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Use of single IRBs for multi-site studies: A case report and commentary from a National Drug Abuse Treatment Clinical Trials Network study

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ABSTRACT

Recent NIH policy stipulates that multi-site studies must use a single or IRB (Institutional Review Board) in order to streamline the review process while maintaining standards for human subjects protection. The Western States Node of the Clinical Trials Network (CTN) used a single IRB for protocol CTN-0067, a clinical trial testing the use of an opioid antagonist (extended-release naltrexone) versus opioid agonists (buprenorphine or methadone) for opioid use disorders among individuals living with HIV. This case study discusses the processes and challenges associated with use of a single IRB. These lessons are also informed by other single IRB experiences within the CTN. The intention of the NIH single IRB policy is to facilitate efficient IRB processes. Advanced planning and transparent communication, however, are critical to avoid stalling IRB approval and protocol implementation. Research teams need to account for local IRB willingness to cede to a single IRB and understand the variations in interpretations of abbreviated reviews. In order to facilitate the effective use of single IRBs, recommendations include assigning staff at each study site for IRB submission coordination and interaction with the lead site IRB staff, training investigators and key regulatory staff on expectations for working with single IRBs, dedicating a regulatory specialist at the lead site to manage the process, developing a communication plan, and supporting the development of strong working relationships with local regulatory staff and the single IRB. The CTN experiences with single IRBs may provide insights for other investigators.

1. Introduction

Institutional Review Boards (IRB) ensure that studies with human subjects are conducted ethically and meet federal standards for conducting research. When trials include multiple study sites and IRBs, variation in IRB processes and regulatory interpretation may delay protocol implementation [6,9,15,16]. A study of IRB processes at 16 sites, for example, observed variation in the type of IRB review required and the number of days from submission to approval (range of 5–172 days) [4]. Expanding numbers of multi-site clinical trials [10] and observational studies [7], makes the task of managing multiple local IRB approvals a critical function of health research management and has implications for the protection of study participants.

Current National Institutes of Health (NIH) policy requires that domestic centers of multi-site studies funded by NIH use a “single” IRB to reduce variation and delays [12]. Exceptions are allowed if federal, tribal, or state laws, regulations and policies prohibit the use of a single IRB. The NIH can also approve exceptions with compelling justification. The single IRB requirement does not apply to foreign sites and some types of NIH awards are exempt (i.e. career development, institutional training, and fellowship awards) [13]. Though this policy is now active, little has been documented about the actual use of single IRBs in multi-site trials. This paper details lessons learned during use of a single IRB for a National Drug Abuse Treatment Clinical Trials Network (CTN) protocol, which can provide insight and guidance for other investigators.

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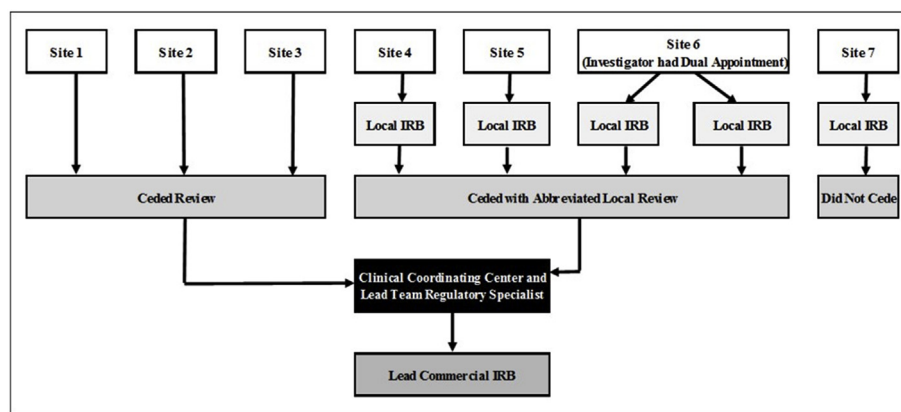


Fig. 1. Diagram of IRB ceding.

