**What Should an Institutional Review Board Know About the Clinical Trial Agreement?**

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**Introduction**

Local institutional review boards (IRBs) normally require investigators to include a copy of the informed consent document (ICD), the protocol, and the investigator's brochure with their applications to conduct industry-sponsored clinical studies. However, IRBs typically do not request a copy of the clinical trial agreement (CTA) between the sponsor and the research site and/or investigator, for three reasons:

- IRBs generally consider most contractual matters outside their purview.
- Study sponsors and investigators might want to keep CTA terms, e.g., compensation to the investigator, confidential.
- The CTA often is still under negotiation when the investigator submits the application.

Nevertheless, CTAs often contain information necessary for the IRB to make the determinations required by the regulations. (The confidentiality issues can be addressed by having one IRB member or an IRB staff person review the pertinent parts of the CTA and provide a report to the IRB.) In this paper, we present several examples of what IRBs should know about a CTA.

**CTAs vs. ICDs**

A CTA is a binding legal contract between a study sponsor and a research site and/or investigator. In contrast, an ICD is not a contract in the normal sense because it is generally considered binding on the investigator and/or research site but not on the research participant. CTAs normally include a “no third-party beneficiaries” provision that means parties like study participants who have not signed the CTA have no legal rights under the CTA.

An ICD contains statements that can be construed to be promises of how the investigator and/or institution will act to protect the rights and welfare of the research participant. To the extent that the subject matter in the ICD and CTA overlap, there is great potential for confusion and legal complications. Lack of concordance on critical elements of the CTA and ICD can significantly disadvantage research subjects, as well as investigators, research sites, and sponsors. Nevertheless, it is not uncommon for different departments of a study sponsor to be responsible for CTAs and ICDs, without being aware that their responsibilities overlap. The same situation can apply at research sites.

The contents of an ICD must conform to FDA regulations (21 CFR 50.25). However, there are no regulatory requirements for what should be in a CTA, although model contracts have been published.1–3 Standard 1-8 of the Accreditation Standards of the Association for Accreditation of Human Research Protection Programs (AAHRPP)4 implies some of the contents of a CTA: “Organization works with public, industry and private Sponsors to apply the requirements of the Human Research Protection Program to all participants.”
Subject Injury

The question of who pays for research-related injuries is under intensive discussion in the clinical trials industry. The relevant regulation states: “In seeking informed consent, the following information shall be provided to each subject: For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.” (21 CFR 50.25(a)(6))

The corresponding AAHRPP Element is I.8.A: “The Organization has a written agreement with the Sponsor that addresses medical care for research participants with a research-related injury, when appropriate.”

Note that the regulation specifies information that the investigator must provide to participants, whereas the AAHRPP element addresses what the agreement between the sponsor and institution must contain. This element has focused institutions’ attention on the importance of assuring that statements about research-related injury and, in particular, who pays for necessary medical treatment, in the CTA and the ICD are consistent.

A sponsor has three possible options with regard to research-related injury:

1. Sponsor pays nothing.
2. Sponsor pays something, often what participant’s insurance does not cover.
3. Sponsor pays all treatment costs.

In our experience, Option 2 is the most commonly elected, followed by Option 3. Option 1 is rarely used.

Option 1, stated explicitly, is unattractive to sites, investigators and participants, plays poorly in the court of public opinion, and probably does not comply with the regulation, “No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject’s legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.” (21 CFR 50.20)

Nevertheless, we have seen examples in which the proposed ICD specifies Option 1 and the CTA offers some version of Option 2. Consider the hypothetical case of a subject who suffers serious injury directly due to participating in a trial. Reading the ICD, the injured participant (and his lawyer) might conclude that there is no recourse to the sponsor. Alternatively, a financially disastrous situation for a trial site can result if the ICD states Option 2 or 3 and the CTA specifies Option 1 or is silent on the matter. A research subject who suffers an injury would look to the site to cover medical treatment costs, but the sponsor would have no obligation.

Option 2 is often qualified with statements that condition payment on subjects having followed instructions, or offers to pay only for emergency care or for a limited time after the injury. As well, research sites have come to recognize the problems associated with paying what insurance does not when the third-party payer is Medicare. If these limitations (which many institutions will not accept) are stated in the CTA but not in the ICD, then the site could become liable for some medical expenses. (Recall, the ICD makes assurances to the participant on behalf of the institution, not the sponsor.) Some sites require that Option 3 be specified when a participant has Medicare or other government-sponsored health insurance.

