Clinical Trial Contracts: A Discussion of Four Selected Provisions

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Clinical Trial Contracts: A Discussion of Four Selected Provisions

Virtually every day, across the country, Academic institutions and pharmaceutical companies enter into clinical trial contracts. Yet, more often than not, negotiating the contract is a contentious exercise, as each side has different goals as it enters into this relationship. Often the principal investigator has some goals that differ from those of the institution that represents him or her, and investigators feel frustrated and isolated throughout this process. Reaching consensus—even on a limited set of issues—continues to pose an extraordinary burden. Recently, the challenges of negotiating contracts with pharmaceutical companies have been recognized and written about in numerous publications, and there are anecdotal reports of a variety of groups throughout the country looking at ways to improve the process. While acknowledging that there is no single correct way to approach a contract negotiation, this paper is meant to provide researchers, administrators, lawyers, and others who engage in a clinical trial contract negotiations with a single document that contains relevant information intended to make the process easier.

New England Journal of Medicine Editor-in-Chief Jeffrey Drazen wrote that “the system would be better served if there were universally accepted contractual language that protected patients’ confidentiality and any proprietary aspects of the data, while ensuring that academic investigators participating in clinical trials have full and unfettered access to the data. If universally adopted, such language would help safeguard the integrity of the research process.” Finding universally accepted language is a laudable goal, but the difficulties in doing so—and possible constraints that anti-trust laws may impose—make it hard to attain.

This paper takes a first step by focusing on four contract areas—intellectual property, publication rights, medical care for research participants, and indemnification—and providing for each: (1) a brief elucidation of the academic and industry perspectives that lead to key areas of disagreement; (2) a checklist of topics that should be addressed by every contract; and (3) sample contract language. Some of this information may appear obvious, but it is hoped that Academic institutions that approach a negotiation well-informed about each side’s perspectives and interests will be better prepared to move forward quickly and conclude the process expeditiously.

1. Intellectual Property

Academic Perspective
Academia’s mission is based on the generation and dissemination of new knowledge through research and teaching. The clinical trial is an integral component of this mission. Principal Investigators (PIs) bring a wealth of knowledge and experience to clinical trials, and the academic site has an infrastructure that can support the trial. The relationship between the Sponsor and the academic site is one of partnership—a Sponsor and the medical center engage in a research enterprise.

With regard to any intellectual property that may result from the trial, academic sites contend that the Sponsor owns only what it developed as specified by the protocol and the Investigator’s Brochure. Academia is not compensated to develop new intellectual property for the Sponsor, so if anything unanticipated results from the project (e.g., a use patent), property rights should be determined in accordance with patent law. Academic sites argue that the Sponsor should have the first option to enter into good faith negotiations for an exclusive license. A fair license agreement should take into account the relative contributions of the parties to the invention. If the Sponsor fails to license the discovery within an original option period, the Sponsor should have no further rights. To provide the Sponsor with an opportunity to match a third party’s subsequent license offer undermines the ability of the academic site to freely negotiate with others in the event the Sponsor does not exercise its license option during the initially agreed to time.

There also is concern within academia that an investigator’s related on-going research might overlap with the industry-funded clinical trial. To avoid potential conflicts with other projects, and to protect investigators’ and Academic institutions’ options for patent or copyright, academic sites must avoid overly broad language on intellectual property issues. State Academic institutions may function under state laws that contain special restrictions on their ability to transfer patents, copyrights, or other intellectual property.

Industry Perspective
Industry argues that ownership of the inventions that arise from the clinical trial is critical to its ability to commercialize the inventions. Companies believe that their substantial intellectual and financial investments in product development and their assumption of all of the risk and liability associated with product development give them the rights to any discoveries made during a clinical trial that might lead to a
copyright or a patent. Industry argues that commercialization is its primary business function and is an activity for which it is better equipped than academia. If an invention during a clinical trial relates to the study drug or device, the company should have all rights to it. Should a Sponsor fail to exercise its license option during the period provided in the contract, industry believes the Sponsor should retain the right to match a third party’s subsequent license offer.

Industry believes that the study sites, whether academic or not, are working for it and are paid to conduct the Sponsor’s clinical trial. Industry often provides academic researchers items such as unapproved drugs that, but for the research agreement, would be otherwise unavailable to the researcher. Industry believes that the study site should not do anything with the study drug other than what is called for in the protocol.