2. Material and methods

The CTN-0067 “Comparing Treatments for HIV-Infected Opioid Users in an Integrated Care Effectiveness Study” (CHOICES 2) protocol was designed to test the use of an opioid antagonist (extended-release naltrexone) versus treatment as usual with opioid agonists (buprenorphine or methadone) for opioid use disorders among individuals living with HIV. CTN-0067 was based on a two-site pilot study (CTN-0055) with a small sample ($n = 51$) that demonstrated acceptability and feasibility of extended-release naltrexone treatment of opioid and/or alcohol use disorder in HIV clinics [1,8].

The National Institute on Drug Abuse (NIDA) approved the initial CTN-0067 protocol for site selection and implementation in May 2017. NIH’s policy on the use of single IRB was not effective until January 25, 2018. However, the lead team opted to use a single IRB despite the fact that the policy was not yet in effect because they hoped to benefit from the potential for a streamlined process and they hoped to gain experience, as they knew it would be a requirement in the near future. Following site selection, development of case report forms, protocol training, and IRB approvals, seven HIV primary care sites began recruiting study participants in February 2018. Study sites are HIV clinics with sufficient capacity for new patients to support study enrollment targets. Teams at each of the seven sites included a medical director and support staff. Three sites have significant numbers of patients likely to meet eligibility criteria who speak only Spanish. All sites serve individuals with a high risk of incarceration, and one site serves geographically rural communities.

The lead team included the principal investigator, co-investigators, regulatory specialist, and other research staff, leadership from the CTN and the Clinical Coordinating Center (CCC), and the Data and Statistics Center at Emmes, which provides protocol development and on-going regulatory support, quality assurance monitoring visits, implementation support and centralized data collection. The lead team’s dedicated regulatory specialist worked with sites and local IRBs to explain the rationale for a single IRB and encourage them to cede review. She also served as a liaison between the single IRB, the CCC and regulatory staff at participating sites to streamline the process. The regulatory specialist received and sent information from and to the single IRB and local sites; sites did not typically communicate directly with the single IRB. During the weekly lead team and all-sites meetings, the regulatory specialist summarized IRB-related activities. She had strong, positive working relationships with contacts at the single IRB and regulatory staff at all participating research sites. Iterative conversations with the single IRB and the CCC articulated a plan for IRB submission (e.g., number of sites ceding, documents to be submitted for review, and proposed study timeline) and ensured that site regulatory staff understood the process for document submission (e.g., required documents, who is responsible, and the location of documents). The regulatory specialist and CCC

developed and provided document templates for local adaptation, when appropriate.

The CTN’s clinical coordinating center contracted with a commercial IRB to serve as the single IRB. One IRB declined to cede review and required a traditional full review. This site was a county health department and unfamiliar with ceding and they did not have policies in place to authorize it. Three sites technically ceded but required an abbreviated review of all study documents and amendments to ensure that the protocol met university standards. One of those sites required an abbreviated review from two IRBs because an affiliated investigator had appointments at two different universities, each of which needed to cede review to the single IRB. Finally, local IRBs for three sites fully ceded review.

All sites that ceded review were required to submit an investigator’s application to the single IRB. These applications provided brief details regarding, roles, credentials, and potential financial interests of the investigators and research staff, and site contact information as well as study population, expected enrollment, recruitment methods, consent process, privacy and confidentiality measures, and local regulations. The regulatory specialist worked with sites to prepare the institutional authorization/reliance agreements between the single IRB and local IRBs, which stipulated that local IRBs would rely on the single IRB for oversight of the study.

According to these reliance agreements, the single IRB served as the privacy office for the sites that ceded review. Per the single IRB’s requirements, the lead investigator was responsible for ensuring that study personnel had been appropriately trained for conducting the study (based on their roles). Site investigators were responsible for ensuring conflict of interest disclosures were completed for their sites. In addition, the reliance agreements for the sites included submission of all consent documents and the protocol. However, one local IRB also required review of the qualitative interview information sheets. See Fig. 1 for more information about site ceding.

3. Results

The process from protocol development to IRB approval of all seven sites was iterative and complex. NIDA approved the protocol in May 2017. Initially, the lead team submitted the protocol to the lead team’s university IRB in June 2017 but the IRB reported that it would not be able to serve as the single IRB. After approximately a month’s deliberation, the lead team selected a commercial IRB to serve as the single IRB and in August 2017, submitted the protocol. Results focus on the following: ceding review, fees associated with a commercial IRB, and IRB concerns related to recruiting from jails.

