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Ancillary Care in South African HIV Vaccine Trials: Addressing Needs, Drafting Protocols, and Engaging Community

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Abstract

There has been debate about sponsor-investigator ethical responsibilities to address participants' medical needs in trials in resource-constrained contexts. Certain ethical guidelines make detailed recommendations. This study explored whether ethical guideline recommendations for care in HIV vaccine trials were being met, and whether stakeholders were facing difficulties addressed by guidelines. It sampled key stakeholders involved in two trials across five sites in South Africa, and reviewed relevant documentation. It concluded that sites were largely meeting guideline recommendations for *addressing needs*, with some exceeding these. Recommendations for *writing protocols* were only partially achieved. Recommendations for *engaging participating community* were mostly met, except for "moral negotiation" recommendations. Suggestions are made to strengthen practices, and to improve guidelines so they address empirical concerns.

Keywords

HIV vaccine trials; ethics; ancillary care; ART; protocol-development; community engagement

Imagine that a member of a research ethics committee is tasked to review a health research protocol for implementation in a resource-constrained setting. What will she require researchers to do to help participants with their medical problems? What will she expect researchers to say about their plans in the protocol? What will she require researchers to disclose to participants? How much involvement will she require from the participating community? Will her expectations match ethical recommendations? This paper addresses these issues (and others) in the context of HIV prevention trials.

A long-standing debate in HIV vaccine trials (HVTs) involves the ethical responsibilities of sponsor-investigators to address participants' HIV needs, particularly in settings where antiretroviral therapy (ART) is unreliable (Guenter, Esparza, & Macklin, 2000; MacQueen & May, 2008; Slack et al., 2005; WHO/UNAIDS, 2004). There has also been a broader debate about what steps researchers should take to address needs identified in trials, especially in resource-constrained contexts, where such steps are not needed for the success

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or even the safety of the trial, but rather represent “positive helping performances” (Richardson, 2012, p. 206) or ancillary care that forms no part of the scientific protocol (Richardson & Belsky, 2004; Richardson, 2007; Taylor, Merritt, & Mullany, 2011).

There has been debate about the party that researchers should direct their efforts to (e.g., participants or volunteers or others); the needs researchers should focus on (e.g., HIV or other needs); the steps researchers should take, especially where care alternatives are inadequate (e.g., direct provision of care); the limitations that can reasonably be placed on such efforts; and the best argument justifying researchers’ ethical obligations.

Commentators have developed accounts of researchers obligations invoking social justice (cf. Shapiro & Benatar, 2005), reciprocity (cf. Macklin, 2006), and beneficence (cf. Stobie & Slack, 2010). A more detailed account asserts that researchers in particular have a special obligation to address participants’ needs that are identified by trial procedures, when certain moral conditions can be met (such as gratitude for burdens) and where steps to address needs won’t be excessively costly (Richardson, 2007; 2012).

There has also been debate about how researchers should engage community representatives, and other stakeholders, about care. Some have argued that researchers should negotiate or bargain with participating communities to allow them to identify “valuable” health-related benefits including ancillary care (Participants, 2004; Weijer & LeBlanc, 2006, pp. 805–806). Critics have countered that this may encourage researchers to locate in the “cheapest” community (London & Zollman, 2010; Schüklenk, 2010).

Recommendations about care have been made in international guidelines for HIV prevention trials (UNAIDS/WHO, 2012; UNAIDS/AVAC, 2011) and in guidelines for specific networks (HPTN, 2009) and for specific countries (MRC, 2003). Recommendations are made about sponsor/investigator responsibilities to participants, volunteers, and participating communities; about HIV needs, sexual and reproductive health needs, and general needs; about responses to be implemented to address needs; about what protocols should say; and about how participating community representatives should be involved. For example, guidelines recommend that participants who become infected with HIV (despite access to offered HIV prevention modalities) should have access to “high quality” or “optimal” care (MRC, 2003; UNAIDS/WHO, 2012).

Some have questioned whether guidelines set unrealistically high standards for low-resource settings (cf. Macklin, 2009; 2010). This is a claim for which empirical data are relevant. More generally, empirical research can inform a critical reflection on ethical norms (Kon, 2009), e.g., by illuminating ethical problems that require attention (Draper & Ives, 2007) or by providing details to inform more contextualized, responsive ethical recommendations (Carter, 2009).

The microbicide field has been more active in assessing care practices (Clouse et al., 2010; Heise, Shapiro, & West-Slevin, 2008; MacQueen et al., 2008; Ramjee et al., 2010) than HVTs (cf. Ngongo et al., 2012). To date no studies in HVTs have explicitly explored correspondence of practices to ethical guidance, nor whether stakeholders face ethical problems that are addressed in guidance. South Africa has hosted many HIV prevention

trials, including HVTs, in partial response to a considerable HIV epidemic (Clouse et al., 2010).

Methods

This study posed two questions: (1) To what extent are ethical recommendations for care in HVTs being met? (2) To what extent are the difficulties facing HVT stakeholders addressed in ethical guidance? It aimed to identify the care practices undertaken by HVT stakeholders, and to identify complexities they experience. It formed part of a larger project exploring both prevention and care in South African HVTs funded by the Wellcome Trust Biomedical Ethics Program (cf. Essack, 2013).

