

Institutional ethics review of clinical study agreements

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Clinical Study Agreements (CSAs) can have profound effects both on the protection of human subjects and on the independence of investigators to conduct research with scientific integrity. Sponsors, institutions, and even investigators may fail to give adequate attention to these issues in the negotiation of CSAs. Despite the key role of CSAs in structuring ethically important aspects of research, they remain largely unregulated and unreviewed for adherence to ethical norms. Academic institutions routinely enter into research contracts that fail to meet adequate ethical standards. This is a failing that can have serious consequences.

Accordingly, it is necessary that some independent body have the authority both to review research contracts for compliance with norms of subject protection and ethical integrity, and to reject studies that fail to meet ethical standards. Such review should take place prior to the start of research, not later. Because of its expertise and authority, the institutional ethics review board (IRB or REB) is the appropriate body to undertake such review. Much recent commentary has focused on contractual restrictions on the investigator's freedom to publish research findings. The Olivieri experience, and that of other investigators, has brought freedom of publication issues into sharp focus. Clinical study agreements also raise a number of other ethical issues relating to human subjects and research integrity, however, including disclosures relating to patient safety, data analysis and reporting, budget, confidentiality, and premature termination of the study. This paper describes the ethical issues at stake in structuring such agreements and suggests ethical standards to guide institutional ethics review.

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Increasingly, clinical research is funded, or jointly funded, under contract with outside sponsors such as pharmaceutical or biotechnology companies, other agencies, or government.¹ The provisions of such contracts, sometimes referred to as clinical study agreements (CSAs), can have profound effects both on the protection of human subjects and the independence of investigators to conduct research with scientific integrity. Despite the key role of CSAs in structuring ethically important aspects of research, they remain largely unregulated and unreviewed for adherence to ethical standards.

In a recent study at Duke University, Schulman and colleagues surveyed 108 US medical schools engaged in clinical research focusing on their agreements with industry sponsors of multicentre trials.² They found that these institutions rarely imposed requirements ensuring the investigator's independence in the design, collection, analysis, or interpretation of data. They also found few provisions ensuring either adequate protection for the freedom of investigators to publish or for the appropriate authorship of manuscripts. The study concludes that academic institutions routinely enter into research contracts that fail to meet adequate ethical standards. This is a failing that can have serious consequences. One important safeguard would be to require institutional ethics review board (IRB or REB) review and approval of all CSAs.

Few institutional ethics review bodies require the contracts negotiated in respect of contractually funded research to be submitted for approval as part of the protocol review process. The Duke study found that only 16% of surveyed research institutions submitted the research contract to their IRB for review and approval, and none at a subsample of elite research institutions. The federal Office of Human Research Protection, which regulates and oversees IRBs, has issued guidelines listing the documents and materials that must be reviewed. The research contract is not among them.³ Yet, the promises and obligations contained in the research contract

can impact in significant ways, on the protection of human subjects and fundamental norms of research integrity.

In negotiating these agreements, the research sponsor, investigator, and research institution each have interests in the conduct and success of the research, and will seek contractual terms to protect those interests. But none of these contracting parties' interests are clearly aligned with the protection of the human subjects or adherence to ethical norms of research integrity. This is not to say that sponsors and researchers are necessarily indifferent or antagonistic to the ethical conduct of these studies. Certain elements of the typical research contract have important implications, however, for the protection of human subjects and the integrity of the study. Sponsors, institutions, and even investigators may fail to give adequate attention to these issues in the negotiation of research contracts. Accordingly, it is necessary that some independent body have the authority both to review research contracts for compliance with norms of subject protection and ethical integrity, and to reject studies that fail to meet those norms. Such review should take place prior to the start of research, not later. The institutional ethics review board is the appropriate body to undertake such review.

In September of 2001, members of the International Committee of Medical Journal Editors (ICMJE) released a statement opposing contractual agreements that restrict investigators' right to access and analyse study data independently or publish research findings freely. They pledge not to review or publish articles where such prohibitions exist.⁴ This constitutes an extremely important initiative. But review that takes place after the research has been completed has at least four significant drawbacks. First, once the research is completed, if scientifically significant findings are made, denying publication becomes difficult to do and arguably also raises ethical concerns. Subjects may feel betrayed if their efforts and sacrifices do not result in the publication of meaningful findings. The social and scientific

value of the research has been squandered. Second, it may prove to be impractical for editors to undertake the comprehensive review required to determine whether a CSA meets ethical standards. Third, this approach will not ensure the review of CSAs for studies not submitted for publication—for example, if the study was not intended for publication or shows negative results. Fourth, denying publication does little to address the problem of under-reporting research findings (and arguably exacerbates the problem), unless the threat itself proves to be effective in ensuring that investigators secure publication rights in advance.

