Contemporary Clinical Trials Communications 19 (2020) 100594

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: http://www.elsevier.com/locate/conctc

Parallel but connected: Nuances of conducting behavioral and social science research alongside ethically challenging HIV remission trials

Gail E. Henderson [a,*], Stuart Rennie [a], Amy Corneli [b], Karen Meagher [c], R. Jean Cadigan [a], Eugène Kroon [d], Jintanat Ananworanich [e], Holly L. Peay [f]

[a] Department of Social Medicine, University of North Carolina School of Medicine, Chapel Hill, NC, USA
[b] Departments of Population Health Sciences and Medicine, Duke University, Durham, NC, USA
[c] Health Sciences Research, Mayo Clinic, Rochester, MN, USA
[d] The Thai Red Cross AIDS Research Centre, 104 Rajdumri Road Krung Thep Maha Nakhon 10330 Krung Thep Maha Nakhon, Bangkok, 10330, Thailand
[e] Department of Global Health, Amsterdam University Medical Centers, University of Amsterdam, and Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands, Meibergdreef 9, 1105, AZ, Amsterdam, the Netherlands
[f] RTI International, Research Trialngle Park, NC, USA

A B S T R A C T

Collaborations between clinical investigators and behavioral and social science researchers (BSSR) produce many benefits, but also may generate challenges and complexities. Ongoing relationships between teams may affect the research carried out by the BSSR team and the way they interpret their findings. Here we describe our experiences conducting the HIV Remission ('Cure') Trials Decision-Making Study (DMS), in Thailand; these trials include potentially risky interventions and interruption of standard antiretroviral treatment, with little personal benefit. The DMS is a longitudinal study of the experiences of individuals recruited to such early-phase trials, and conducted alongside these trials. It originated in clinical investigators' concerns about the ability of those recruited to make voluntary and informed decisions about scientifically complex studies, and is led by an independent group of BSSR and ethics researchers. In conducting this study, we experienced three overarching challenges to achieving a successful and dynamic collaboration: managing emerging findings as data were collected alongside clinical trial participation; evolving interconnectedness and shifting partnership boundaries among investigators; and the process of incorporating new research questions. By describing these challenges, we provide experiential evidence on how to manage multidimensional aspects of these collaborations. We describe how our research teams came together as well as the challenges and opportunities we experienced along the way. Our aim is to raise awareness of the scientific, practical, and ethical complexities of establishing and maintaining this kind of broad multidisciplinary collaboration over time. By describing our experiences, we hope to advance an agenda for others who undertake similar partnerships.

1. Introduction

Collaborations between clinical investigators and behavioral and social science researchers (BSSR) are often aimed at improving participant experiences and overall research outcomes [1]. While there are many benefits, these collaborations also generate their own complex challenges [2]. Ongoing relationships may affect the research carried out by the BSSR investigators and the way they interpret their findings [3]. As the trend toward multidisciplinary team science increases, a better understanding of collaborative dynamics is needed [4]. BSSR and clinical research collaborators face distinct challenges to achieving shared visions of research rigor, integrity, and collaborative success. By anticipating, identifying, and addressing these challenges, they may collectively avoid biased aims, methods and conclusions; failed research relationships; and other unintended negative consequences.

The history of research on prevention and treatment of HIV/AIDS is instructive, as calls to incorporate BSSR into clinical research are long-standing (e.g., MacQueen 2011) [2]. Several authors [5,6] have similarly called for integrating BSSR and HIV "cure" research, now commonly referred to as "remission" research. Gaist and Stirratt (2017) [7] present a functional framework of HIV/AIDS-related BSSR, highlighting its role in strengthening the design, conduct, and interpretation of biomedical HIV research, which was subsequently applied to "cure" research [8].

Global research partnerships also set the stage for articulating collaborative success between BSSR and clinical investigators. Commentaries endorse an aspirational justice framework in global HIV research, given power and resource imbalances that often characterize such collaborations (e.g., Lavery et al., 2010, Lancet 2013, Pratt and Loff 2015) [9–11]. Parker and Kingori (2016) [12], for example, outline

* Corresponding author.
E-mail address: gail_henderson@med.unc.edu (G.E. Henderson).

https://doi.org/10.1016/j.conctc.2020.100594
Received 2 February 2020; Received in revised form 9 June 2020; Accepted 14 June 2020
Available online 16 June 2020

eight features of "good" global health research collaborations, which include fostering valuable science with competent partners; respect for partners' needs, interests, and agendas; open communication; and justice and fairness in the collaboration.