A range of stakeholders were sampled, namely staff at sites implementing a phase I HVT and a phase IIB HVT in South Africa, as well as representatives from the trial network, community advisory boards (CABs) at affected sites, and research ethics committees (RECs) that had reviewed HVTs. The phase I HVT explored vaccine safety and ability to induce immune responses by measuring safety data, including adverse events, and T cell responses in vaccine recipients versus placebo recipients. The phase IIB HVT explored vaccine efficacy by measuring HIV infection, viral load set-point, and CD4 counts,[1] in vaccine recipients versus placebo recipients (as well as safety and immunogenicity).

Sensitizing visits to sites took place where strategies to invite potentially interested persons were developed collaboratively. E-mail outreach to network and REC representatives was undertaken. A semi-structured interview explored care practices for participants, volunteers, and communities, and for HIV, sexual and reproductive, and general needs. Perspectives (including perceived complexities) were also explored. Written informed consent was obtained for interviews. Site leadership gave permission to release documents. Interviews took place between September 2010 and September 2012.

The data set consisted of transcribed interviews with 37 stakeholder representatives (some care specific, others prevention specific, others mixed); as well as documents from five sites, including protocols, and informed consent forms (ICFs). Template materials were also sent by the network. Interviews and document review were undertaken to achieve triangulation of data sources (Yardley, 2008). Text was coded for practices and perspectives using a deductive and inductive approach to thematic analysis (cf. Braun & Clarke, 2006; Quinn Patton, 1990; Sandelowski, 2000; Willig, 2008). Practices and perspectives were collated for each participating site. Reported practices were also compared with written documents. A sample of interviews was coded by an independent coder, and all interviews were co-coded with a co-researcher for one issue.[2] Coding differences were resolved by “reconciliation discussions” (Boyatzis, 1998, p. 152).

[1]Viral load set-point is the number of copies of HIV in the blood that has stabilized after a period of acute infection, and CD4 counts measure the number of CD4 cells (T-helper cells) in the blood—both help to establish the progression of disease in HIV-infected people.

[2]More specifically, addressing Sexually Transmitted Infections.

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The study was approved by all RECs affiliated to sites. A pre-research stakeholder consultation was held to build support and identify concerns. A post-study stakeholder consultation was held to establish if results about practices could be confirmed (cf. Kelly, 2006) and to solicit input on the study implications. Data was anonymized; however, it was recognized that some trials or affected organizations might be identifiable from publicly available information. To compare guidelines with practices, guidelines were selected that govern SA HVTs specifically, namely MRC (2003), and international guidance applicable to HVTs, namely UNAIDS/WHO (2012) and UNAIDS/AVAC (2011).

Results

Addressing Needs

ADDRESSING PARTICIPANTS' HIV NEEDS—Site staff at all affected sites reported testing participants regularly for HIV infection, providing intensive counseling to participants on-site, terminating HIV-infected participants in the *phase I* protocol, monitoring HIV-infected participants' CD4s and Viral Load in the infected track of the *phase IIB* protocol to measure vaccine impact on disease progression, and offering enrollment to HIV-infected participants into disease-monitoring protocols. Site staff at all sites reported referring participants for ART to co-located PEPFAR-funded clinics (three sites) or to the public sector (two sites), addressing Opportunistic Infections by referral to co-located PEPFAR clinics or public sector, and addressing Prevention of Mother To Child Transmission (PMTCT) needs by referral to the public-sector clinics.

Site staff recognized the advantages of "on-protocol" monitoring, namely that serial monitoring from the time of sero-conversion enables early referral for ART on CD4 count eligibility, which advantages participants in relation to nonparticipants. One representative remarked:

> We can actually monitor the participant and give them advice and make sure that they get started on treatment when they're supposed to and they're not sitting somewhere and only end up at a clinic when they have other problems … and they don't just disappear in the masses [c15, site staff, site E].

Network representatives reported sourcing funding from Pharma for an HIV treatment fund should national coverage fail, requiring researchers to develop detailed written plans for addressing HIV, facilitating ART access between sites, and disseminating best practices to researchers about HIV care. They reported that funds secured from the trial sponsor were restricted to research activities. Site staff at all sites recognized the network's HIV treatment fund:

> They were very proactive in identifying that … some sites may have difficulty accessing treatment and so they sought to find a mechanism to provide those funds which I think actually is quite remarkable that they were prepared to make that level of commitment [c18, site staff, site D].

Representatives from all sites described numerous steps to help participants to access HIV care, including checking participants' referral preferences, counseling participants to overcome denial and access HIV care, sharing letters and medical information with referral

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sites, securing participants' permission to share medical information about HIV, reaching agreements with referral sites about sharing information, developing plans for referral, requesting feedback from participants about HIV care at referral sites, and building relations with referral sites by providing training or posting staff and collaborating on educational events. Some sites reported additional practices, e.g., booking appointments, alerting referral sites, accompanying participants, and intervening at referral sites. All sites encountered denial in a select number of cases when counseling participants to access HIV care.