Ceding review. The single IRB required a few amendments, but these were relatively minor consent form revisions and were addressed by the regulatory specialist in consultation with the sponsor and

principal investigator. Even with the revisions required by the single IRB, study documents were approved quickly, approximately two weeks after the initial submission. For the three sites that ceded review entirely, IRB review was also quick. Sites submitted their investigator applications and were added to the protocol in September 2017. The single IRB approved all three of the sites by the end of October 2017.

For the three sites that required abbreviated reviews, local IRBs conducted these reviews independent from the single IRB. Abbreviated reviews took anywhere from about 2 weeks to as many as 4 months to complete. For the site with a 2-week abbreviated review, the local IRB conducted its review before ceding review to the single IRB. Two weeks later, the site submitted the investigator application and received approval from the single IRB in one week.

The site that required two local IRB abbreviated reviews had varying experiences with each. The first local IRB conducted its abbreviated review in a little over 2 weeks by mid-October and ceded review at that point. The second local IRB did not come to a decision about ceding review until a month after the first local IRB had already ceded review. After completing an abbreviated review, the second local IRB indicated it would cede review, but not until after the site had received approval by the single IRB. The regulatory specialist submitted the site's application to the single IRB near the end of November 2017 and the single IRB approved it by the end of December 2017. The site then resubmitted the protocol and consent forms along with documentation of the single IRB approval. Near the end of January 2018, the second local IRB requested additional clarification. After the site responded to this request, the second local IRB officially ceded review the second week of February 2018.

Finally, the site with the longest abbreviated review was also the site whose local IRB requested changes to the qualitative interview information sheet. The local IRB officially ceded review mid-November 2017 at which point, the site submitted their investigator application. Once the site received approval from the single IRB near the end of November 2017, they submitted the protocol, consent forms, and other study documents requested. Despite ceding review, the local IRB requested changes that were outside the scope of local context information. The single IRB worked with the local IRB on these revisions but the site did not receive approval from the local IRB until the second week of February 2018, four months after initial submission of the application to the local IRB. In addition, this same site was also required to submit the protocol to their institution's Clinical Research Unit after receiving local IRB approval, further delaying study recruitment.

For the one site that refused to cede, there was uncertainty about whether the local IRB would agree to cede and it took about two months for the local IRB to make a decision. Once the local IRB decided that it would not cede review, the application was submitted near the end of September 2017. Final approval of the application was received the first week of December 2017. IRB approval for this site took about two months longer than for the sites that ceded review entirely. However, despite concerns that a full review would significantly delay the process, the site actually received IRB approval two months sooner than two sites that ceded but required abbreviated reviews. In all, five IRBs required some level of protocol review. Two of the sites that required abbreviated reviews had significant delays and during this time, recruitment was on hold for those sites. This had implications for the entire study and all sites. Sites that had already received IRB approval had hired their staff and were ready to begin recruitment. However, as soon as those sites started recruitment, it "started the clock" with the sponsor in terms of the recruitment window and budgets allocated for the duration of the study for all sites. See Fig. 2 for summary of the timeline of IRB approval.

Fees. Commercial IRBs fee structures can be complicated and require charges for the initial submission, modifications to submissions and annual continuing reviews. There were also fees for the review of every document specific to each study site (local recruitment flyers, reminder cards, holiday cards, appointment cards, etc.). Participating

sites required consent forms specific to their location (local contact information, local lead investigator's information) with additional fees if there was a change of site investigator or site addresses after the initial review. In addition, there were fees for reviewing/acknowledgment of all certified translated documents (informed consent forms, recruitment materials, and assessments) to be used in the conduct of the study at sites with the Spanish speaking populations.