Missing is guidance about how to define and tackle complex situations that arise in such collaborations. This paper reports on our experience with a longitudinal BSSR study running alongside clinical HIV remission research. Such "parallel" BSSR studies are defined as taking place during clinical trials but with a separate protocol, consent process, funding, and limited BSSR team access to clinical data [13]. We present a real-world case of how BSSR researchers from University of North Carolina and RTI International (USA) work alongside HIV remission trial clinical investigators at the South East Asia Research Collaboration in HIV (SEARCH), in Bangkok, and the US Military HIV Research Program (MHRP) in the USA to explore ethically challenging issues inherent to these trials. While our authors include two leaders from the clinical research side (Drs. Ananworanich and Kroon), this report focuses on the social science and ethics team's perspectives on the collaboration. Our purpose is not to develop a principle-based, aspirational checklist to assess collaborations, nor is it to highlight the noteworthy contributions that BSSR can make to clinical trial outcomes. Rather, by describing our experiences, we offer practical guidance that might assist in recognizing and navigating the nuances of these complex research relationships as distinct forms of multidisciplinary research collaborations.

2. The Case: SEARCH HIV Remission Trials Decision-Making Study

To introduce the case, we first review the SEARCH HIV remission clinical trials, followed by a description of the Decision-Making Study (DMS), the collaborators involved, and the DMS data.

2.1. Clinical HIV remission trials

SEARCH010 is a research cohort established in 2009 by the Thai Red Cross AIDS Research Centre in Bangkok, Thailand and supported in part by the US MHRP. After ten years, it includes 643 individuals diagnosed and treated at the earliest stage of HIV (clinicaltrials.gov NCT00796146), with very low HIV burden, preserved immunity and sometimes seronegative status. Beginning in 2016, SEARCH investigators recruited 67 existing cohort members to participate in four early phase HIV remission trials. The remission trials aim to understand factors related to long-term control of HIV. All included analytic treatment interruption (ATI), a controversial procedure to test the efficacy of the intervention used to suppress HIV viral load without antiretrovirals (i.e., HIV remission) [14]. Three of the trials included an experimental agent and were placebo-controlled, while the fourth entailed only ATI. Participants undergoing ATI are taken off standard antiretroviral treatment (ART) and followed in a controlled setting until viral rebound occurs, after which ART is re-started. Although the SEARCH trials did not demonstrate significant effects of the single entity interventions under study (e.g., Colby et al., 2018 [15]), other research is evaluating novel strategies with combination interventions and new entities with the goal of inducing longer-term antiretroviral-free remission (Li, Smith, & Mellors 2015, for a reference summarizing ongoing remission trials, see http://www.treatmentactiongroup.org/cure/trials [16]).

2.2. Decision-Making Study (DMS)

The collaboration began at a small international conference about HIV remission research. SEARCH clinical investigators were concerned about generating unrealistic expectations for an HIV "cure," and the challenges involved with treatment interruption. The BSSR study arose from the concerns of clinical investigators and other stakeholders about these ethical issues: Would cohort members feel free to decline to participate in remission trials? Would they understand the likely risks and benefits? Would they entertain unrealistic expectations about being cured of HIV? How might prior and future HIV clinical research be compromised if it was learned that participants did not make voluntary, informed decisions about their participation?

These ethical issues inspired our decision-making study (DMS), funded by a National Institutes of Health grant mechanism for ethics and HIV research. The DMS has conducted longitudinal, primarily qualitative interviews with SEARCH cohort members who join ("participants") or decline ("decliners") any of the four HIV remission trials. A quantitative decisional conflict measure [17] is also administered at each interview. To date, we have conducted over 200 interviews with 74 individuals: 54 participants and 20 decliners. In addition to our primary aim of studying perceptions of risk and benefit and decision satisfaction or regret over time, the DMS has two other specific aims. One is to assess how to manage and disseminate results from the study, including providing "real-time" results to the clinical team; and the other is to develop recommendations to the broader research community for the ethical conduct of remission trials involving ATI.

2.3. The BSSR and SEARCH collaborators

Four individuals formed the core leadership of the DMS collaboration: two US-based social scientists and two SEARCH clinical investigators who are investigators on both the DMS grant and the remission trials. The broader *DMS BSSR team* is also interdisciplinary, including two bioethicists, other social scientists, and two research associates who conduct the interviews and provide translation and cultural guidance. The *SEARCH clinical trial team* includes several remission trial investigators and study coordinators in Bangkok; senior SEARCH clinical investigators are either US-trained Thais or foreign nationals living in Bangkok.

2.4. DMS data

The DMS has a distinct dataset that includes the participant and decliner interviews and decision conflict survey data across four remission trials. During the consent process, participants recruited to the DMS study were assured that these interview data would not be accessible by the clinical team, with the few exceptions (e.g., urgent concerns for participant safety) clearly outlined in the DMS consent form. Similarly, the clinical trial data are maintained by the clinical team and are not accessible to the DMS-BSSR team. That is, the DMS study runs in parallel to the SEARCH research cohort and associated clinical trials. In the course of the collaboration, there were several presentations to the SEARCH team on the DMS findings, and two surveys of the clinical team to assess how learning the study's findings potentially impacted their research practices [18]. As described below, these occasional connections grew over time in both depth and frequency, leading to our view of the collaboration as "parallel but connected."

3. Findings: The Complexities of Collaboration

In this section, we describe the complexities experienced over a three-year period of this BSSR-clinical collaboration. We faced standard challenges which are well known to collaborating teams, such as maintaining privacy and confidentiality of the participants. Yet complexities could arise in the context of "standard" challenges. For example, in theory, disseminating high-level de-identified data or analyses to clinical collaborators poses no ethical problem; in practice, when a trial involves very few participants, seemingly benign information such as high-level demographics may still be identifiable to a clinical team.