Representatives from all RECs described scrutinizing plans for HIV care in protocol review and strongly endorsing "assisted referral" to care. One stated, "we don't just say, 'treatment is available, go find it, here's a letter'" [c5, REC 4]. Representatives from all RECs recognized researcher commitment to HIV care. One remarked, "my sense is that investigators themselves want to be doing the right thing and are willing to put resources into doing the right thing" [c19, REC 1].

Responsibilities to address HIV needs were understood mainly as reciprocity-based efforts in return for burdens assumed by participants and contributions made by participants. A representative stated:

> The very nature of our clinical trials is trying to identify individuals who are at highest risk for acquiring this disease who have sort of given their bodies to the clinical trial for an experiment that we don't know will work or not … and there's an obligation to do the most we can for those who do become infected in these clinical trials, and especially with the advances that we have, it's really a payback that is a real obligation and honor to provide [c14, network].

Site staff recognized that referral to co-located PEPFAR-funded HIV care has certain advantages over referral to public-sector care, suggesting that some participants are at a perceived relative advantage to other participants depending on referral site characteristics. A respondent noted:

> Our participants are privileged in a way in that they bypass the public sector rigmarole which is sitting and waiting in long queues for hours, delays in ARVs [c2, site staff, site A].

Site staff reported that public-sector care in one province may differ from that in another province, in terms of length of waiting lists, shortage of human resources, and actual implementation of amended ART initiation policy, suggesting again that participants' quality of care may be differentially impacted by referral site conditions. Site staff also recognized that national ART-initiation criteria had lagged behind international recommendations, and they recognized that national drug access differed from the international setting (i.e., third line regimens, new drug co-formulations) pointing to perceived differences in care across country settings. Representatives from most RECs strongly endorsed following national treatment guidelines for HIV.

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ADDRESSING PARTICIPANTS' STI, CONTRACEPTIVE, AND PREGNANCY NEEDS

Sexually Transmitted Infections (STIs): Site staff at all sites reported following national syndromic management guidelines, providing STI counseling on-site, ensuring STI treatment by on-site provision of treatment (four sites) versus referral to public-sector facilities (one site), and reporting STIs as adverse events. There were various strategies to support on-site provision of treatment, including using a "site kitty," self-purchasing, or procuring from the Department of Health (DoH), with some sites experiencing difficulties securing the latter strategy. Site staff at most sites recognized advantages of on-site treatment for participants (less time-wasting and less stigmatizing attitudes than at public-sector facilities), suggesting that the strategy adopted may introduce certain quality differences in care for participants. One remarked: "The nurses, they are too cheeky for (participants). They ask them 'last month you were here with an STI, you came back again, so we are not going to tolerate this thing'" [z4, site staff, site B].

Participants and Contraception: Site staff at all sites recognized the importance of contraception for fetal safety. They recognized stricter contraceptive requirements for the phase I HVT. They reported providing contraceptive counseling on-site. They addressed contraceptive needs by on-site provision of hormonal contraception, procured from DoH primarily (four sites) versus referral to public-sector clinics (one site). Representatives at three sites saw advantages for the research itself of on-site provision (better control and monitoring) but also for the participant (more sophisticated counseling, less waiting, better toxicity-tracking)— "we are technically also providing a better service for participants" [c11, site staff, site E].

Network representatives asserted that funding could be provided to sites unable to address STI needs, but generally described relying on site resources and referral resources for addressing contraception and STIs. One representative remarked: "How the site manages that, whether they refer out to the clinic next door … that's up to their local management" [c9, network].

Participant and Pregnancy: Site staff at all sites described regular pregnancy testing, providing counseling for pregnancy options, referring to public-sector pregnancy services (antenatal services or Termination of Pregnancy), sharing results with referral sites, and monitoring pregnancy outcomes. At two sites, quality counseling for TOP was reportedly impacted by site staff values.

ADDRESSING PARTICIPANTS' OTHER NEEDS—Site staff at all sites reported that various needs were diagnosed in participants using tests, physical exams, and medical history, such as anemia, hypertension, and respiratory tract infections. These were reported as adverse events (including their resolution). Network representatives viewed treatment provision for such needs as outside their responsibility, and relied on researchers to have referral systems for treatment, while carefully following up on resolution of such conditions. Site staff described that they addressed such needs by providing on-site treatment (at two sites, one of which could also refer to private care funded by a "site kitty") versus referral

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(three sites). On-site treatment was viewed as an advantage for participants (involving significantly less time-wasting than at public-sector facilities), suggesting again that difference in strategy may introduce subtle differences in care between participants. One respondent noted, “They will tell you the security guard sent me away. It happens all the time” [c2, site staff, site A], while another stated, “They sit there the whole day [laughs]. They miss work” [c3, site staff, site B].