These differing perspectives have lead to the following key areas of disagreement:

Use Patents: Some contractual issues may be relatively easy to resolve, while others will remain difficult. In the latter category is ownership of what are popularly called “use patents,” where in the course of a trial, though not as part of a protocol, an investigator discovers a new use for something, such as a drug. An example of what may become a “use patent” was the recent subject of an article in AMNews which reported that “conversations between physicians and male patients over prostate health are likely to become more complicated given new findings that a drug now used to forestall balding and improve urinary flow may also prevent prostate cancer.” (July 14, 2003, p. 24) In other words, wholly outside the protocol, but in the course of observing the clinical trial participant, an observation has been made by the researcher that suggests a wholly novel and unanticipated use for the drug.

Pharmaceutical companies feel strongly that all rights to any uses of the drug or substance for which they hold a patent belong to them, and that they should at least be given an option for an exclusive license. Academic institutions believe just as strongly that anything discovered during the trial but outside the protocol belongs to them since it is through their work and expertise wholly outside of what is called for in the protocol that the discovery is made.

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A contract should: (1) define what type of discovery(s) may be eligible for a “use patent;” (2) provide that when such a discovery occurs in the course of conducting a protocol, ownership belongs to the Academic institution; and (3) give the Sponsor an option for an exclusive license that must be exercised within a pre-determined period of time.

**Ownership of genotypic information.** When genotypic information is discovered in the course of a trial, most Academic institutions believe that, as a matter of public health, it should be openly available or, if owned, rights to restrict use of that information should be focused on highly specific and demonstrated tangible utility, and be time-limited. The pharmaceutical industry believes that the trial Sponsor should own such information.

**Suggestion:** A contract should: (1) define “genotypic information” and (2) provide that rights to restrict use of that information be focused on highly specific and demonstrated tangible utility, and be time-limited.

**Definition of “Confidential information”:** The Sponsor wants the broadest possible definition, so that “confidential information” includes all materials the Sponsor provides to the investigator with regard to the study and all information and data generated by the study. Academic institutions want a narrow definition agreed to in writing that will decrease the risk of accidental disclosures and permit publication of results without causing a breach of confidentiality.

**Suggestion:** Define “confidential information” to include all materials, documents, and information disclosed by Sponsor to Academic institution that is marked “Confidential.” Information that is disclosed orally or visually and identified as confidential at the time of disclosure, must be reduced to writing within 15 days of such disclosure. Confidential information shall not include:

a. Information that is in the public domain, or enters the public domain through no fault of the Academic institution or study site;

b. Information that is known or becomes known to the Academic institution from independent sources;

b. Information that is required to be disclosed by law, rule of court, or regulation, but only to the extent required for such disclosures;
d. Information that is independently developed by investigators at the study site; and

e. Information that was in the possession of Academic institution prior to the date of disclosure.

In light of the federal HIPAA Privacy Rule, and state privacy laws, consideration also should be given to incorporating a provision by which both parties agree to abide by any applicable state or federal laws or regulations governing the protection of individually identifiable patient information.

**Every clinical trial contract should address the following:**

- Scope of the definition of inventions (this is particularly important when the researcher is working on more than one project simultaneously); determination of inventorship.
- Disclosure of inventions/discoveries/improvements
- Ownership of:
  - inventions/discoveries/improvements (includes scope of the project)
  - an invention that is made outside the protocol but is conceived and reduced to practice in the course of the study
  - a serendipitous discovery made in the course of following the protocol
- Licensure
  - Amount of time given to exercise option for licensure; amount of time for which the option lasts
  - Whether the license is exclusive or not
  - Who pays costs of patent applications?
  - What happens if licensing negotiations break down? Does the site have obligations to Sponsor?
- Define “confidential information”; amount of time provided for Sponsor to verify confidentiality (e.g., 30 days) NOTE: Some parties may wish to put the definition of “confidentiality” in a separate section of the contract.
Agreement to abide by state and federal confidentiality laws about individually identifiable patient information