As much as possible, SEARCH and DMS collaborators anticipated challenges that could emerge. When challenges arose, they were documented and discussed at regular BSSR investigator meetings; in some cases, SEARCH investigators provided input or preferences on how to

address an issue. Generally, we anticipated that our analysis process would be complicated by the need for translation across languages and cultures, and indeed, nuance in interpretation of ethically relevant concepts has been required throughout our study. For example, our DMS analysis included a few instances when the appropriateness of "influence" over participants was deliberated. Influence has subtly different meanings in Thai vs. US contexts, and this had to be carefully analyzed given that context.

And yet even with our planning, unexpected complexities and/or anticipated complexities that were unexpectedly important, have arisen during our collaboration. We report here on three key domains that highlight complexities over the course of the study and may be useful for others to consider when crafting a successful parallel BSSR study: 1. Managing emerging findings, 2. Evolving interconnectedness and shifting partnership boundaries, and 3. Incorporating new research questions. For each, we present the complexities, our collaborative approaches, and conclude with concrete recommendations for each domain (Table 1).

3.1. Managing emerging findings in the context of a parallel study

We designed the DMS protocol so that all interviews with trial participants and decliners were conducted by a team member living in Bangkok. The SEARCH clinical team, who helped with DMS recruitment, were not permitted access to these primary interview data. This protected participant confidentiality which was promised when they agreed to join the DMS. The only exception to this requirement was when participant safety was at stake. This was outlined by the BSSR team protocol and described in the consent form. As the study unfolded, the clinical team provided input to the DMS team on scientific, contextual, and cultural questions about de-identified data, and the DMS team analyzed data for articles co-authored by both teams. At the same time, DMS leaders sought to develop standards for sharing interview results with the clinical team (the second specific aim of our study).

3.1.1. Complexity: protecting participants while preserving collaborative harmony

The practicalities of sharing findings within such collaborations are complex. When the ethics of a research practice is itself under study, the possibility that BSSR findings will confirm or exacerbate ethical concerns is built into the collaborative research design. Clinical trialists who invite ethics collaborations may hope that BSSR findings will validate their work, while being aware of the possibility that challenges will be uncovered. From the BSSR side, possible self-censoring can result from close ties between the two teams, indebtedness for data collection opportunities, and the significance of the studies involved. To protect the integrity of the research, BSSR teams may construct walls between the social science and clinical trial domains. Yet, in this case, reporting on emerging findings was part of the DMS study aims, to enable subsequent trials within the SEARCH cohort to benefit from data on participant experiences. This also allowed the DMS team to turn to SEARCH and MHRP clinical researchers for feedback on trial context, and facilitated post-hoc interpretations of interview data. But our more collaborative approach also raised the concern of possibly comprising how those

Table 1
Recommendations.

A. Managing emerging findings in the context of a parallel study
• Define the roles and responsibilities of the BSSR and clinical teams, as early in the collaboration as possible.
• Recognize that clinical researchers will likely have no or very limited access to individual BSSR study data, to protect participants' privacy and the confidentiality of their data. At the same time, recognize early phase trials with small numbers of participants present unique challenges to protecting confidentiality.
• Reach agreement on rules for disclosure and dissemination of BSSR findings, and any exceptions to those rules. This includes findings that are directly related to protocol adherence, unreported side effects, and mental health concerns that arise during the BSSR data collection—i.e., those that should likely be disclosed to the trial team for safety purposes, which should be clearly stated in the consent form for the BSSR study.
• Anticipate both positive and negative findings by the BSSR study regarding clinical research conduct and participant experiences, and be prepared to address consequences of such findings.
• Establish a method for group consultation to resolve ethical issues that arise while the clinical research is ongoing. These may also involve input from independent parties, with attention to not unduly disrupting trial processes.
• Anticipate the challenges of studying trial decliners, as they may be more likely to voice concerns/negatives about the trial and/or the trial team.
B. Evolving Interconnectedness and shifting partnership boundaries
• Define the ways that conflicts and biases are inherent to collaborations, and address them proactively and through an ongoing basis.
• Agree upon authorship requirements at the beginning of the collaboration. Maintaining fairness requires regular communication about authorship status among all researchers from manuscript design to final drafts.
• Recognize that reference to international criteria may not be sufficient to resolve all authorship issues in evolving BSSR and clinical research collaborations. Accommodation should be made for authors who contribute significantly to the conduct of research, but due to low English proficiency, are not able to significantly contribute to the writing. Rules for authorship are difficult when there are many authors and when different disciplines and diverse skills are represented. These are common issues, but international BSSR and clinical collaborations may add another layer.
C. Incorporating new research questions
• Anticipate that when ongoing BSSR and clinical research collaborations jointly initiate new projects, expectations and roles may subtly alter. Attention to possible shifts within the same collaboration can help to minimize potential misunderstandings.
• Consider all the collaboration issues described above for the initial study when forming new research collaborations, even those using the same or similar instruments.
• Develop approaches that encourage new research generation, including research concepts identified collaboratively or by the clinical or BSSR investigators. A major strength of collaborative studies is that they may led to downstream research that is rapid, highly translational, and anticipates rather than responds to social/behavioral and ethical concerns.

conclusions would be presented. This concern was amplified in the context of small interviewee numbers, and the importance of neither over- nor under-emphasizing one or two findings from participants who had outlying experiences or perceptions.