Prior expert ethics review has important advantages. It comes at the beginning of the process, so that ethically acceptable terms can be secured prior to spending resources or putting subjects to risk or inconvenience. Such review is also effective—boards have particular expertise in research ethics and the responsibility to provide independent review of all clinical studies. They have the authority to disallow protocols that do not comply with established norms.

Negotiating obligations between the sponsors of contracted research, and the institution and investigator, raises a number of difficult ethical issues. The conflicting interests of the parties are not purely commercial. A number of issues commonly arising in research contracts may affect the human subjects of research, some of which are not directly related to the conflict of interest concerns referred to by the ICJME. Much of recent commentary has focused on contractual restrictions on the investigator's freedom to publish research findings.⁴⁻¹⁰ This is an extraordinarily important problem that IRB review could helpfully address. The Olivieri experience, and that of other investigators, has brought freedom of publication issues into sharp focus. Clinical study agreements also, however, raise a number of other ethical issues relating to human subjects and research integrity. These include: publication restrictions, budget, data analysis and reporting, confidentiality, financial costs and compensation for injury, indemnification, and premature termination of research. This paper identifies some ethical issues at stake in structuring such agreements and describes ethical standards to guide ethics review. This list is intended to suggest the range of issues that can arise. A careful review of particular agreements may disclose other problems.

PUBLICATION

Sponsors may seek to restrict or impede the publication of research findings for a number of reasons: to protect their intellectual property in the treatment being studied, to keep negative findings from becoming widely known, and to control the dissemination of information. Withholding research findings is, however, a violation of the fundamental goal of medical research, which is to advance scientific knowledge in order to cure illness and relieve suffering.¹¹ The broad dissemination of research findings, both positive and negative, allows others to integrate evidence based knowledge into clinical care, to subject findings to critical analysis,¹²⁻¹³ and to build upon findings to further advance scientific knowledge.⁷ If findings are not published, the scientific and social value of the study is lost and subjects are betrayed.¹⁴ Suppressing reports of research funding skews the literature and can result in clinicians making inappropriate treatment decisions—using either unsafe or less effective medications or other treatment approaches.⁵ Clinical data must be widely available and subject to independent analysis and critique, ultimately for the benefit of patients.¹²⁻¹³ This is particularly true of clinical trials involving drugs and devices intended for the market.

Prohibiting restrictions on the publication of research findings is supported also by considerations relating to the

protection of human subjects. In order to meet ethical standards, research must be socially valuable. Research subjects should never be exposed to the risks and inconveniences of research without a reasonable possibility of corresponding social/scientific benefit. If findings are not published the scientific and social value of the study is lost and the subject is betrayed.¹⁴

These worries are not idle.¹⁵ In a recent study, Blumenthal and colleagues found that 19.8% of a random sample of academic life scientists from major research institutions had delayed publication of findings for longer than six months at the urging of the sponsor.⁶ In 1990 a group of researchers at the University of California at San Francisco completed a study funded by Boots Pharmaceuticals Inc (after its takeover of the original sponsor, Flint Laboratories) comparing the efficacy of the sponsor's synthetic thyroid, Synthroid, to three rival preparations. Both the sponsor and the researchers had expected to show that Synthroid was superior. However, the research found the preparations to be equally effective. Because of restrictions provided in the research agreement signed by the investigators, Boots was successful in blocking publication of this significant finding for almost seven years.¹⁰⁻¹⁶ Nancy Olivieri's contract with the sponsor, Apotex Research Inc, provided the basis for Apotex to terminate the trial at the Toronto site and threaten Olivieri with legal action if she disclosed her concerns about safety to any third party without its consent.⁹ Neither this nor the Synthroid situation could have arisen if the institutional review board had reviewed the contracts in advance, and insisted that restrictions on publication be withdrawn.