Statement of what is not covered under the contract, e.g., existing inventions of the parties; information publicly available prior to date of the agreement or that becomes publicly available through no wrongful act of the recipient; information known to recipient prior to the date of disclosure; information disclosed by any recipient with prior written approval; information that is independently developed; information that is required to be disclosed by law or court order

**Sample Contract Language** *(Note: as with any well-drafted contract, it will be necessary to define essential terms such as “material” and “information.”)*

a) All inventions made in the direct performance of the contract will be promptly disclosed to Sponsor. Academic institution shall not obtain or attempt to obtain patent coverage on Sponsor-provided materials or information without the express written consent of Sponsor. All inventions made in the direct performance of the protocol that necessarily use or necessarily incorporate the study drug or device provided by the Sponsor shall be the sole property of Sponsor. In circumstances in which Sponsor desires to secure protection of such inventions, the Academic institution will cooperate with the Sponsor, at Sponsor’s expense, for the purpose of filing and protecting patent applications. Cooperation includes the execution of any and all lawful papers that may be deemed necessary or desirable by Sponsor for the filing and protection of applications and for assignment of the same to Sponsor, including all declarations, oaths, specifications, and instruments of assignment for filing and recordation in the U.S. and foreign patent offices.

b) Discoveries or inventions made by the Principal Investigator or other Academic institution employees that were not anticipated by Sponsor’s protocol, shall be the sole property of the Academic institution. Sponsor shall be given a time-limited first right to negotiate an exclusive, royalty-bearing license to make, use, and sell such patentable inventions made in the course of the work conducted under this agreement.

c) All other discoveries made by one or more employees of Academic institution and one or more employees of Sponsor shall be owned jointly by Academic institution and Sponsor. Sponsor shall be given a time-limited option to
negotiate an exclusive license to Academic institution’s rights in any other inventions.

d) Nothing contained in the agreement shall be deemed to grant either directly or by implication, estoppel, or otherwise any license under any patents, patent applications, or other proprietary interests to any other inventions, discoveries, or improvements of either party.

2. Publications

General Comment
Scientific papers may not be acceptable to high quality peer-reviewed journals if the Sponsor has more than a certain limited degree of control over content and the decision to publish. Submitted papers must be in compliance with the Uniform Standards for Manuscripts Submitted to Biomedical Journals developed by the International Committee of Medical Journal Editors. When the Uniform Standards were revised in 2001, editors of thirteen leading biomedical journals wrote that:

[W]e strongly oppose contractual agreements that deny investigators the right to examine the data independently or to submit a manuscript for publication without first obtaining the consent of the sponsor. Such arrangements not only erode the fabric of intellectual inquiry that has fostered so much high-quality clinical research, but also make medical journals party to potential misrepresentation, since the published manuscript may not reveal the extent to which the authors were powerless to control the conduct of a study that bears their names. . . Many of us will ask the responsible author to sign a statement indicating that he or she accepts full responsibility for the conduct of the trial, had access to the data, and controlled the decision to publish.”

Academic Perspective
The Academic institution cannot accept language that restricts publication in any way. Publication is necessary for the Academic institution to fulfill its academic mission and disseminate the fruits of research. Research integrity is the cornerstone of the academic endeavor, and Academic institutions must demonstrate that research is being conducted in an unbiased manner, irrespective of the funding source. The key way Academic institutions demonstrate this is by having an unrestricted ability

to publish the methods, data, and results of the research. Some argue that research on human subjects that is not published is unethical; first, by needlessly exposing subjects to risk without benefit to general knowledge and second, by risking exposure of others because the research results are not available. If a Sponsor requires the investigator to transfer a copyright to it, it is unclear how this would affect the attitudes and judgments of peer-reviewed journals regarding the appropriateness of the publication by the Academic institution-based investigator. An additional consideration is that the ability to publish shows that a research activity is related to the tax-exempt purpose of the institution and does not suggest factors that might implicate the unrelated business income tax.

Lead investigators must have access to all of the primary data. In turn, they must accept responsibility for the integrity of the data, the analyses, and the conclusions. A Sponsor may have a time-limited right to review a manuscript, but not the right to either approve or consent to publication. A Sponsor’s objections to publication should be limited to sections of manuscripts that contain information that has previously been marked as “confidential information” or that affect the Sponsor’s ability to protect patent or other intellectual property rights as covered under the agreement. The right to publish is rendered meaningless unless confidentiality protections extend only to Sponsor-provided information and not to data generated at the site or to study results. As long as the standard used to determine what will be deleted is objective, deleting a Sponsor’s confidential information is acceptable.