One reason HIV "cure" research is controversial is concern that participants may not fully appreciate the risks of ATI, which include both the sacrifice of the benefits of effective ART and the risks of its cessation to self and others – even if temporary [19]. In fact, the DMS findings about participant and decliner decision-making processes, based on over 200 longitudinal interviews, were overall quite positive. Most of the interviews we conducted with people recruited to the trials, especially with those who decided to participate, document a strong informed consent process and good understanding of what was involved in remission trials with ATI. We also found that time and burden of participating in remission trials were the most common reasons given for declining, and that most people did not feel overly pressured to join [20,21]. This predominantly "good news" was easy to convey to the SEARCH clinical trial team, and in turn, was easy for SEARCH investigators to share at professional forums.

Still, a few concerning findings surfaced, which we reported in our joint publications [20,21], and which might be magnified in other settings. For example, some trial participants reported having more anxiety than they anticipated during ATI; some indicated expectation for a cure based on their participation in the trial; and some experienced the SEARCH optional research procedures, e.g., lymph node biopsies and spinal tap, to be quite burdensome—more so than the study team realized (and as described below, this generated new research questions). If we had discovered serious ethical concerns, sharing them with the clinical team and presenting them externally would have been more challenging, and is clearly an important challenge other BSSR teams could confront.

Emerging findings from interview data might also have unanticipated consequences for third parties. For example, a few of our participants described discomfort at repeated recruitment attempts for one of the remission trials. Reporting this to SEARCH lead investigators raised the possibility of identifying a member of the trial team who is not involved in the BSSR study, and in our case, the identification was a certainty since only one person recruited for each remission trial. BSSR studies like the DMS need to anticipate the possibility for controversial findings to reverberate in unanticipated ways internally through clinical trial teams.

3.1.2. Collaborative approach: ongoing dialogue to deal with the complexities

As the research collaboration evolved, trusting relationships helped navigate emerging concerns. We provide two examples.

First, interviews with decliners demonstrated their concern about the risks of going off ART, especially if it involved possible seroconversion, as well as the burdens of time and travel. In one trial, two of the six decliners interviewed mentioned feeling "selfish" for not participating. Working jointly across teams, we developed an explanation for this potentially worrisome decliner response: "(It) may reflect concern about violating social norms of harmony and accommodation in interpersonal relations (called *Krengjai*) in the predominantly Buddhist Thai culture," and indicates that decliners may require more support around these issues when they decide not to participate in remission trials [21].

Second, we deliberated over how to respond to the report by a small number of participants of possible intrusive recruitment or undue influence, identified when we reviewed the transcript of the participant's interview months after the events occurred (as introduced in the 'complexity' section above). After consulting our team interviewer, SEARCH investigators, and an advisory group, we determined that while serious, these issues could be addressed with the research team without having to break our promise of volunteer confidentiality. Instead, we opted to discuss these cases as examples of recruiting from an established cohort, in the context of clinical relationships. This was elaborated in a co-authored manuscript, again written as a collaboration among the research teams. We wrote:

> "[L]ong-standing, close relationships with the SEARCH team played an important role in decision making. This was reported in a positive frame by all participants except one, whose description of initial decision making raises unease about whether the SEARCH staff were too influential, particularly as the "opportunity" to contribute to science might be construed as pressure, or possibly manipulation. Inherent conflicts of interest when recruitment occurs within long-standing clinical and research relationships, such as those in SEARCH, have been well-described. Managing such conflicts is possible when they are identified and when transparent recruitment and informed consent processes are employed" [21].

3.2. Evolving interconnectedness and shifting partnership boundaries

As relationships between different collaborative partners develop, decisions about authorship and understandings of conflicts of interest also change. These are important features of any research collaboration, and potentially more complex with interdisciplinary and international partners. For some, publication in journals outside of their normal disciplines is, in itself, an educational experience. "Evolving interconnectedness" is thus an important part of the story, and introduces challenges that should be addressed.

Our experience with authorship made us aware that parallel studies are *not only* parallel, but they are also dynamically *connected*. That connection has essential benefits, but also produces challenges, particularly as connectedness, itself, is not static. For example, as clinical teams become more integrated into BSSR data interpretation, conflicts of interest may arise. This manifests itself in different ways. In our study, closer ties between the DMS BSSR and the SEARCH clinical investigators could bias the DMS analyses, or may foster greater validity regarding how data are interpreted and represented, or both. These themes recur as the DMS attempts to simultaneously maintain independence and acknowledge dependence in interpreting and presenting data over time.