Prisoners. The CTN-0067 study does not directly enroll participants from correctional facilities. However, sites were encouraged to conduct outreach to jails to encourage prospective participants to enroll upon their release. These individuals are at a high risk of re-incarceration and the study anticipated the need to conduct follow-up interviews with study participants should they be incarcerated after recruitment. The single IRB had a process for identifying the need and connecting the regulatory specialist with a representative from Office of Human Research Protection. The regulatory specialist worked directly the representative to obtain certification to conduct follow up interviews with study participants while incarcerated or in court mandated facilities/programs.

4. Discussion

The CTN-0067 lead team found that using a single IRB offered both opportunities as well as challenges. The experiences of the CTN-0067 lead team with a single IRB may be helpful to other investigators and research teams as they implement a single IRB approach for multisite studies.

Single IRB selection. The lead team anticipated that their university would function as the single IRB based on early communications with their designated university IRB analyst. After NIDA authorized study implementation, the lead team met with the university IRB chair to discuss implementation and learned that the university IRB had limited experience serving as a single IRB for multi-site trials. The IRB chair believed the additional workload was beyond the IRB's current staffing capacity for timely review. With the chair's support, the lead team decided that a commercial IRB would be more efficient and timelier. The lead team felt it was important to maintain their role of working with an IRB; thus, in consultation with NIDA, the lead team opted for a commercial IRB rather than tasking one of the study sites with that responsibility.

Direct discussions with lead site IRB chairs about capacity and willingness to serve as the single IRB should be held prior to finalizing the protocol timeline. A commercial IRB is a solution if the lead site IRB has limited capacity and experience in the role as a single IRB, but this adds additional expense.

Ceding Review. Since the NIH policy is now in effect, all local IRBs (with some exceptions) are required to cede to a single IRB as a condition of site selection and funding. However, the CTN-0067 lead team found that even when a local IRB agrees to cede review, it is necessary to clarify if the local IRB requires any additional review or oversight at the start or throughout the course of the study beyond a submission of IRB approved documents from the single IRB. Abbreviated reviews have the potential to delay the process substantially when these reviews are not limited to ensuring that local language is included in site-specific consent forms.

Variation in ceding among the IRBs of the research sites requires the study team to assess local IRBs' willingness to rely on the proposed single IRB. If the site requires a local IRB review in addition to the single IRB review, the research team may need to consider other sites more comfortable with ceding their research oversight. However, some scholars have expressed concern about the ethical aspects of single IRBs. Moon [11] argues that as local IRBs are still liable should human subjects harms occur during a trial, they are more adept at interpreting local research participation and consent requirements which may differ between sites.

