

**Comparison of Provisions from
Institute of Medicine’s Forum on Drug Discovery, Development and Translation’s
template “Clinical Trial Agreement”
and
NCI CEO Roundtable on Cancer’s
“Proposed Standardized/Harmonized Clauses for Clinical Trial Agreements”**

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Revised October 8, 2009**

The IOM template is a complete agreement intended as a fair starting point for negotiations of phase 2 and 3 multi-center, clinical trials conducted under a company’s protocol (ie, company-sponsored). It was developed in a series of meetings with representatives of several universities and several pharmaceutical companies, but without formal endorsement by either the universities or the companies. The aim was to reduce negotiation time by developing a common starting point. It was not expected that every company or every academic center would agree to every provision verbatim, and recognized that some of the terms could not be accepted by some organizations for legitimate legal or policy reasons. The IOM template is annotated with comments in those places where variations may need to be considered.

In contrast, the NCI CEO Roundtable document includes only selected contract clauses, i.e. those provisions that most often cause negotiation delays. The NCI document comes in two flavors – one for company-sponsored studies, and the other for investigator-initiated studies for which a company is providing drug and/or funding.

The following compares the NCI proposed clauses for Company-Sponsored Clinical Trial Agreements with the corresponding provisions of the IOM template.

Intellectual Property:

The IOM template grants the Sponsor title to inventions made in the Study that relate to the Study Drug and to inventions made by use of the drug in violation of the protocol. For that set of inventions assigned to Sponsor, the Sponsor grants back to Institution the right to use those inventions for non-commercial research and for patient care purposes. The Sponsor is granted a first option to license, on reasonable terms negotiated diligently in good faith, Institution’s rights in any other inventions made in the Study. Should the parties be unable to reach agreement on licensing terms, then Sponsor is granted a one-year, right of first

¹ This document is based upon an earlier version prepared for the Institute of Medicine’s Forum on Drug Discovery, Development and Translation. The views expressed are those of the author, and do not necessarily reflect the views of the Institute of Medicine, others who worked on the IOM template agreement, or Duke University.

refusal before Institution licenses that invention to any third party on more favorable terms than last offered to Sponsor.

The NCI CEO clause grants the Sponsor title to all inventions arising from the Study, but with a grant back giving the Institution rights to use those inventions for Institution's internal, non-commercial research and for educational purposes.

Comment: The NCI CEO clause grants much broader rights to Sponsor by requiring the Institution to assign its rights in all inventions to the Sponsor. The IOM template notes that even the somewhat more limited rights granted by that document may conflict with IRS guidelines on use of facilities with tax exempt bonds, when that funding has been used to finance the facilities in which the Study is conducted.

Subject Injury:

The IOM template provides that the Sponsor shall reimburse cost of medical expenses to treat any injury or illness that is directly related to administration of the Drug or the proper performance of a protocol procedure, so long as the protocol has been adhered to and any written instructions from Sponsor followed.

The NCI CEO clause has a similar provision.

Comment: Although the IOM template does not require the Sponsor to pay expenses that have already been paid by a third party (ie, insurance), neither conditions the Sponsor's obligation on charges being first submitted to a Subject's insurance.

Indemnification:

In the IOM template, the Sponsor provides indemnification against claims of bodily injury or property damage arising from administration of the Drug or proper performance of any protocol procedure, except if caused by (i) a failure to follow the protocol, accepted medical practice, or applicable law or regulation, or (ii) negligence or willful misconduct by the Institution or its personnel. The Institution provides a reciprocal indemnification to Sponsor to the extent a claim arises from (i) or (ii). The provision includes a requirement that both the Sponsor and the Institution carry adequate liability insurance and provide a certificate of insurance upon request.

The NCI CEO clause is similar, except that the Sponsor's indemnification is more limited reaching only to personal injury or death to a study subject and claims arising from the Sponsor's use or publication of the Study data. This document does not include an insurance provision.

Comment: The IOM template recognizes that many state institutions cannot provide the reciprocal indemnification, and that some require reference to specific types and amounts of insurance. The NCI CEO clause gives significantly less protection to those performing commercially-sponsored clinical research than does the IOM template.

Data:

The IOM template distinguishes between “Study Deliverables”, which are case report forms, electronic databases created under the protocol and Study reports prepared by Institution for Sponsor, and “Source Documents” as defined in the ICH GCP guidance. The Sponsor owns Study Deliverables, the Protocol and other materials provided by the Sponsor; the Institution owns Source Documents and other documents prepared by Institution that are not Study Deliverables. The Sponsor has the right to use the information and data contained in the documents owned by the Institution, subject only to applicable laws and regulations and the terms of the informed consent granted by the Study subjects. The Institution agrees not to provide data from Source Documents to a third party in a manner that would allow the third party to reconstruct the Study, except in connection with peer review of a Study publication. The Institution shall store all data and records as required by applicable laws, regulations and the Protocol for the time required by law or regulation, and, at Sponsor’s request and expense, up to three years longer. The Institution will notify the Sponsor before destroying any Study Deliverables.

The NCI CEO clause defines “Medical Records” as medical records connected with the Study, such as treatment entries and diagnostic images, and “Study Data” as all other records and reports required to be delivered to the Sponsor pursuant to the Protocol. The Institution retains title to all Medical Records; the Sponsor to all Study Data. The Institution provides copies of all Study Data to the Sponsor and provides the Sponsor with access to the Medical Records for monitoring purposes. The Institution is granted the right to use the Study Data for its internal, non-commercial research and for educational purposes and for preparation of publications, subject to the confidentiality and publications provisions of the agreement. The Institution shall store all data and records as required by applicable law and regulations and for such additional period as may be requested by the Sponsor, but at Sponsor’s expense. Institution will notify the Sponsor before destroying any Medical Records or Study Data.