3.2.1. Complexity: multi-team, multidisciplinary authorship

At the beginning of the collaboration, the DMS team wondered whether the clinical team's lack of access to primary interview data might preclude them from authorship. In response, the leadership group developed a description of carefully delineated boundaries, which addressed authorship in our first article: "No clinical investigators have access to the data or the analysis files, and are not involved in the coding or interpretation of the interview data nor the interviews themselves. They are, however, queried as expert resources when the analytic team have questions about interpretation of HIV or trial-related issues, and have participated in manuscript development" [20]. As we worked on subsequent articles, the process of writing and revising significantly enhanced the depth and interconnectedness of the BSSR-clinical collaboration, and created more appreciation for the insights and contributions of the clinical team. As leaders of the remission trials, their expertise was essential for our second article, "Going off ART in a Closely Monitored HIV 'Cure' Trial" [21] which described the trial that involved treatment interruption without any interventions. For this article, all authors worked together to develop evidence-based recommendations for improving informed consent, supporting participants during the trial, and supporting decliners in their decisions not to participate.

Authorship issues were also triggered *within* the multi-disciplinary BSSR team. One issue was the sheer number of authors on a publication. This may slow down paper writing, and, while normative for clinical investigators, may be problematic for junior social and behavioral research scientists whose disciplines may not recognize as legitimate a large number of authors [4]. Even within social science research teams, authorship contributions for collecting and analyzing qualitative

and quantitative data may be controversial. As interconnectedness of collaborations evolves, expectations for authorship both between and within teams may shift and should be addressed, proactively if possible. Critical topics include what journals to target, who within the collaboration will take leadership for negotiating authorship issues, and how to maintain fairness and ongoing communication.

3.2.2. Collaborative approach: ongoing and transparent conversations, willingness to adapt

An important approach to authorship deliberations and any conflict of interest is transparency and vigilance, which depends on frank discussion of the nature of the relationship and expectations of contributions from each side—a complex endeavor involving renegotiation of boundaries and roles. Many teams nominate an independent board of advisors to identify and address conflicts. The DMS team established such a board, but it was rarely used as the relationship with the SEARCH clinicians quickly matured. In addition, our largely affirming, ethically reassuring findings reduced the need to bring in outside advisors.

3.3. Incorporating new research questions

It is the fundamental nature of clinical research that new findings will result in new clinical questions. The same may be true for BSSR research questions developed in the context of a parallel study. Each new research direction presents an opportunity to re-examine roles and responsibilities, clarify expectations, make more explicit the contributions of the BSSR team, and address issues such as data governance, ownership, and authorship. Furthermore, important research questions for BSSR can originate from clinical research collaborators, which in turn can make BSSR data highly relevant for the ethical conduct of future studies. While these processes are not unique to BSSR teams collaborating with clinical researchers, the rapidity and creativity with which new research questions emerged in our multidisciplinary project led us to hypothesize that the very nature of such cross-disciplinary collaboration lends vigor and pace to scientific advancement/translation. That is, with different sets of knowledge and ideas about where research should be going, a benefit of such collaborations is moving these new ideas along the research pipeline—concepts that may not have evolved without the collaborative process and/or that may have trailed scientific advancement rather than anticipating it.

3.3.1. Complexity: context of developing and pursuing new research questions

The way collaborations negotiate new research question development depends on the context in which the new questions emerge, who would be leading the project, and the type of study being considered. Some questions may emerge as joint efforts across BSSR and clinical teams; some are accommodated within the original BSSR scope of work; and some require additional negotiation or funding. Below we describe three paths in which new projects within our collaboration emerged: joint new projects, projects initiated by the clinical team, and projects initiated by the BSSR team.

3.3.1.1. Joint new projects. An advantage of our BSSR semi-structured and dynamic approach to longitudinal data collection was the capacity of the DMS team to identify and incorporate new questions into ongoing data collection from the four trials. For example, our initial interviews revealed that the trial's request for participants to undergo optional procedures, such as lymph node biopsies, was perceived by some participants as more burdensome than expected [21]. In response, the BSSR team proposed an additional survey that the clinical team wanted to jointly pursue. The goal was to learn more about participants' concerns with and decisions about these optional procedures, and then share the findings with the entire SEARCH team. This survey thus marked a shift from the independent, "parallel" study that launched our collaboration to an "embedded" study [13].

3.3.1.2. Projects initiated by the clinical team. The most significant request from the clinical team has been to investigate the SEARCH cohort members' attitudes toward remission trials with longer treatment interruption. "Extended ATI" involves discontinuing antiretroviral treatment for a longer period than in the SEARCH remission trials, which re-start ART at the first sign of viral rebound. HIV researchers hypothesize that extended time of viremia during ATI will permit the participant's own immune system, in concert with an intervention, to reduce the amount of virus [14]. At the same time, extended ATI will possibly increase the risk of clinical complications for participants, and has already been shown to increase the risk of HIV transmission to non-participants [22–25].