Site staff at most sites reported soliciting feedback from participants about care received at referral sites, with reports at one site of inadequate feedback from participants and referral sites. They assessed the functions and capabilities of referral sites and raised awareness about their own capabilities (at two sites, myths had to be “busted” that sites would take over all participants care). REC representatives described requiring researchers to address such conditions or “co-morbidities” as adverse events management, for which referral was endorsed. Across all needs, representatives from RECs and sites reported recognizing and valuing diverse strategies to address needs: “There may be many ways that (researchers) can catch things—refer appropriately, provide treatment where feasible” [c5, REC 4].

ADDRESSING VOLUNTEERS’ NEEDS—The following was reported for persons who accessed screening for HVTs, but were not necessarily enrolled.

Volunteers with HIV: Site staff reported testing volunteers for HIV, providing counseling on-site (post-test counseling and risk-reduction counseling), providing offers of extra support, checking HIV care referral preferences, referring for HIV care at co-located PEPFAR clinics (two sites) or in the public sector (three sites), and providing letters and results (not CD4s or viral load measures).

> So we have the same standard of making sure that they are properly counseled, and that they really understand their disease and get good referrals to Anti-Retroviral care. But we don’t extend the same level of our own follow-up and involvement as we do in our participants who seroconvert on our protocols [c11, site staff, site E].

Volunteers with STIs: Site staff reported assessing volunteers for signs and symptoms of STIs in both protocols, performing syphilis testing for phase I volunteers (and excluding infected volunteers), and not excluding volunteers with STIs for the phase IIB protocol. They addressed STIs by referral to the public sector (one site) versus providing volunteers with on-site treatment (three sites, including both implementing the phase I HVT), and at one site the strategy was unclear. Various strategies were used to support on-site treatment, namely purchasing drugs using a “site kitty,” PEPFAR funds, or procuring from the DoH.

Volunteers and Contraception: Site staff recognized that volunteers must be personally willing to use contraception to be eligible (using two methods for the phase I HVT). Contraception was ensured by referral to public-sector facilities (two sites) and by on-site provision (three sites). In the main, sites successfully managed to partner with the DoH to secure contraception for on-site provision (one site reported temporary resistance based on concerns about service duplication).

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Volunteers with Other Needs: Site staff reported identifying other needs in volunteers using study procedures (e.g., hypertension), enrolling or excluding volunteers depending on protocol criteria, and addressing volunteers' other needs by referral to the public sector (four sites) versus providing on-site treatment (one site).

> If they had hypertension, obviously you'd want to stabilize it, before you moved them out and if you diagnosed a bladder infection or something like that, you'd want to treat it so that they weren't uncomfortable. But you wouldn't get involved in a whole long-term plan for screen-outs. You would do what is reasonable [c4, site staff, site B].

Writing Protocols

Protocols tended to say little about planned steps to help participants access care for conditions other than HIV (see Table 1). In most cases, silence in protocols was *not* remedied at the level of supporting documentation. However, in a few instances, supporting documentation (letters, application forms) showed that RECs queried, and researchers declared, site-specific strategies for responding to various needs. Some application forms were structured to elicit descriptions of care steps, e.g., "whether the research involves health-care services."

Some respondents described seeing protocols as the natural home for steps linked to scientific objectives:

> There's also an assumption in doing so [setting out care strategy] that you will monitor it and you will provide oversight, you will require consistency across all of the sites in a particular fashion. If you prescribe it in the protocol any deviation from that is an actual deviation from the protocol [c14, network].

Ensuring Informed Consent

ICFs set out several steps that would be taken to help participants access care for HIV infection (see Table 2). For other medical needs, statements in ICFs (that treatment would not be provided directly) contradicted reported practices at trial sites.[3] In addition, benefits reportedly associated with the research itself (e.g., monitoring that allows early referral for ART) and benefits reportedly associated with on-site treatment strategies (e.g., less time-wasting) were not stated in ICFs as potential benefits. Several consent practices were reported in interviews that supplemented ICFs, including counseling participants to report health problems, informing participants about how their needs will be addressed, and counseling participants to access care.

Engaging Participating Community

Network representatives described involving CAB representatives in protocol-development teams, recognizing threats such as inadequate knowledge or power, and building capacity of CAB members for protocol development and review. One representative reported: "We

[3]In the phase I trial at both of the affected sites participants were given on-site STI treatment, and at one of the sites treatment was given for other conditions on-site. In the phase IIB trial at four of the five sites participants were given on-site STI treatment, and at two of five sites participants were given on-site treatment for some other ailments.

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don't just place the protocol in front of them, and have them comment, they're actually provided some support" [z9, network].

Representatives from all sites involved local service-providers on the site CAB. Representatives from some sites reported that ex-trial participants were also members of the CAB. Representatives at all sites reported discussing the sites' approach to care with CAB members, and addressing questions from CAB representatives about care. Representatives at some sites strongly endorsed the value of enlisting CAB members to help improve care implementation. Some stakeholders questioned how to proceed in the face of "unreasonable" views solicited during a CAB consultation process: A respondent remarked:

> It's a presumption that people would want a wider range of care to give participants access to, perhaps the option of attending a traditional healer or other practices in medicine that are not necessarily evidence-based, and I think that would create a conflict for researchers … I almost get the feeling that people will be slighted if we started picking and choosing between people what we listen to and what we don't [c7, site staff, site D].