Because the protection of the sponsor's intellectual property does serve a socially valuable purpose, to encourage innovation and invention, some limited delays on publication may be acceptable to permit these rights to be protected. Giving advance notice also allows the sponsor to discuss the findings and offer alternative interpretations, although final authority as to content must always remain with the investigator. Delays in publication mandated by the contract are acceptable only for as much time as is reasonably required to make appropriate filings to protect the sponsor's patent and other intellectual property rights. For this purpose, and to allow adequate consultation, 60 to 90 days is generally sufficient. Delays for other reasons, or longer delays, are not justified in the absence of compelling justification. It is also clearly desirable that contractual terms relating to such research be reviewed prior to commencing research, in order to ensure that problems are addressed at the outset, and to avoid the pressure to compromise later.

DISCLOSURE TO ENSURE PATIENT SAFETY

In order to meet professional standards of care, the CSA must explicitly give researchers the discretion to determine what warnings or disclosures should be made to subjects and others to ensure patients' safety and clinical best interests. Accordingly, when an investigator wishes to disclose research findings relevant to patient safety, such as potential toxicities or drug interactions, there should be no restriction on the investigator's ability to notify enrolled research subjects, the ethics review board, government regulatory authorities, and, if a multisite trial, other investigators and their subjects and ethics review boards. In the contract, the investigator should retain the unfettered discretion to make the determination whether any research findings have implications for patient safety. Making this question a matter to be determined jointly with the sponsor, or by arbitration or litigation, would constitute an abdication of the clinical judgment of the physician/researcher. The researcher must maintain the discretion to determine what warnings or disclosures should

be made to subjects in their clinical best interests and to meet professional standards of care.

DATA ANALYSIS AND REPORTING

The integrity of the analysis and reporting of data is key to the scientific validity of a study. The sponsor will typically have an interest in a particular outcome, usually that the proposed treatment is at least as effective as its rivals and has an acceptable safety profile. This creates a potential conflict with the scientific interest in ensuring a methodologically and statistically valid study design and analysis from which to draw conclusions.¹⁵ As noted earlier, the ICMJE affirmed that investigators should have the right to publish findings without restriction and to have access to, and control the analysis of, all data. "As editors, we strongly oppose contractual agreements that deny investigators the right to examine the data independently ... without first obtaining the consent of the sponsor."¹⁷ Accordingly, it is the individual investigator, or a cooperative team of investigators in a multicentre trial, that should be responsible for assessing methodological issues, and analysing and reporting the data.

The Pharmaceutical Research and Manufacturers Association (PhRMA) in its *Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results*, released in June 2002,¹⁸ has accepted the principle of investigator freedom to publish research findings. "Sponsors commit to ... not 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 exist, the parties should try to resolve them through appropriate scientific debate." While the acceptance by PhRMA of this important ethical principle is laudable, vigilance in safeguarding this freedom is warranted. First, the history of pharmaceutical company attempts to muzzle research findings, as exemplified by the Boots Pharmaceuticals Inc and Olivieri cases, and others⁶ demonstrates the powerful incentives for a sponsor to suppress results. Second, the PhRMA principles are explicitly voluntary. There is no mechanism for enforcement, or to punish companies that do not comply. Third, it is not clear what happens if the "differences of opinion or interpretation" cannot be resolved. One important way of dealing with disputes about publication is to ensure that, from the start, the freedom to publish is protected by unambiguous contractual provisions.

The research contract, then, should permit investigators to independently access and analyse all data and to report findings.³ As noted earlier, the Schulman study showed that contracts rarely do so.² In multisite research, responsibility for the data analysis and publication is more complex. It may be appropriate for data analysis and manuscript preparation to be delegated to a coordinating committee of site investigators. Each investigator must, however, be satisfied as to the committee's qualifications and independence, and that the process for analysis, reporting, and publication of results is similarly protected. The coordinating committee must have publication safeguards as stringent as those required in single site trials. The research contract should explicitly provide for such mechanisms, and documents establishing and governing the coordinating committee should be subject to ethics board review.

BUDGET

Close review of the research budget may disclose a variety of problems. In order to be ethical, clinical research must not only be scientifically valuable, but its completion must be feasible.¹⁴ Subjects should not be exposed to the risks and inconveniences of research unless it is reasonable to suppose

that the scientific question can be answered. The budget then should assure reviewers that there are sufficient funds and other resources available to ensure the timely completion of the study. Conversely, since research funds are limited and should not be wasted, research expenses should be no more than are reasonably required to complete the study.¹⁴ A review of the budget may disclose unnecessary or unjustified costs.