The Academic institution recognizes its obligation to not knowingly jeopardize the Sponsor’s intellectual property rights. From the Academic institution’s perspective, a Sponsor’s objection to publication can be addressed in several ways: (1) the Academic institution will proceed with publication; (2) the dispute will be submitted to a mediator/arbitrator for a brief time specified in advance; or (3) a decision about how to proceed will be made by a publications committee that includes a Sponsor representative as one of its members. If there is a publications committee, the majority of the committee should be comprised of independent representatives.

In the case of multi-site trials, the first publication should represent the work from all sites. If there is no multi-site publication within one year after termination of the study, an investigator should be able to petition the Sponsor for access to all data from all sites, which could be used to interpret the data from the investigator’s site. The investigator would then be free to publish the methods, data, and results of the study. Contract language should state that publications will conform to requirements under the Uniform Standards for Biomedical Journals.
Publications issues also may arise in the context of copyright discussions. Academia often sees copyright as a contentious topic because it affects publication. If the Academic institution gives away copyright privileges, it may preclude the ability to publish, which is vital to the Academic institution and researcher. It is important to recognize that most major journals require the transfer of copyright from the investigator to the journal in order for the information to be published. An example is the following excerpt from the JAMA publication requirements, which uses the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (over 500 journals use the Uniform Requirements):

**Copyright Transfer.** In consideration of the action of the American Medical Association (AMA) in reviewing and editing this submission (manuscript, tables, and figures), the author(s) undersigned hereby transfer(s), assign(s), or otherwise convey(s) all copyright ownership, including any and all rights incidental thereto, exclusively to the AMA, in the event that such work is published by the AMA.¹⁴

Even in the academic community this transfer of copyright is not uniformly supported. For example, the recently launched Public Library of Science (PLoS) allows authors to decide whether to retain copyright or transfer copyright to his/her institution or to PLoS. Regardless of who owns the copyright, PLoS requires authors to grant to the public domain an irrevocable license to print, copy, or use the work in any lawful way, subject to the condition that proper attribution is given whenever the work is reproduced or redistributed.

**Industry Perspective**

It is critical that clinical trial results are made available in a timely manner to communicate important new information to the medical community, patients, and the public at large. As Sponsors of these clinical studies, industry is responsible not only for the design and conduct of ethical, scientifically rigorous clinical trials, but also for the receipt and verification of the data from these trials. Industry also ensures the accuracy and integrity of the entire study database, which the Sponsor owns. Industry is committed to the timely communication of meaningful results of controlled trials, regardless of the outcome, through publication in peer-reviewed journals, abstract submission with a poster or oral presentation at scientific meetings, or


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through some other means. In all cases, the study results will be reported in an accurate, objective, balanced, and complete manner.

Some studies that Sponsors conduct are exploratory in nature and primarily serve the purpose of generating hypotheses for possible future trials. Because these trials may be highly proprietary, Sponsors do not commit to make the results of these studies immediately available, unless they generate information of significant medical importance.

PhRMA has published a set of Principles\(^5\) that states:

> As owners of the study database, sponsors have discretion to determine who will have access to the database. Generally, study databases are only made available to regulatory authorities. Individual investigators in multi-site clinical trials will have their own research participants’ data, and will be provided the randomization code after conclusion of the trial. Sponsors will make a summary of the study results available to the investigators. In addition any investigator who participated in the conduct of a multi-site clinical trial will be able to review relevant statistical tables, figures, and reports for the entire study at the sponsor’s facilities, or other mutually agreeable location.” (pages 22-23)

PhRMA Principles also address the issue of Sponsor review as follows:

> Sponsors have the right to review any manuscripts, presentations, or abstracts that originate from our studies or that utilize our data before they are submitted for publication or otherwise communicated. Sponsors commit to respond in a timely manner, and not to suppress or veto publications or other appropriate means of communication (in rare cases it may be necessary to delay publication and/or communication for a short time to protect intellectual property). Where differences of opinion or interpretation of data exist, the parties should try to resolve them through appropriate scientific debate. (PhRMA Principles, pages 23-24)

Companies also are concerned about less formal disclosures of confidential information, such as casual discussions among faculty researchers, and worry that pro-

proprietary corporate information shared with an Academic institution scientist in a collaborative project might leak to the public or to competitors⁶.