At all sites, CAB representatives were involved in a pre-trial review of relevant *materials*. At some sites, CAB members (or a subgroup) accessed entire protocols, whereas at other sites CAB members accessed materials such as protocol summaries or ICFs. At all sites CAB members were informed about HIV sero-conversions; however, actual numbers were not presented to all CABs. At most sites, direct access to participants by CAB members was not permitted, whereas at one site CAB members accessed participants after signing confidentiality agreements and receiving photo-ID cards. CAB members perceived access to participants as a powerful strategy to advocate for participants needs:

> What works well is that as CAB members we do follow up to participants. That is, we visit them, even on the site … When the site staff sees you there sitting next to a participant, they won't think you're coming to spy on them, instead they feel encouraged to say that the participants won't feel alone [z3, CAB B].

Discussion

ADDRESSING NEEDS

Participants' HIV Needs—Guidelines recommend that participants acquiring HIV have access to a certain package of care, including counseling, immune monitoring, PMTCT, ART, STI treatment, and family planning and reproductive healthcare for pregnancy and childbirth (MRC, 2003; UNAIDS/WHO, 2012; UNAIDS/AVAC, 2011). Reported site practices indicated good correspondence with this package. Outreach practices to referral sites also corresponded with recommendations to collaborate with service providers, to understand referral sites, and to build their capacity (MRC, 2003; UNAIDS/WHO, 2012; UNAIDS/AVAC, 2011). Network steps to source funding for ART resonated with recommendations to ensure that resources are contributed to treatment (MRC, 2003), to put appropriate financial arrangements in place (UNAIDS/WHO, 2012), and to allocate funds for care delivery (UNAIDS/AVAC, 2011).

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Practice data showing that HIV needs are addressed largely by referral to co-located PEPFAR-funded care or public-sector care indicates that HVTs were generally relying on integration into domestic care systems and not "stand-alone endeavors" (cf. MacQueen et al., 2008, p.15). Referral mechanisms and encountered challenges (e.g., inadequate feedback) resonated with previous explorations (Heise et al., 2008; MacQueen & May, 2008; MacQueen et al., 2008).

Stakeholders recognized a strong positive obligation to address participants' HIV needs (cf. Participants, 2008). Responsibilities were framed as responses to risk/burden assumption by participants, in a manner that resonates with "justice as reciprocity" (Macklin, 2006) or gratitude for uncompensated risks/burdens (Richardson, 2012). This finding does not necessarily establish this as the most convincing reason, nor suggest that one should unreflectively accept lay intuition (cf. Draper & Ives, 2007), but shows stakeholders may be especially receptive to justifications formulated in this manner because they are continuous with their existing convictions (Birnbacher, 1999, in deVries & Gordjin, 2009).

Participants' care generally followed national treatment guidelines. Certain guideline statements recommend that investigators *integrate* with national treatment plans, *integrate* with local systems (UNAIDS/WHO, 2012), and modify treatment plans in line with *updated national guidelines* (UNAIDS/AVAC, 2011) which suggests that participants' HIV care should be indexed to national norms. Practices corresponded well with these recommendations. Other guideline statements recommend that participants in high- and low-income countries should be "treated equally regarding access to treatment and care" (UNAIDS/WHO, 2012, p. 48), and the standard of treatment should be "equivalent across high, low and middle-income countries" (UNAIDS/WHO, 2012, p. 65) and that participants should get access to "internationally recognised optimal care and treatment, *including ART"* (UNAIDS/WHO, 2012, p. 48, emphasis mine). These stakeholders recognized that host-country HIV care deviates from international settings in respects other than access to an ART regimen, e.g., ART-initiation criteria and drug co-formulations.

Participants' STI, Contraceptive, and Pregnancy Needs—These somewhat scattered recommendations include that participants have access to STI treatment (MRC, 2003; UNAIDS/WHO, 2012, under Prevention), family planning, pregnancy and childbirth services (UNAIDS/WHO, 2012, under Prevention), and appropriate reproductive and sexual health counseling and ancillary services including family planning (UNAIDS/WHO, 2012, under Women). Reported practices corresponded well with recommendations. Perceived advantages of on-site provision of STI treatment and contraception resonate with "soft science" justifications, where care steps inadvertently serve scientific interests (cf. Richardson, 2012). TOP counseling concerns, while not widespread in this study, suggest that the impact of provider promotion of services should be recognized (Essack, 2013; Heise et al., 2008).

Participants' Other Needs—Guidelines make surprisingly few recommendations about general needs, merely recommending participants have regular, supportive access to and contact with health-care workers (MRC, 2003; UNAIDS/WHO, 2012). Reported practices exceeded current recommendations.