The budget may also disclose or hint at unexplained payments or expenses, raising questions about the existence of conflicts of interest. Amounts paid to researchers or consultants should be no greater than those customarily paid, and be based on a reasonable estimate or accounting of costs genuinely incurred. Structuring the budget for other purposes may create ethically inappropriate incentives. Sponsors often seek, for example, to include payment provisions that encourage rapid enrolment of subjects. Differential compensation for different levels of recruitment (higher per subject payments for those recruited above a set target), may encourage investigators to recruit subjects who would not otherwise be appropriate, in order to reach higher paying thresholds. Financial inducements based on speed of recruitment and "competitive recruitment" in multisite trials (which penalise investigators at sites that recruit at a slower pace than others) may create the same dangerous incentives. Payments made to others for referrals, so called "finder's fees," have been determined to be unethical by a number of professional organisations, including the AMA,¹⁹ and should not be permitted. Reviewing the budget also allows confirmation of information found elsewhere in the study protocol and consent form. It can help ensure, for example, that provision for payments to subjects is reasonable and consistent with that disclosed in other protocol materials.

CONFIDENTIALITY

The research contract should ensure that information about subjects remains confidential, with exceptions only as are strictly necessary to facilitate the conduct of the study, or otherwise as required by law. While research auditing procedures and good clinical practices may require that a representative of the sponsor review research charts and records, such access should be no more than is required for adequate oversight. To the extent possible, anonymous records only should be subject to such perusal.

Research contracts will often seek to protect the confidentiality of the sponsor's intellectual property. Although such provisions are not necessarily unreasonable, investigators must be permitted to disclose information reasonably required to publish relevant findings, such as methodology and some drug information, and to obtain and maintain the valid informed consent of subjects. Investigators must be at liberty to disclose to subjects whatever information is necessary, in their own clinical judgment, to ensure their health, safety, and proper diagnosis. If the contract includes broad restrictions on the disclosure of confidential research information, as many do, then the freedom to provide adequate information to subjects must be explicitly permitted in the contract.

FINANCIAL COSTS AND COMPENSATION FOR INJURY

Subjects should not be obliged to contribute to the cost of medical care relating to the study. Accordingly, research related medications, treatments, and diagnostic procedures should be supplied at no charge to research subjects, or to their insurance companies. Clinical study agreements should make appropriate provision for compensation for injury, or other legal liability to subjects. The sponsor should be responsible for medical harms directly resulting from

research participation, whether or not such injury results from the negligence of the sponsor. Under no circumstances may the contract purport to waive any of the sponsor's, the investigator's, or the institution's legal obligations to research subjects, which include liability for negligence, breach of contract, breach of fiduciary obligation, or any other legal liability.²⁰

Research contracts will sometimes provide that compensation for injury will be paid only if the subject complies with the requirements of the study protocol and the instructions of the investigator. While it is fair that the sponsor not be held responsible for injuries suffered as a result of the subject's intentional and serious violation of the study protocol, the contract should not restrict or discourage a subject's freedom to make reasonable health care decisions while in the study. Accordingly, a limitation on the sponsor's obligation to compensate a research subject should be based only on a serious and unreasonable departure from clear, research related instructions that directly cause the injury or harm in question.

INDEMNIFICATION

In order to protect the independence and integrity of the investigator and the institution, the research contract may make explicit provision for adequate indemnification to protect the investigators and the institution against losses or harms they may suffer from participating in the study. While such provisions are common in research contracts, there are typically a number of exceptions to the sponsor's obligation to indemnify, including, for example, harms and losses caused by the wilful, reckless, or negligent acts or omissions of the investigator or institution.