Comment: Although the details are somewhat different both provisions attempt to distinguish between records created uniquely for the study (ie, Study Deliverables and Study Data) and those that may be associated with the Study but are created in the course of the Institution’s normal operations (ie, Source Documents and Medical Records). In both cases the Sponsor is granted the right to use all information relating to the Study, although in the IOM template that right is

subject to the terms of the informed consent and HIPAA authorization. Other sections of both documents address uses of the various data forms in publications.

Confidentiality:

The IOM template has a one-way confidentiality provision defining Confidential Information as that information provided by the Sponsor to the Institution and the Study Deliverables (see Data discussion above). Any information provided by Sponsor must be marked as such or confirmed in writing to be considered confidential unless it would generally be regarded as confidential. The confidentiality obligation extends to five years after termination of the agreement. During this period, the Institution may not disclose the information to any third party, and may not use the information except for the performance of the Study, related patient care, clinical or educational purposes and in research not funded by a for-profit entity. The Institution may use the Confidential Information for publications prepared in accordance with the Publication provision. The Confidentiality provision has the usual exceptions to confidentiality and permits disclosures for such things as Informed Consent discussions with Study subjects, as needed for medical treatment of a Subject, and as may be required by law or order of a governmental authority. Both the Sponsor and Institution agree to maintain the terms of the agreement in confidence. Upon termination the Institution must return any Confidential Information provided by the Sponsor unless retention is required by applicable law or regulation.

The NCI-CEO clause also has a one-way confidentiality provision defining Confidential Information as everything disclosed by Sponsor to the Institution, plus Study enrollment information, information on the status of the Study, regulatory communications, the regulatory status of the Study Drug/Device, the Study Data, and Inventions. The clause does not have a marking requirement. The confidentiality obligation extends to five years after termination of the agreement. During this period, the Institution may disclose the information only on a “need to know” basis within the Institution, and may not use the information except for the performance of the Study, for defined publication purposes, and as may be required by law. The Institution must destroy, or return to Sponsor, all Confidential Information, except Study Data, upon the earlier of the Sponsor’s request or termination of the Agreement.

Comment: The IOM template notes that some Institutions are subject to public records laws that will not permit the terms of the Agreement to be kept secret. Both documents have broad confidentiality obligations with five year durations, but are reasonably clear that the obligations won’t be used to block publication of the research results.

Publication Rights:

The IOM template provides that if the Study is a multicenter one, then the individual Institution will not publish anything relating to the Study until after the earlier of a peer-reviewed, multi-center publication or twelve months after the Study database being finalized. At that time the Sponsor agrees to cooperate with one or more of the Study investigators to enable publication of the multi-center results, including multi-center supporting data within the next twelve months. The Sponsor is granted 30 days in which to review any proposed publication (15 days to review abstracts, presentations and posters), plus an additional 60-day delay if required for patent applications to be filed. The Institution agrees to consider the Sponsor's comments in good faith and to remove any Confidential Information as requested by Sponsor, except analysis of Study results, a summary of the Protocol, and supporting data and identifying information regarding the Study Drug as reasonably required for publication. This document requires the Sponsor to register the study in accordance with ICMJE requirements.

The NCI-CEO clause provides that if the Study is a multicenter one then the individual Institution will not publish anything relating to the Study until the earlier of a multi-center publication or eighteen (18) months after completion of the Study at all sites. The Sponsor is granted 30 days in which to review any proposed publication and may require either removal of any Confidential Information, other than Study Data, or an additional sixty-day delay to allow patent filing. Unpublished Study Data remains confidential until released only through this process. The clause requires the Sponsor to register the trial in accordance with applicable laws and regulations, but does not require that registration to be compliant with the standards of the International Committee of Medical Journal Editors (ICMJE). The clause forbids any media interviews or other interactions relating to the study, except with the Sponsor's consent.

Comment: Neither provision address the possibility of a central, academically-controlled publications committee, although the IOM template does require the Sponsor to cooperate by providing data to a group of investigators if there has not been a peer reviewed, multi-center publication within one year of the study database being finalized. The IOM requires registration in accordance with the ICMJE guidelines which are more stringent than the regulations referred to in the NCI-CEO clause.

Miscellaneous:

Order of Precedence: The IOM template has the Agreement control in case of conflict with the Protocol. The NCI CEO clause has the Agreement control as to legal issues and the Protocol control as to treatment of Study subjects.

Compliance with Laws: The IOM template requires both the Sponsor and the Institution to comply with all applicable laws and regulations and to conduct

Study-related activities in a manner consistent with the Informed Consent. The NCI CEO clause places the obligation only upon the Institution, and also requires compliance with good clinical practices, which the IOM template references as a possible requirement. A statement of the Sponsor's compliance with all applicable laws and regulations is important for an AAHRPP accredited institution.

Company Review of Informed Consent Form: The IOM template requires the Institution to seek IRB approval of an informed consent that is mutually acceptable to the Sponsor and the Institution. The NCI CEO clause gives the Sponsor review rights with respect to the Informed Consent. In the latter, if the Sponsor identifies any inconsistency between the Informed Consent Form and the Agreement, and the Institution doesn't correct the inconsistency, then the Sponsor may terminate the Agreement.

Human Subjects Protection Standards: Neither the NCI-CEO clauses nor the IOM template fully addresses the standards required for accreditation by the Association for Accreditation of Human Research Protection Programs (AAHRPP).

HGS: 10-8-09