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This study found perceived differences in participants' HIV care depending on referral site characteristics. It also found perceived differences in care for contraceptive needs, STIs, and other ailments, depending on the adopted strategy (on-site treatment versus referral). Particular strategies seem associated with relatively modest advantages for some participants versus others, at least in the short term. This indicates that stakeholders face the challenge of potential quality differences among participants' care *within* the same host country. That sites address needs via direct or indirect referral strategies has been identified empirically (Heise et al., 2008; MacQueen et al., 2008), as have concerns about comparability of care across sites (MacQueen et al., 2004). Current guidelines offer very little direction on within-country differences. Previous guidelines asserted that trial sponsors should ensure that "core elements of the package" of care are consistent (UNAIDS/AVAC, 2007, p. 29). This misses the issue here—that participants access the same elements of care, but the strategy or the referral site characteristics introduce modest but nontrivial quality differences between participants at different sites.

Volunteers' Needs—Ethical guidelines recommend volunteers with HIV should receive intensive counseling (UNAIDS/WHO, 2012) and be referred to existing clinical, support, and care services (MRC, 2003; UNAIDS/WHO, 2012). Guidelines make few recommendations for addressing volunteers' non-HIV needs—only that the screening process involves medical tests/examinations (UNAIDS/WHO, 2012) and that referral processes for screen-outs should be in protocols (MRC, 2003). Reported practices were consistent with implied recommendations (to refer), and some sites exceeded implied recommendations by providing on-site treatment for certain conditions. The manner in which site practices easily exceeded guideline recommendations underscores the relative "thinness" of guidance for volunteers.

DRAFTING PROTOCOLS

Protocol Drafting and Participants—Guidelines recommend that protocols describe "expected benefits" for participants that include HIV care and contact with healthcare workers (MRC, 2003). Guidelines recommend that protocols describe "accurate statements" about anticipated benefits of scientific procedures *and* ancillary services, products, or interventions (UNAIDS/WHO, 2012, p. 43). Protocol-drafting practices in this study were only partially consistent with recommendations. Firstly, protocols said very little about steps to be taken to help participants access care for conditions *other than HIV*. That is, while protocols described help-based steps for HIV, protocols largely omitted help-based steps for other conditions. Secondly, protocols did not frame either science or helping-based steps as potential benefits.[4]

Protocol Drafting and Volunteers—Guidelines state that protocols should spell out referral processes for persons excluded from trials (MRC, 2003). Here again, correspondence was partial because such steps were declared for HIV needs, but not for other needs.

[4]Incidentally, because written protocols were relatively silent on non-HIV care strategies, written protocols did not (in and of themselves) introduce much variance in non-HIV care between participants *in different protocols*.

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Helping responses declared in protocols reflected *a much smaller subset* of the overall range of helping responses reported in interviews. That protocols say little about care strategies, and that site staff do more than protocols say, has been documented in microbicide trials (Philpott et al., 2011). Interview data suggests protocol declarations are viewed as potentially locking investigators into ethically approved strategies that might prevent flexible, innovative responses. These concerns supplement previous findings that protocol omissions were driven by sponsor restrictions on using research funds for care (cf. Heise et al., 2008; Philpott et al., 2011).

ENSURING CONSENT

Guidelines recommend that care for HIV infection should be in ICFs (UNAIDS/AVAC, 2011). Correspondingly, ICFs from sites did state several steps to help participants get care for HIV infection. Guidelines more broadly recommend that participants should be informed about HIV care they will receive (MRC, 2003; UNAIDS/WHO, 2012). Site staff engaged in repeated verbal disclosures to participants about how their various health needs would be addressed, which exceeded guideline recommendations to ensure understanding of HIV care alone, and indicates that ICFs were not the only information source about care strategies at sites. ICF statements did conflict with actual strategies, however, which may undermine coherent understanding of the care approach.

Findings suggest some disconnect between perceived benefits reported in interviews and the low-profile of declared benefits in ICFs. Participants should understand potential benefits, as part of comprehending the personal implications of HVTs (Lindegger & Richter, 2000; Lindegger et al., 2006) or research "impact," including "additional potential for clinical benefit" (Wendler & Grady, 2008, p. 207). Understanding is likely best facilitated through regular verbal discussions with site staff (cf. Flory & Emanuel, 2004) *and* appropriate written material (Woodsong & Abdool Karim, 2005).

ENGAGING PARTICIPATING COMMUNITY

Guidelines generally underscore the importance of community engagement; however, they also make specific recommendations about engaging community representatives for care. They recommend that community representatives *make inputs* into care decisions (MRC, 2003), that their capacity to do this is built (MRC, 2003; UNAIDS/WHO, 2012), and that the trial team *discusses* HIV care with stakeholders, and "*negotiates*" non-HIV care, with stakeholders (UNAIDS/AVAC, 2011, p. 55). Guidelines assert that participation of the community can lead to "equity" in care decisions (UNAIDS/WHO, 2012, p. 20).

Practices described by site and network representatives to involve community representatives in protocol development, to involve site-level CAB members in protocol or materials review, to discuss with CABs the sites approach, to respond to their ad hoc questions, and to seek CAB inputs on how to implement care approaches corresponded with recommendations to seek input and discuss care (MRC, 2003, UNAIDS/AVAC, 2011). Practices also reflected some effort to integrate community perspectives at various stages of trial design and implementation (cf. Heise et al., 2008), as well as to hear suggestions for how care could be improved or delivered (Vallely et al., 2009).