In summary, industry and academia differ in their perspectives on publication rights in the following key areas: the amount of time provided for Sponsor to determine what is confidential, including the protection of intellectual property; investigator access to data from multi-site studies; and control of information, as evidenced in part by issues about deletion of confidential information and control and timing of publication.

The July 2003 meeting hosted by the Association of American Medical Colleges (AAMC) and the Pharmaceutical Research and Manufacturers of America (PhRMA), “Addressing the Issues: Academic and Industry Perspectives on Clinical Trials,” brought together approximately 100 individuals from academia and pharmaceutical companies to discuss some of the most pressing issues presented by industry-sponsored clinical trials. The meeting provided general sessions to address broad issues, and workshops in which individuals from pharmaceutical companies and Academic institutions discussed issues of mutual importance. The group examining publications issues agreed on the following:

1. Decisions about publication and authorship should be made in the course of planning the protocol.
2. Not every investigator is an author.
3. Each author must have access to the database and not simply to summary tables.
4. The Sponsor should have the right to review a manuscript being sent for publication without the right to veto publication. However, Sponsor concerns about publication of proprietary information need to be addressed, and the Sponsor may request that the review of the database take place at the Sponsor’s location rather than sending the database to each investigative site.
5. Journal editors need to be encouraged to accept the results of negative trials, and/or there should be a registry of data from failed trials.

In summary, the group urged that the issues around publication of industry-sponsored trials be marked by greater levels of transparency, including the creation

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of publication committees for most multi-site trials, earlier involvement of authors in the manuscript process, access to the study database by all authors, making available study results to all investigators pre-publication, and broad agreement to follow the CONSORT guidelines. The group was unanimous in urging that publication issues be addressed in the contract, and that protocol language be consistent with contract language.

**Suggestion:** In accord with the International Committee of Medical Journal Editors requirements on publication ethics, the contract should specify that researchers will have free access to the data and will be able to analyze the data independently, to prepare manuscripts, and to publish them.

**Every clinical trial contract should address the following:**

- Academic institution/PI's right to publish/present or otherwise disseminate at symposia
- Academic institution/PI's access to data from other sites when participating in multi-site study
  - Specific requirements related to investigator’s right to publish data from a multi-site trial
  - What happens if investigator has a good faith belief that early publication is important for reasons of public health, safety, or public welfare
- Sponsor's right to review
  - Substantive comment vs. editorial changes
  - Reasonable consideration of Sponsor's comments
  - Amount of time allowed for review (30-90 days is “standard acceptable publication delay”)
- Determination of authorship, and order of authors’ listing, in regard to publications resulting from multi-site trials

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7 CONSORT: The Consolidated Standards of Reporting Trials was developed by a group of investigators and medical journal editors. It is supported by the International Committee of medical journal Editors. It consists of a checklist and flow diagram for reporting on randomized controlled trials.

8 The University Industry Research Collaboration Initiative, op cit. p.52
Amount of time Academic institution/Sponsor will withhold submission in order for Sponsor to seek patent protection

Definition of “confidential information”

**Sample Contract Language:**
Publication, presentation, or use must not disclose any confidential information furnished by Sponsor. The Academic institution agrees that any proposed publication or presentation relating to the study conducted under this agreement will be submitted to Sponsor for review at least 30 days prior to submission for publication or presentation. In the event that the proposed publication or presentation contains patentable subject matter or other confidential information that needs protection, the Academic institution will, upon written request from Sponsor within the 30 day review period, delay the publication or presentation for a maximum of an additional 60 days to allow Sponsor or the Academic institution to file a patent application. Such Sponsor required modifications will not result in withholding any study results from academic publication.

Academic institution agrees that at Sponsor’s request during the initial thirty (30) day review period, the proposed publication will be modified to delete Sponsor-provided confidential information and/or to present the clinical study data in a manner that will not compromise such confidential information.