Motivations to join or decline a trial with treatment interruption was a key focus of our original DMS project. For some cohort members invited to join these trials, going off ART in a controlled setting was seen as a benefit; in addition, being part of a cohort of individuals diagnosed with HIV at the earliest stage of infection, and thus best suited to satisfy remission trials' eligibility criteria, also contributed to a positive identity [20]. Thus, the request to explore participant attitudes toward *extended* time of viremia during ATI opened a new and exciting opportunity to continue this line of research. This has involved piloting hypothetical scenarios developed in consultation with SEARCH investigators, and developing valid ways to explore cohort responses using a survey, as well as preparing to conduct interviews with cohort members invited to participate in any new trials with extended ATI.

3.3.1.3. Projects initiated by the BSSR team. The experience of studying small clinical trials recruited from a much larger research cohort (e.g., SEARCH) generated new research questions about the roles that cohorts play in recruitment and retention for clinical trials, and how culture influences cohorts and the individuals in them—relatively new topics in the research ethics literature. To explore this, we initiated a collaboration in a Dutch cohort of individuals diagnosed and treated at the acute stage of HIV infection, similar to the SEARCH cohort. The Dutch clinical researchers who developed this cohort are closely aligned with the SEARCH investigators. Based on those relationships, we initiated a collaboration with Dutch social science and clinical colleagues to conduct a small study in their cohort that includes interview and survey instruments from the DMS. The overall goal is to advance understanding of HIV research cohorts by exploring similarities and differences between the socio-cultural contexts of Bangkok and Amsterdam. We anticipate that this Bangkok-Amsterdam comparison will be very enlightening and that both sides must be alert to findings and perceptions that are likely strongly culturally colored.

3.3.2. Collaborative approach

Collaborative approaches to new research questions, within the context of established parallel studies such as ours, will depend on many factors. As illustrated by the three projects, these include how new questions are identified and developed, and whether new partners are involved. The new joint project on optional research procedures arose from emerging data on the perceived burden of these procedures. The extent of burden was surprising to the clinical team, and when the BSSR proposed a follow-on survey, the clinical team was enthusiastic about facilitating its implementation. Transitioning to an "embedded" BSSR study, with de-identified survey data, may be relatively straightforward. In contrast, given the controversies that surround the science and ethics of ATI, and increased risks of extended ATI trials, the clinical researcher-initiated project is likely to confront similar complexities as confronted the original DMS parallel study. The team, therefore, anticipates the need to carefully consider these complexities and the implications of the data that are gathered about extended ATI, while recognizing that these studies cannot independently settle questions about the ethical

acceptability of this new research design. The third example is research initiated by the BSSR team, derived from increasing awareness gained from the DMS parallel study about how important cohort membership is for decision-making processes. Extension to other similar sites, using similar questions and data collection instruments, will enable comparison of cohort-based recruitments. This is a product of the BSSR-clinical collaboration, yet interestingly, data collected from new sites may affect the ways that researchers understand findings from the original site.

4. Discussion

In this article, we describe a decision-making study of individuals invited to participate in HIV remission trials conducted in Bangkok. The ethical questions about recruitment to HIV remission trials with ATI, which framed the DMS, were co-created with the investigators whose trials were to be studied. Close collaboration such as the one described here can be both an advantage and a source of challenges to be managed. We highlight facets of the collaboration which may give rise to distinct conflicts, challenges, and pitfalls, and offer recommendations (see Table 1) for similarly situated investigators.

Our case demonstrates particular features of an empirical examination of key ethical concerns inherent to HIV remission trials. Despite our ongoing reflection about collaborative structures and interrelated research design, the DMS was initiated without our ability to anticipate all potential challenges at the outset. It is doubtful that all collaborative pitfalls are avoidable, even with the best planning, particularly when external political and economic forces place pressure on one or more partners [26]. Troubleshooting and improvisation, in addition to planning and standard operating procedures, are inevitable. Importantly, we have not faced issues of severely constrained resources and related pressure to balance different priorities, which possibly could have weakened the strength of the collaboration.

We are fortunate that our collaboration evolved naturally and successfully, but recognize distinct advantages to having more nuanced and frank discussions at the beginning and at regular periods throughout the collaboration. Clear lines of responsibilities can be articulated and agreed upon, possibly through an explicit agreement. Early and ongoing communication both between and within teams, and the ability and willingness to have difficult conversations about conflicts of interest, authorship, and data access are critical components. In our experience, trust-building occurred in the process of creating the products of the work, despite not having such an explicit agreement. The good will on the part of the clinical leadership team, mutual respect, and the fact that the BSSR study was perceived as valuable for the clinical work, combined to create these positive outcomes. Shared goals are also exemplified by excitement over new projects that have the potential to advance science through anticipating new social/behavioral and ethical challenges. We conclude that our case of close collaboration between social and behavioral scientists, clinical researchers, and bioethicists is a rich source of knowledge production whose implications are just beginning to be explored [27].

Acknowledgements

We gratefully acknowledge support from NIH, NIAID, 1R01AI127024, “Integrating Decision-Making Studies into HIV Cure Trials: A Real-Time Longitudinal Assessment” and from the US Military HIV Research Program. Thanks also to assistance from Kriste Kuczynski and Sinéad Isaacson, and the volunteers who kindly participated in our Decision-Making Study.