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However, reported practices were not consistent with recommendations to “negotiate” non-HIV services with community nor to take into account services community stakeholders “would like to see” offered to participants (UNAIDS/AVAC, 2011, p. 56). For example, reported practices did not include bargaining with CAB representatives about additional substantive benefits (MacQueen et al., 2008; Weijer & LeBlanc, 2006).

Previous research has pointed to CAB presence and activity as a central feature of contemporary HIV prevention trials (MacQueen & May, 2008; MacQueen et al., 2008). This study did not identify general concerns with a lack of practices to engage community in care decision-making (cf. Heise et al., 2008) but did identify subtle concerns. One concern was that select stakeholders question what community views should be “allowed,” e.g., requests for non-evidence-based care, or even requests for benefits that are not health-related. This concern appears inadequately addressed in guidelines, which are silent about what should be done when solicited views conflict with other substantive norms, e.g., to provide optimal care. MRC (2003) gestures at this issue, setting out that community participation should enhance the “ethical soundness” of an HVT, suggesting that inputs undermining “ethical soundness” might be legitimately rejected.

Limitations

Neither trial participants nor referral site representatives were sampled, due to anticipated onerous additional review requirements. This means that valuable perspectives remain untapped. Actual services were not directly observed. The interview schedule did not explore the full spectrum of HVTs being implemented at sites over the interview period because of researcher capacity. This manuscript does not present results about “achieving consensus” about care, or providing services to community, due to space constraints.

Conclusions

This study has informed the debate about care by, firstly, documenting where ethical standards for stakeholder practices are being met to address claims about the feasibility of such standards (cf. Draper & Ives, 2007) and, secondly, by identifying complexities for which ethical guidance needs to be more fully elaborated (cf. Braddock, 1994, in De Vries & Gordijn, 2009). Findings do not suggest that ethical recommendations are unachievable in this setting. Guidance may have to be refined to address stakeholder concerns.

This study concludes that all sites were generally meeting current guideline recommendations for addressing needs of both participants and volunteers, while some sites were in fact taking steps that exceed recommendations. It concludes that site staff were addressing *needs* not confined to conditions centrally important to the trial (HIV) but also many other conditions identified by trial procedures (cf. Participants, 2008). It concludes that network and site staff representatives were implementing *responses* for various identified needs that are beyond those needed for scientific success and safe conduct, that is, responses more correctly described as helping performances (cf. Richardson, 2012). This study identified potential within-country differences in the quality of participants’ care, due to referral site characteristics or site strategies to address needs, which is an ethical concern inadequately addressed in current guidance.

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In terms of protocol-drafting practices, this study concludes that guideline recommendations to describe ancillary services in protocols were only being partially met. In many instances, such descriptions were omitted from supporting documentation submitted to RECs. Concerns about preserving flexible, nimble care responses are not anticipated in guidance, which tends to emphasize transparent declarations to RECs. In terms of consent, this study concludes that recommendations for ICF drafting were being met, as were recommendations for informing participants about care. In terms of engaging community, this study concludes that reported practices corresponded well with many recommendations, with the exception of recommendations to "negotiate" care services with community representatives. Concerns about managing inputs that may conflict with substantive protections are not addressed in guidelines.

Recommending changes to "policy" based on the findings of a single study must be done cautiously (Sugarman, Kass, & Faden, 2009). However, the data have possible implications for practices, guideline refinement, future research, and capacity building.

Best Practices

Some commentators have called for a standard "approach" to care services (Ngongo et al., 2012, p. 2), whereas others have asserted that there is no single solution to addressing participants' care needs (MacQueen et al., 2008). While sites can *aspire* to similar strategies (e.g., on-site provision of STI treatment and contraception, with associated advantages), it may be constraining to *mandate* this. Instead, site staff should be alert to quality problems with all strategies and strive for reasonably commensurate outcomes for participants.

Researchers should place descriptions about ancillary care in dedicated "ethical considerations" sections of the protocol or in site-level documents that can be flexibly amended, such as a site "Bill of Rights and Responsibilities." Written declarations could build in contingencies, e.g., "STIs will be addressed by on-site treatment where feasible, or by referral to the public sector." REC application forms should elicit clearer descriptions, e.g., "Describe here how you will help participants address medical needs identified in trials, even when this forms no part of the scientific protocol you are pursuing" (cf. Richardson, 2012). Each site should set out their approach (and possible associated benefits) in consent-related material that can be easily amended as strategies change. Consent materials for sites that can implement on-site treatment should be adapted to reflect that reality.

Efforts to engage CABs to improve care decision-making and implementation should be continuous and intensified. Sites should critically reflect on policies for CAB/participant interaction, and for CAB access to materials (e.g., entire protocols versus supplementary materials). While site staff do solicit and accept inputs from CAB members on the site's approach to care, more formal reviews of approaches should be undertaken with CABs. Site staff should prepare better written materials for review by CABs collating the site's steps for care. Network representatives should consider collating and distributing to affected sites the care-related concerns identified by community representative in protocol development at the level of the network, and how they were addressed.