In summary, it is essential for the IRB to be assured that the injury language in the ICD parallels the language in the CTA to protect the welfare of research participants. This assurance can be handled in different ways. For example, a human research protection (HRP) department staff member could make the comparison or the IRB application form
might require a statement from the investigator that the injury language in the ICD is consistent with the language in the CTA. (That this attention to detail can also protect the institution and the investigator is a secondary benefit.)

**Significant New Findings**

FDA regulations require "A statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject." (21 CFR 50.25(b)(5)) Research sites usually comply with the regulation in the form of a promise in the ICD like "The research study doctor or research study staff will let you know of any new information that may affect whether you want to continue to take part in the research study." (St. Louis University) or "If we discover new information about the study that could affect your decision to stay in the study, you will be notified." (Penn)

The following AAHRPP elements indicate what a CTA must include for the research site to keep this promise to participants:

- **Element I.8.B.** In studies where Sponsors conduct research site monitoring visits or conduct monitoring activities remotely, the Organization has a written agreement with the Sponsor that the Sponsor promptly reports to the Organization findings that could affect the safety of participants or influence the conduct of the study.

- **Element I.8.C.** When the Sponsor has the responsibility to conduct data and safety monitoring, the Organization has a written agreement with the Sponsor that addresses provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to the Organization.

While the statement in the ICD is simple, negotiations between the research site and the sponsor about how to address the requirements of these elements can be complex. For example, determining the meaning of "promptly" in I.8.B may depend on the nature of the study and require negotiation. (AAHRPP Tip Sheet 25 offers suggestions for model language in these matters.) Another complication is that sponsors often do not describe operations of their data monitoring committees (DMCs) in the protocol or CTA, and may not even write DMC operating procedures until after the study is underway.

The 2011 revision of the AAHRPP standards contains a new element, I.8.E, that is not based on FDA regulations: "When participant safety could be directly affected by study results after the study has ended, the Organization has a written agreement with the Sponsor that the Researcher or Organization will be notified of the results in order to consider informing participants.” This contract provision may not have a counterpart in the ICD, but it has the effect of extending the promise made in the ICD to future findings. The AAHRPP standard requires the IRB to ensure compliance even though this protection does not have to be in the ICD. When successfully negotiated into a contract as a survival clause, it is often coupled with a specific time frame, which the AAHRPP standard does not address. In some cases, such a clause might not be necessary, as when alarming information about a “successfully concluded” trial would likely emerge in professional journals or the popular press. However, the provision could become necessary when information about risks emerges after closing a Phase 1 or 2 trial that is not pursued because the results suggest it is not feasible to continue to Phase 2 or 3.

**Good Clinical Practice**

Who can object to something that is “good?” While agreeing in a CTA to follow Good Clinical Practice is reasonable, albeit undefined, agreeing to observe ICH-GCP (E6) is problematic
for several reasons. First, ICH is an abbreviation for International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use\textsuperscript{10}, so referring to it in a contract to conduct research on a medical device raises questions about applicability. (There are corresponding ISO standards for medical devices\textsuperscript{11}, but they are rarely used in the U.S.) Second, adherence to ICH-GCP (E6) is not required for submissions to the U.S. Food and Drug Administration. Rather, investigators are required to obtain informed consent according to FDA regulations at 21 CFR 50 and to conduct drug research according to 56 CFR 312 regulations and medical device research according to 56 CFR 812 regulations. And, although most FDA requirements for investigators and IRBs are consistent with E6, several elements of E6 are absent from FDA regulations.\textsuperscript{12,13} To complicate matters, many institutions have elected to incorporate some of these E6 requirements into their procedures, such as E6 (4.8.11), which requires that research participants receive a signed copy of their consent forms.