While local IRBs and regulatory staff should play a role in providing

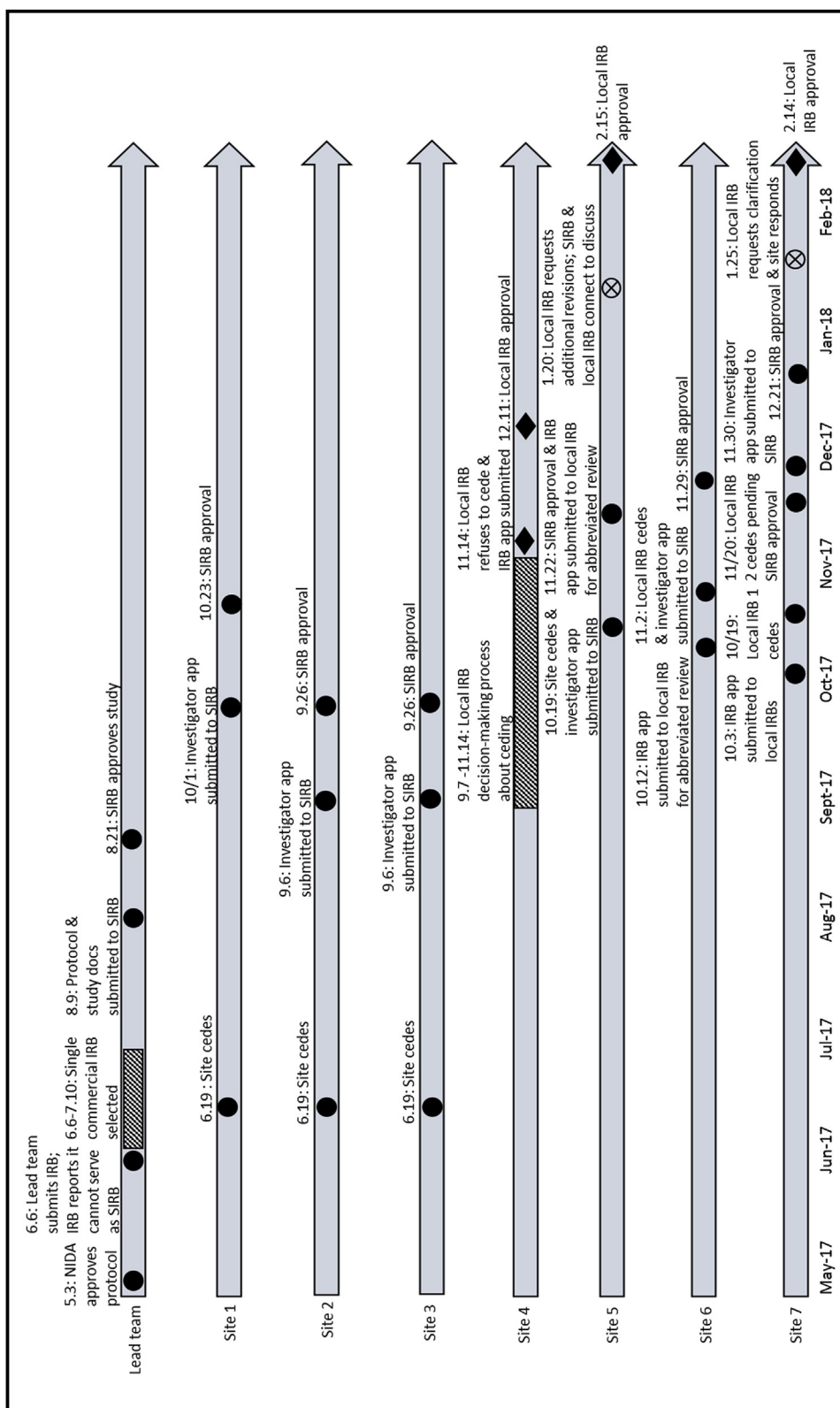


Fig. 2. Timeline of IRB approval.

local context and ensuring compliance with local, state and institutional policies, clarity about the purpose as well as the scope of abbreviated local IRB reviews is critical to avoid delaying recruitment. In order to avoid unexpected delays, investigators should ensure that authorization agreements stipulate what is allowable in terms of local reviews. Some reliance agreements, such as the SMART IRB Reliance Agreement [14],

outline the roles and responsibilities of each IRB as well as stipulate which types of revisions the ceding IRB may request. In the CTN-0067 lead team's experience, however, other reliance agreements, such as an Institutional Authorization Agreement, leave the guidelines for revision requests open-ended and allow ceding IRBs to make requests that could potentially delay study implementation. In situations where the single

Table 1
Key lessons learned during implementation of the CTN0-0067 trial.

Opportunities
<ul style="list-style-type: none"> ● Designated representative from IRB assigned to study ● Quicker review turnaround times ● Standardized documents for all sites ● One online portal for document storage ● All documents submitted for review at the same time creates a streamlined submission process ● Some commercial IRBs have existing relationships with translation companies and will facilitate translation of study documents ● The single IRB may have existing Institutional Authorization/Reliance Agreement templates for sites that agree to cede to the single IRB
Challenges
<ul style="list-style-type: none"> ● Single IRB may be less experienced with trials recruiting from a specific population ● Commercial IRBs charge a fee for initial submission, as well as fees (per site) for amendments to documents, continuing reviews, and study close-out ● Sites that require abbreviated local IRB review may request changes to documents approved by the single IRB and delay study implementation ● Academic IRBs may have limited experience serving as single IRBs and may not have the staffing capabilities to successfully serve as the single IRB

IRB and the local IRB come to different decisions, the single IRB should have the final authority, except in situations involving local context, regulations, and information. However, these potential disagreements between the single IRB and local IRB can still delay study implementation as it takes time to manage. Funding institutions should consider the real-world implications for budgets and timelines when multi-site studies do not cede review in entirety or in part.