References

[1] J. Ives, M. Dunn, B. Molewijk, J. Schildmann, K. Bærøe, L. Frith, R. Huxtable, E. Landeweer, M. Mertz, V. Provoost, A. Rid, S. Salloch, M. Sheehan, D. Strech, M. De Vries, G. Widdershoven, Standards of practice in empirical bioethics research: towards a consensus, BMC Med. Ethics (2018), https://doi.org/10.1186/s12910-018-0304-3.

[2] K.M. MacQueen, Framing the social in biomedical HIV prevention trials: a 20-year retrospective, J. Int. AIDS Soc. (2011), https://doi.org/10.1186/1758-2652-14-S2-S3.

[3] C.M. Montgomery, R. Pool, Critically engaging: integrating the social and the biomedical in international microbicides research, J. Int. AIDS Soc. (2011), https://doi.org/10.1186/1758-2652-14-S2-S4.

[4] E. Leahey, From sole investigator to team scientist: trends in the practice and study of research collaboration, Annu. Rev. Sociol. (2016), https://doi.org/10.1146/annurev-soc-081715-074219.

[5] H.L. Peay, G.E. Henderson, What motivates participation in HIV cure trials? A call for real-time assessment to improve informed consent, J. Virus Erad. 1 (2015) 51–53. http://www.ncbi.nlm.nih.gov/pubmed/25866844%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4392850.

[6] C.I. Grossman, A.L. Ross, J.D. Auerbach, J. Ananworanich, K. Dubé, J.D. Tucker, V. Noseda, C. Possas, D.M. Rausch, Towards multidisciplinary HIV-cure research: integrating social science with biomedical research, Trends Microbiol. (2016), https://doi.org/10.1016/j.tim.2015.10.011.

[7] P. Gaist, M.J. Stirratt, The roles of behavioral and social science research in the fight against HIV/AIDS: a functional framework, J. Acquir. Immune Defic. Syndr. (2017), https://doi.org/10.1097/QAI.0000000000001399.

[8] K. Dubé, J.D. Auerbach, M.J. Stirratt, P. Gaist, Applying the behavioural and social sciences research (BSSR) functional framework to HIV cure research, J. Int. AIDS Soc. (2019), https://doi.org/10.1002/jia2.25404.

[9] J.V. Lavery, S.V. Bandewar, J. Kimani, R.E. Upshur, F.A. Plummer, P.A. Singer, “Relief of oppression”: an organizing principle for researchers’ obligations to participants in observational studies in the developing world, BMC Publ. Health (2010), https://doi.org/10.1186/1471-2458-10-384.

[10] B. Pratt, B. Loff, A comparison of justice frameworks for international research, J. Med. Ethics (2015), https://doi.org/10.1136/medethics-2014-102072.

[11] Integrity in research collaborations: the Montreal statement, Lancet 382 (2013) 1310, https://doi.org/10.1016/S0140-6736(13)62126-1.

[12] M. Parker, P. Kingori, Good and Bad Research Collaborations: Researchers’ Views on Science and Ethics in Global Health Research, PLoS One (2016), https://doi.org/10.1371/journal.pone.0163579.

[13] A. Corneli, K. Meagher, G. Henderson, H. Peay, S. Rennie, How biomedical HIV prevention trials incorporate behavioral and social sciences research: a typology of approaches, AIDS Behav. 23 (2019) 2146–2154, https://doi.org/10.1007/s10461-018-2358-0.

[14] B. Julg, L. Dee, J. Ananworanich, D.H. Barouch, K. Bar, M. Caskey, D.J. Colby, L. Dawson, K.L. Dong, K. Dubé, J. Eron, J. Frater, R.T. Gandhi, R. Geleziunas, P. Goulder, G.J. Hanna, R. Jefferys, R. Johnston, D. Kuritzkes, J.Z. Li, U. Likhitwonnawut, J. van Lunzen, J. Martinez-Picado, V. Miller, L.J. Montaner, D. F. Nixon, D. Palm, G. Pantaleo, H. Peay, D. Persaud, J. Salzwedel, K. Salzwedel, T. Schacker, V. Sheikh, O.S. Søgaard, S. Spudich, K. Stephenson, J. Sugarman, J. Taylor, P. Tebas, C.T. Tiemessen, R. Tressler, C.D. Weiss, L. Zheng, M.L. Robb, N. L. Michael, J.W. Mellors, S.G. Deeks, B.D. Walker, Recommendations for analytical antiretroviral treatment interruptions in HIV research trials—report of a consensus meeting. Lancet HIV, 2019, https://doi.org/10.1016/S2352-3018(19)30052-9.