Thus, while it is acceptable, even laudable, to develop procedures that go beyond FDA regulations, problems can arise when an institution commits to observing ICH-GCP (E6) without limitation. For example, E6 (4.3.3) recommends that “the investigator inform the subject’s primary physician about the subject’s participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.” IRBs do not usually inquire whether an investigator, who is, say, a cardiologist, plans to discuss a research protocol with participants’ primary physicians. Indeed, it might be especially difficult for a researcher to comply with the recommendation when enrollment must occur within a short time window. As another example, E6 (4.8.10) requires that “Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:…..(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.” IRBs do not typically require a description of the risks and potential benefits of alternative treatments in ICDs. Indeed, consent form templates provided by sponsors seldom contain much information about alternative treatments that might be available. However, if something goes terribly wrong, an injured subject who managed to see the protocol or the CTA specifying E6 could claim that he or she was not adequately informed per the investigator and institution agreement in the CTA. (The protocol is typically an appendix to the CTA.) For example, an injured subject might say:

\begin{itemize}
  \item My family doctor said that if he had known about this experiment he would have told me to stay away from it!
  \item or
  \item Had the doctor described the risks and potential benefits of approved drugs for my condition, I would have taken them instead of signing up for this experimental concoction that ruined my life.
\end{itemize}

Many IRBs now state publicly or in their approval letters that they follow ICH-GCP (E6) only to the extent that it is consistent with FDA regulations. Whether this provides sufficient cover for a situation that contractually obligates an institution to follow E6 is not clear. (For example, an E6 guideline that goes beyond FDA regulations could still be consistent with those regulations.) Even if E6 compliance is successfully negotiated out of a CTA, a reference to it in the protocol can still cause liability problems. In this regard, note that the most common citation in FDA warning letters to investigators is "failure to follow the protocol."

In summary, institutional policies should clearly specify whether pharmaceutical research will be conducted according to ICH-GCP (E6). If it does, then IRB procedures and consent templates should be consistent with the provisions of E6. If it does not, then the IRB (or
someone in the HRP department) should verify that CTAs, ICDs and protocols are scrubbed of all references to following E6 without a qualification like “...only to the extent consistent with FDA regulations.”

**Unethical Inducements**

The IRB may wish to examine the CTA to determine whether the sponsor is offering the site and/or investigator unethical inducements, such as bonuses for enrolling subjects or unreasonably large compensation. These issues are addressed in AAHRPP Element II.3.C.1: “The IRB or EC (Ethics Committee) has and follows written policies and procedures to review proposed participant recruitment methods, advertising materials, and payment arrangements and determines whether such arrangements are fair, accurate and appropriate.” This element is based on FDA regulations (21 CFR 56.111) on recruiting participants. However, any recruitment bonuses are unlikely to appear in the CTA or budget (they are, after all, considered unethical by the AMA\(^\text{14} \)) , and the IRB might have to rely on specific questions in the application form to elicit this information. Furthermore, it is not uncommon for bonuses to be offered *after* a trial starts, for example when recruitment lags behind original projections; consequently, an IRB might inquire about any changes in financial arrangements as part of continuing review.

**Billing for IRB Services**

Most IRBs charge for reviewing industry-sponsored research, and many research sites include these fees as “pass-through costs” in the budgets negotiated with sponsors. However, difficulties can arise if the contract specifies payment of an *approval* fee rather than a *review* fee. For example, the sponsor may decide to pull a study from a site because the IRB requires too many changes in the consent document or insists on more stringent monitoring. Beyond the practical concern is an ethical issue about what the IRB really does and what the sponsor should be paying for.

**Remedies**

Many industries — airlines and construction, for example — use checklists to synchronize processes.\(^\text{15} \) Cooper has developed a checklist that covers many of the matters discussed in this article\(^\text{16} \), and it can be adapted to different administrative styles. For example, a checklist can specify when people in the business office and the research office should consult on terms for injury language. Alternatively, the IRB might rely on an institutional policy requiring that the person presenting a contract to a signatory official give assurance that he or she has personally checked the relevant documents and determined that they are in agreement.

Regardless of what methods are implemented, persons responsible for checking and comparing documents and making necessary assurances to the IRB should be trained in what to look for, and the entire process should be subjected to follow-up audits to determine whether it is working as planned.

**Conclusion**

The CTA and, to a lesser extent, the trial budget contain information that an IRB must rely on when deciding whether to approve a clinical trial. It is probably not necessary for IRB members to see the actual CTA, but someone needs to ensure that the CTA, protocol, budget and ICD are all consistent with regulations, AAHRPP standards, and among
themselves on several important points that can affect participant safety and welfare...and institutional liability.

References

2. MAGI. Model Clinical Trial Agreement. 2011.

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