Fees. Because CTN-0067 turned to a commercial IRB late in protocol development, costs associated with use of a commercial IRB were not included in the approved study budget. Budgets for IRB oversight may need to account for all the costs associated with the use of commercial or academic institutional IRBs, and timelines may need to be adjusted as institutions and local sites become familiar with working with single IRBs.

The following recommendations may help reduce the costs of working with a commercial IRB. When budgeting for a single IRB, discuss the need for site-specific materials versus the use of templates. Once approved, some IRBs allow sites to insert their own contact information without further approvals. Plan for sites to submit their initial site submission. Commercial IRBs may not allow the modification of multiple types of documents in one submission (e.g., recruitment materials should be submitted separately from consent form modifications). In order to reduce the costs associated with commercial IRBs, documents should be batched appropriately and submitted together as one modification to the extent possible to limit fees associated with each modification submission. The lead team found that having a process that allows for a designated regulatory specialist to be responsible for modification submissions for all sites helped streamline the modification submissions.

If the trial involves documents in languages other than English, the lead research team or sponsor should identify a translation company before submission to the IRB. Commercial IRBs sometimes have existing relationships with translation companies, so it is helpful to indicate the intention to use translated documents during early negotiations with the single IRB representatives and understand the cost structure and submission requirements and possible short cuts with multi-lingual documents on record with the IRB.

Prisoners. When selecting a single IRB, investigators should ensure that the IRB can review the study in accordance with the Department of Health and Human Services' regulations (45 CFR part 46, subpart C) and provide a prisoner representative to serve on the board reviewing this protocol. Early in the submission process, the research team should alert the single IRB that a prisoner representative is required for review of the study. This is a critical consideration in the IRB selection criteria

and capabilities discussion. Research teams should learn whether the prisoner representative is an active member of the Board or whether a special meeting will be required that might delay IRB review.

This paper has described a wide range of learning experiences with a single IRB from the CTN-0067 study. See Table 1 for a summary of key lessons learned during the implementation of the CTN-0067 trial. While there have been limited studies focused on the use of single IRBs, there are a few experiences with the Single IRB that are similar to CTN-0067 team's experience. For instance, the Tuberculosis Trials Consortium found that local review was time consuming and also resulted in changes that decreased the readability of the consent forms [2]. The Clinical Trials Transformative Initiative found that IRBs conflate institutional responsibilities with ethical review responsibilities and recommended the use of a written document that clearly outlines those responsibilities for both the Single IRB as well as the local IRBs [5]. Finally, Check et al. completed a literature review of articles on the use of single IRBs and found that several reported local reviews that were redundant as well as inefficient and had implications on study recruitment [3].

In order to realize the full benefits of single IRBs, some system-level changes are necessary. Three actions can help facilitate the effective use of single IRBs: 1) have dedicated staff at each study site for IRB submission coordination and interaction with the local IRB staff, 2) train investigators and key regulatory staff on expectations of working with single IRBs, and 3) use a regulatory specialist at the lead site who can manage the entire process, develop a communication plan, and support the development of strong working relationships with local regulatory staff and the single IRB.

5. Conclusions

The National Drug Abuse Treatment Clinical Trials Network now has experience with seven protocols that involved a single IRB using both commercial IRBs and university IRBs. With experience, logistics have gone more smoothly. We found that the research sites associated with a university have had more difficulty ceding to a single IRB, especially if it is a commercial IRB, than a site not associated with a university.

The CTN has also learned that IRBs may be inexperienced with various protocol designs implemented within the CTN and may require discussion, explanation and modification of IRB processes designed for typical randomized clinical trials. It is also necessary to educate study sites to work efficiently with the single IRB. Knowing which sites will cede, and to what degree, prior to submitting a proposal budget to the sponsor, enables the projection of more accurate project start dates and sufficient funding to meet all needs of the research project. An awareness of how different IRB choices may have implications for the protocol, budget, or implementation process is critical to the project's success. CTN-0067 was among the first CTN protocols to work with a commercial IRB and learned through trial and error to become more efficient and to take full advantage of the single IRB.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.conctc.2019.100319>.

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