[15] D.J. Colby, L. Trautmann, S. Pinyakorn, L. Leyre, A. Pagliuzza, E. Kroon, M. Rolland, H. Takata, S. Buranapraditkun, J. Intasan, N. Chomchey, R. Muir, E. K. Haddad, S. Tovanabutra, S. Ubolyam, D.L. Bolton, B.A. Fullmer, R.J. Gorelick, L. Fox, T.A. Crowell, R. Trichavaroj, R. O’Connell, N. Chomont, J.H. Kim, N. L. Michael, M.L. Robb, N. Phanuphak, J. Ananworanich, P. Phanuphak, N. Teeratakulpisarn, S. Chottanapund, M. De Souza, J. Fletcher, P. Tantivitayakul, P. Eamyoung, D. Sutthichom, P. Prueksakaew, S. Puttamaswin, S. Tipsuk, K. Benjapornpong, N. Ratnaratorn, C. Munkong, K. Tanjnareel, R. Kanaprach, R. Rerknimitr, P. Wattanaboonyongcharoen, P. Rojnuckarin, S. Manasnayakorn, A. Schuetz, S. Akapirat, B. Nuntapinit, N. Tantibul, H. Savadsuk, Y. Phuang-Ngern, S. Jongrakthaitae, W. Chuenaron, N. Churikanont, S. Getchalarat, S. Krebs, B. Slike, A. Tokarev, E. Sanders-Buell, M. Bose, C. Ogega, J. Buahen, M. Ouellette, C. McCullough, O. Butterworth, E. Turk, L.A. Eller, M. Milazzo, J. Mitchell, C. Subra, N. Lima, J. Garnett, F. Fatmi, A. Sy, N. Dawson, S. Spudich, V. Valcour, F. Maldarelli, I. Sereti, J. Lifson, R. Paul, R. Fromentin, P. Dawson, Rapid HIV RNA rebound after antiretroviral treatment interruption in persons durably suppressed in Fiebig i acute HIV infection brief-communication, Nat. Med. (2018), https://doi.org/10.1038/s41591-018-0026-6.

[16] J.Z. Li, D.M. Smith, J.W. Mellors, The Need for Treatment Interruption Studies and Biomarker Identification in the Search for an HIV Cure, AIDS (2015), https://doi.org/10.1097/QAD.0000000000000658.

[17] A.M. O’Connor, Validation of a decisional conflict scale, Med. Decis. Making (1995), https://doi.org/10.1177/0272989X9501500105.

[18] H.L. Peay, S. Isaacson, N. Ormsby, A. Corneli, R.J. Cadigan, G.E. Henderson, How do HIV cure trial researchers respond to an embedded social science study?. 10th IAS Conf. HIV Sci., 2019. Mexico City, Mexico, https://onlinelibrary.wiley.com/doi/full/10.1002/jia2.25327.

[19] S.A. Garner, S. Rennie, J. Ananworanich, K. Dube, D.M. Margolis, J. Sugarman, R. Tressler, A. Gilbertson, L. Dawson, Interrupting antiretroviral treatment in HIV cure research: scientific and ethical considerations, J. Virus Erad. (2017).

[20] G.E. Henderson, H.L. Peay, E. Kroon, R.J. Cadigan, K. Meagher, T. Jupimai, A. Gilbertson, J. Fisher, N.Q. Ormsby, N. Chomchey, N. Phanuphak, J. Ananworanich, S. Rennie, Ethics of treatment interruption trials in HIV cure research: addressing the conundrum of risk/benefit assessment, J. Med. Ethics 44 (2018) 270–276, https://doi.org/10.1136/medethics-2017-104433.

[21] G.E. Henderson, M. Waltz, K. Meagher, R.J. Cadigan, T. Jupimai, S. Isaacson, N. Q. Ormsby, D.J. Colby, E. Kroon, N. Phanuphak, J. Ananworanich, H.L. Peay, Going off antiretroviral treatment in a closely monitored HIV "cure" trial: longitudinal assessments of acutely diagnosed trial participants and decliners, J. Int. AIDS Soc. (2019), https://doi.org/10.1002/jia2.25260.

[22] J.D. Lelièvre, L. Hocqueloux, Unintended HIV-1 transmission to a sex partner in a study of a therapeutic vaccine candidate, J. Infect. Dis. (2019), https://doi.org/10.1093/infdis/jiz012.

[23] A. Ugarte, Y. Romero, A. Tricas, C. Casado, C. Lopez-Galindez, F. Garcia, L. Leal, Unintended HIV-1 infection during analytical therapy interruption, J. Infect. Dis. (2019), https://doi.org/10.1093/infdis/jiz611.

[24] L. Dawson, Human immunodeficiency virus transmission risk in analytical treatment interruption studies: relational factors and moral responsibility, J. Infect. Dis. (2019), https://doi.org/10.1093/infdis/jiz090.

[25] N. Eyal, L.G. Holtzman, S.G. Deeks, Ethical issues in HIV remission trials, Curr. Opin. HIV AIDS 13 (2018) 422–427, https://doi.org/10.1097/COH.0000000000000489.

[26] N.M.P. King, G. Henderson, J. Stein, Beyond Regulations: Ethics in Human Subjects Research, University of North Carolina Press, 1999.

[27] M. Konrad, Collaborators Collaborating: Counterparts in Anthropological Knowledge and International Research Relations, 2012.