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Research Agenda

In future interviews about consent practices, it may be helpful to explore the reasons for omissions in protocols and ICFs about recognized benefits. In future research into strategies for engaging community, perspectives about “negotiating” with communities should be fully explored.

Implications for Ethical Guidelines

This study suggests stakeholders might experience some confusion regarding whether participants’ HIV care should be indexed to national norms or to international norms (cf. McGrory et al., 2010) in ways distinct from ART access. Guidance should contain clearer direction about what stakeholders should do (if anything) when they observe between-nation differences in key aspects of HIV care, apart from ART access. This study found perceived quality differences (modest but nontrivial) in care between participants at different sites in the same country. More explicit direction on this issue is recommended. Guidance currently speaks to differences between countries, tending to argue for equivalent standards (UNAIDS/WHO, 2012). One might infer that the same is called for across “micro” settings such as sites; however, an explicit stance on the issue may be helpful. Perhaps “reciprocity” reasoning (and its limitations) could be expanded in guidelines because stakeholders seem to find this reasoning appealing. More substantive recommendations are needed about addressing participants’ non-HIV needs, as well as addressing volunteers’ needs.

Guidelines should contain a broader recommendation that participants should understand how their needs will be addressed (not limited to HIV), and that participants should understand which responses stem from the scientific protocol, and which responses stem from helping efforts—an approach adopted in the HPTN (2009) guidelines. Guidelines should offer clearer direction about how to proceed when inputs solicited in a consultation process conflict with substantive recommendations, as this might encourage even more active solicitation of community views.

Educational Implications

Other research initiatives can learn from the relatively intensive planning for ancillary care implemented in HIV vaccine trials, the active involvement of multiple role-players sharing care responsibilities, as well as the subtle complexities evidenced across the domains of addressing needs, writing protocols, obtaining consent, and engaging community. Within HVTs, we need to continue to optimize strategies across these domains. Inter-stakeholder networking forums focusing on specific concerns may be useful, such as those between RECs and researchers to resolve transparency versus flexibility tensions. This study complements a burgeoning empirical literature on ancillary care as part of the international conversation on this complex topic.

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TABLE 1
Summary of Protocol Descriptions Regarding Care Steps

Issue	Description
Participants' HIV needs	The phase I protocols described planned steps for HIV infection justified by safety (e.g., *discontinuing vaccinations*) as well as several steps to assist participants (*providing counseling, referring for counseling/ART/ management, developing a treatment fund, developing site ART plans*).
	The phase IIB protocols described steps consistent with scientific objectives (e.g., *monitoring viral load and CD4s*) as well as several steps to assist participants (*referring to medical professionals for treatment, developing site ART plans*).
Participants' contraceptive, pregnancy, and STI needs	Protocols for both trials outlined steps for contraception consistent with safety concerns (e.g., *assessing contraceptive compliance*). Protocols did not describe how contraception would be ensured (e.g., on-site provision versus referral).
	Protocols for both trials outlined several steps for pregnancies consistent with safety (e.g., *discontinuing vaccinations*). Protocols did not describe how access to pregnancy services would be ensured.
	The phase I protocols did not describe how STIs would be addressed, whereas the phase IIB protocols broadly described there would be "access to syndromic management."
Participants' other needs	Protocols for both trials described steps for other needs consistent with assessing vaccine safety (e.g., *assessing adverse events*).
	In the phase I protocols, steps to assist participants to access care were declared for only a few select needs, such as cardiac problems (*appropriate referrals*).
	The phase IIB protocols described no steps to ensure access to services.
Volunteers' needs	Protocols for both trials described steps to help volunteers identified as HIV-infected at screening (*providing counseling, referring for management*).
	Neither protocol set out how care services would be ensured for STIs or identified pregnancies or other general conditions.

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TABLE 2
Summary of ICF Descriptions Regarding Care Steps

Issue	Description
Participants' HIV needs	The phase I ICFs described steps consistent with scientific objectives (e.g., *discontinuing vaccinations*) as well as steps to help participants to access care (e.g., *we will counsel you about your HIV infection, we will help you get care and support*). The phase IIB ICFs described some steps linked to scientific objectives (e.g., *testing how the body controls HIV infection*) as well as steps to help participants to access care (e.g., *you will be helped to get treatment for your infection*).
	Supplementary material set out steps to help participants to access care (*we will refer you to medical professionals, we will tell you where you will be able to receive care and medications, you will get access to ART according to country guidelines*).
Participants' non-HIV/other needs	The ICFs for both trials stated that participants must agree to birth control, and outlined some steps for pregnancy (e.g., *discontinuing vaccinations if pregnant*) but made no statements about how participants would be helped to access services.
	The ICFs for both trials stated the tests/exams in the HVT might detect health problems and they stated: "You will be helped to get treatment but you will not be provided with treatment for problems unrelated to the study."
	Supplementary material set out steps (*referral to available counseling, support, medical, and treatment services for illnesses*).
Volunteers	The ICF for the phase IIB HVT stated that screening tests may show a person cannot join, but no care steps were outlined.
	The ICF for the phase 1 HVT at one site was the same as above, whereas the other ICF outlined steps (*we will tell you about places where you need to get support or medical care*).