In the case of multi-site trials, if there is no multi-site publication within one year after termination of the study, the Investigator may petition the Sponsor for access to all data from all sites. The Institution and the Investigator agree that the first publication of the results of the Study shall be in conjunction with the presentation of a joint, multi-center publication of the Study results, with the investigators from all appropriate sites contributing data, analyses, and comments. Such publication shall not disclose any of Sponsor’s proprietary information, as defined in this Agreement. However, the one year delay in publication or presentation shall be waived if the investigator has a good faith belief that publication or presentation should not be delayed for reasons of public health, safety, or public welfare.
3. Indemnification

Academic Perspective
Academic institutions take the position that indemnification should be provided in consideration for undertaking a study and using the Sponsor’s experimental compound or device and the Sponsor’s protocol. They also may believe that they have no obligation to assume responsibility, that is, to relinquish any demand for indemnity from the Sponsor, on account of conduct other than their own institutional negligence, recklessness, or willful misconduct. In some jurisdictions, under some circumstances, employers are not responsible for the willful misdeeds or misconduct of their employees. Any exception to the Sponsor’s obligation to indemnify must be the result of a nexus between the exception and the claims. For example, an Academic institution may fail to obtain proper informed consent from Subject A, but Subject B, from whom proper informed consent was obtained, files a claim. The Academic institution should not be excluded from indemnification for Subject B’s claims because of a problem relating only to Subject A. There should be objective standards to determine the circumstances that warrant indemnification. Making indemnification subject to the “maintenance of proper records,” as industry often wants, is problematic since this is an undefined term and leaves open the possibility that its meaning will be difficult to resolve and subject to reasonable challenge.

When a study is being managed by a Clinical Research Organization (CRO), the agreement between the Academic institution and the CRO may say that the Sponsor will indemnify, but the Sponsor is not a party to that agreement. The CRO should be prepared to present documentation indicating that the Sponsor will indemnify, and that the CRO has the authority to bind the Sponsor to this commitment. Alternatively, the Sponsor can provide the Academic institution directly with a separate letter of assurance.

Industry Perspective
The Academic institution should indemnify and hold harmless the Sponsor for the willful misconduct, negligence, and/or intentional acts of the Academic institution’s agents/employees since it is not possible for the Sponsor to prevent such acts. The Sponsor is willing to indemnify the Academic institution for injuries to patients as a result of the Sponsor’s protocol. Any claims for Sponsor indemnification must be supported by appropriate documentation.
These differing perspectives have lead to the following key area of disagreement: whether the Sponsor will indemnify and hold harmless the Academic institution for the willful misconduct and/or intentional acts of its employees/agents.

**Every clinical trial contract should address the following:**

- Whom the Sponsor indemnifies and holds harmless: Academic institution, Investigator, Subinvestigator, and/or IRB (list of Indemnitees)
- Exceptions to indemnification that should apply if claim or loss is caused by a failure of Indemnitee to comply with some requirement (terms of protocol, regulations, etc.), or claim or loss is due to negligence or the like of Indemnitee
- Conditions required for indemnification (such as notification of Sponsor after notice of claim)
- Specify: (1) who controls defense of the lawsuit, and any limits to that control; and (2) who pays, and under what conditions
- Scope of indemnification
- Insurance requirements
- Survival of obligation to indemnify

**Sample Contract Language:**

Sponsor will indemnify, defend, and hold harmless Institution, its affiliated hospitals, its trustees, officers, agents and employees from any demands, claims, or costs of judgments that may be made or instituted against any of them by reason of injury (including death) to any person or damage to property, arising out of or connected with performance of the clinical study; provided, however, Sponsor will have no liability for loss or damage to the extent resulting from the Institution’s: (1) failure to adhere to material terms of the Sponsor’s Protocol or Sponsor’s written instructions concerning use of the Study drug or device, (2) failure to comply with applicable FDA or other government requirements, or (3) negligence or willful misconduct by the Institution, its trustees, officers, agents, and employees as finally determined by a court of law. Sponsor has the right to select defense counsel and direct the suit. Academic institution must cooperate in the defense.
4. Medical Care of Clinical Trial Participants In The Event of an Adverse Consequence

General Comment
When an adverse event occurs, the issue is rarely whether the Sponsor will pay; rather, the disagreements are more likely to center on the extent to which the Sponsor will pay, including whether the patient’s insurer must be billed first, and whether there will be compensation beyond payment for related medical expenses.

