benefits with potential participants during informed consent. In addition, IRBs may encourage consideration of these often-unacknowledged benefits during risk/benefit evaluations. We suggest that researchers and IRBs address this possibility and be encouraged to develop appropriate ways to describe such benefits.

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Authors' Contributions

A.G., S.R., and J.D.T. designed and implemented this study. A.G. and E.P.K. conducted the qualitative research and data analysis. All authors contributed to the interpretation of the data. A.G. produced the first and all subsequent drafts of the manuscript with assistance from E.P.K. G.H. provided the initial critical review of the manuscript, followed by S.R., J.D.T., and all other authors. J.K. provided support on technical matters. E.P.K. offered administrative support. All authors reviewed the manuscript and approved its publication.

Author Disclosure Statement

The authors have no conflicts of interest.

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