Academic Perspective
If a subject is injured from a drug or procedure that is required only because the subject agreed to participate in the research, the Sponsor should cover the cost of that injury. There have been some recent reports of Sponsors asking the Academic institution to bill the cost of subject’s injury to the subject’s insurance company and then agreeing to pay only for what is not covered by insurance. This is unacceptable from an ethical point of view and is against the policies of some Academic institutions. Additionally, contracts with private insurers may forbid billing for non-covered services, so that the submission of a bill may be seen as an attempt to defraud. Finally, Sponsors should not place dollar caps on medical treatment.

A Sponsor’s claim of patient negligence should be reviewed carefully. Subjects can become confused, misunderstand information presented by the investigator, or the drug may cause forgetfulness. Short of the subject’s willful failure to comply with instructions given by the investigator, the subject should not be found negligent.

The section of informed consent documents describing payment for protocol-induced subject injury should be written in language that is easy to understand and that reflects accurately the language of the clinical trial agreement covering this subject, or other form of Sponsor commitment for payment for subject injury. In the event that a study is given an exemption from this policy, the informed consent documents must state accurately how payment for treatment of protocol-induced injuries will be handled.

Industry Perspective
It is appropriate to provide reasonable medical treatment when a patient is injured during participation in a clinical trial provided that the injury is a result of participation in the trial. It is appropriate for the Sponsor to reimburse the institution for this treatment when the injury is the direct result of the study drug or procedure or the Sponsor’s protocol which the patient would not have undergone in
usual clinical practice. It is not appropriate for the Sponsor to pay for the treatment when it is the result of investigator, investigator staff, patient negligence, or failure to adhere to the protocol or other written instructions of the Sponsor.

These differing perspectives have lead to the following key area of disagreement: The criteria that must be met (e.g., confirmation from an independent physician that an injury resulted directly from the study drug or device; approval rights for treatment for which Sponsor will pay) before a Sponsor will assume responsibility for the costs of adverse events and injuries.

**Suggestion:** The contract should contain a prohibition against billing of patient’s insurer. Financial responsibility for payment of treatment to trial participants resulting from an injury or illness suffered in the course of the trial should rest with the Sponsor.

Additionally, Sponsors should not place dollar caps on medical treatment. If a subject is injured from a procedure that is required only because of the research, the sponsor should cover the cost of that injury.

**Every clinical trial contract should address the following:**

- As required by the FDA, serious adverse events must be reported to the Agency within 24 hours of the principal investigator’s becoming aware of the event. Notice to the Sponsor and the IRB also should occur at this time.

- Scope of what will or will not be covered

- Extent to which participant’s insurance coverage affects Sponsor’s obligations to pay for care

- What Sponsor agrees to do if an adverse event occurs as the direct result of subject’s participation in study

- Payment for diagnosis, medical treatment, and patient care expenses

- Circumstances under which Sponsor will not pay

- Obligation of Sponsor to provide on-going efficacious drug for chronic disorders from the time the trial is completed until the drug is approved for marketing by the FDA
Sample Contract Language:
The Sponsor shall reimburse for reasonable and necessary medical expenses incurred by Research Subjects of Academic institution for any medical care, including hospitalization, in the treatment of adverse reactions arising from study of drugs, devices, or research procedures following their administration in accordance with the Protocol, except to the extent the expenses are attributable to the negligence or willful misconduct of any person in the employ of the Academic institution, as determined by the parties through a process agreed to in advance. Natural progression of an underlying pre-existing condition does not constitute an adverse reaction. No other compensation of any type will be provided by the Academic institution or the Sponsor to the Research Subjects.

Research sites may not be required to bill third party insurance companies in lieu of recovery of these costs directly from the Sponsor. If full coverage for a research-related adverse event has already been obtained from insurance, government programs, or other third parties, the Sponsor shall coordinate payments under the terms of the research subject’s benefits directly with the benefit provider.

Any study-related illness, adverse event, or injury that results in a claim for payment for treatment under the provisions for coverage of research-related injury is considered to be a serious and unexpected adverse event. As required by Federal regulation, these must be reported to the IRB in accordance with the IRB policy and procedure on Adverse Event Reporting, and must be reported to the appropriate Federal authorities, if required under Federal law or regulation.

5. Emerging and Miscellaneous Contracting Issues

Below is a brief discussion of three emerging issues related to clinical trials that may become contentious points when negotiating a clinical trial contract. They are mentioned here to alert Academic institutions to consider how to handle them.

1. Billing the insurance carrier of a patient enrolled in a clinical trial for services provided in the course of the trial. In September 2000, Medicare issued a national coverage decision that allows for the
coverage of routine costs of care for patients enrolled in qualifying clinical trials. The Medicare policy excludes from coverage “items and services customarily provided by the research sponsors free of charge for any enrollee in the trial.” Some private health insurers also offer this type of coverage, but others specifically exclude such costs from coverage.

Where this option is available, the costs of disease-specific routine health care can be billed to these carriers. Where these costs are not eligible for coverage by the patient’s payer, the IRB may require that they be borne by the Sponsor. The Sponsor should be willing to accept these conditions if requested by the IRB. In no case should Sponsors require the Academic institution to bill the cost of subject’s injury that is a consequence of participation in the trial to the subject’s insurance company and then only pay for what is not covered by insurance. This is unacceptable from an ethical viewpoint and is against the policies of some Academic institutions. If the patient’s insurer has a specific exclusion that applies to clinical trials, submitting a bill for services rendered in the course of a trial may be considered fraudulent and therefore illegal.

Even when an insurer, such as Medicare, allows for billing of some services during a clinical trial, there is an issue of how to determine which services are eligible for billing. A discussion of billing-related issues is outside the scope of this paper. However, institutions should have in place a system by which the protocol is reviewed prospectively to determine: (1) the trial’s eligibility for billing and (2) whether each service is classified as “billing” or “no billing.” It is essential that the results of these determinations be shared with the appropriate institutional billing office and that any billable services related to an eligible trial be clearly marked. Consideration should be given about whether or not to include billing-related issues as part of the clinical trial contract since they may affect the budget for the trial. No institution should be required to submit a bill to Medicare or any other payer which may raise issues of billing for a false claim.

2. Provision of efficacious drugs for chronic disorders. Some patients enter a clinical trial with the expectation that if the trial results show that the drug being tested is efficacious for the treatment of a chronic disorder, then the Sponsor should offer them the drug, at no cost, and indefinitely into the future. Some in academia contend that if the drug
is efficacious, and the IRB makes a determination that the Sponsor shall offer study participants the drug for a specified period of time after the trial (or until such time as it is approved for marketing by the FDA) at no charge to participants, then the Sponsor must agree. Some in industry argue that while the drug being tested may be efficacious, there may be other, currently approved drugs that can treat the chronic condition effectively; therefore, there should be no obligation on the part of the Sponsor to provide the tested drug free of charge once the patient’s participation in the trial ends.

3. Signature of Principal Investigator on Contract. A miscellaneous issue concerns whether or not a principal investigator should sign the contract. Sponsored research contracts are entered into between the academic institution (or other relevant organization) and the pharmaceutical or device company. The PI is not a party to the agreement, but is a key person in ensuring that the terms of the agreement are followed. The contract must be signed by the appropriate individuals representing the institution. Consideration should be given to requiring that the PI also sign the contract as an attestation that he/she has read and understood the terms of the contract.

Conclusion

Collaboration of pharmaceutical, biotech, and medical device companies with academic institutions remains essential for advancement of new knowledge, development of new products, and improvement of patient care. The terms of the partnership are established by a contract, though the negotiations to reach agreement can be arduous. The contract must balance the often opposing desires of each side, yet promote the shared interest of engaging in research that is valuable to each party and to the patients who are the ultimate beneficiaries. This paper has examined four contract provisions, noted several emerging and miscellaneous issues, and proposed sample language. Where appropriate, suggestions are provided for addressing selected topics. This paper should be considered a work in progress, one that may be rewritten from time to time as research advances, intellectual property regimes evolve, and both sides come to understand how better to achieve their shared goals.
Bibliography of Related Resources