Another common provision restricts the sponsor's obligation to indemnify if the institution or investigator makes any admission of wrongdoing without the consent of the sponsor. While provisions of this kind may be common in commercial agreements, it is not appropriate in the context of research involving human subjects. Increasingly, health care institutions have accepted an ethical obligation to disclose medical errors or misadventures to their patients.²¹⁻²³ It is appropriate that health care professionals be forthcoming with their patients, even when disclosure of an error is embarrassing, or may place the practitioner or institution in legal jeopardy. This ethical principle applies also to errors that cause harm to research subjects. Indeed, there is some evidence to suppose that such disclosure will in fact tend to defuse the threat of litigation, not encourage it.²¹ Nonetheless, the ethical imperative of disclosure should not be a basis for relieving the sponsor of its obligation to indemnify. The investigator and the institution should not be forced to choose between meeting their ethical obligations of disclosure, and maintaining their entitlement to the sponsor's indemnity.

PREMATURE TERMINATION

Attention should be paid to termination provisions in the research agreement. There are a number of circumstances in which the CSA, and so the study, may validly be terminated. Lievre and colleagues have identified efficacy, safety, and feasibility as valid reasons.²⁴ Certainly research should be stopped if the study intervention is proven, on statistically valid grounds, to be either ineffective (in which case subjects should no longer receive the experimental therapy) or clearly effective (so that subjects in control or comparison groups may be given a therapy shown to be effective). The study may also be terminated for reasons of safety, if the side effect profile of the experimental therapy proves unacceptable. It is also appropriate to discontinue the study when it becomes apparent that, for reasons not reasonably knowable at the outset, the study is no longer feasible and cannot be

completed. There might, for example, be problems with recruitment, resources, research personnel, or facilities and equipment.

It is not, however, acceptable that the sponsor be permitted to terminate the study for other reasons, such as commercial or public relations reasons. The ethical justification for requiring the completion of the study is similar to that for requiring scientific significance and methodological validity. Subjects should not be exposed to risks without the prospect of corresponding social and scientific advance. Sponsors have a social as well as a scientific obligation to ensure that subjects' sacrifices are useful and that benefits to subjects are maintained. This ethical principle is violated when sponsors seek the authority to terminate a study for non-scientific reasons such as an apparent lack of commercial viability, change in marketing strategy, or because results in the study prove to be negative for the sponsor.²⁵ Once subjects are exposed to the risks and inconveniences of research participation, the sponsor is obliged to ensure that the scientific question is answered.

DISCUSSION

The threat posed by private industry sponsorship to academic independence, and the conflicts of interest that arise by reason of these relationships, have recently resulted in increased concern and closer scrutiny.^{8, 26-28} The promises and obligations contained in the CSA can impact, in significant ways, on these fundamental norms of research integrity and on the protection of human subjects. As a legally binding contract, provisions of the CSA trump the review board approved protocol where they conflict. While a multifaceted response to this problem is indicated, the involvement of the review board, at an early stage, is surely an important element.

Although some aspects of the contract do not impact on subject protection or ethical integrity, the issues raised here are clearly within the authority of the institution's ethics review board. Where particular contractual provisions have ethical implications, the established ethics review mechanism should take responsibility. Not doubting the good intentions of members of the institutional research contracts office, or other body charged with negotiating these agreements, the interests they are accustomed to protecting on behalf of the investigators and institutions are not identical with the interests of protecting human subjects and ensuring the integrity of the research. Members of the institution's contracts office will rarely have experience of thinking about how different issues may impact on human subjects or on the integrity of research. Institutions have a conflict of interest in CSAs, because they benefit from sponsors underwriting research there. Investigators anxious to get their research under way may be unfamiliar with, or insufficiently cautious about, these ethical issues. The IRB has primary responsibility for these matters, and this obligation should not be off loaded to another authority. The IRB should not shrink from its responsibility to do a comprehensive review of research related materials, including the research contract and budget, to ensure that subjects are protected and the integrity of the research is preserved.

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ECHO

Ethical issues in end of life decisions need public airing



Please visit the *Journal of Medical Ethics* website [www.jmedethics.com] for a link to the full text of this article.

Public debate in Britain about moral differences between helping someone to die and withdrawing or withholding treatment can only help patients and their doctors, says a specialist from the standpoint of ethics and decision making in end stage lung disease.

Two well known cases—those of Miss B and Mrs Diane Pretty—have highlighted issues around mechanical ventilation. It has been argued that they are similar philosophically and the divisive decisions applied to each arose from purely legalistic argument.

Doctors are bound by oath not to harm. They must weigh up the likely outcome of treatment against burden for the patient and quality of life. When expectations conflict—as in doctors’ underestimates of survival in chronic lung disease versus patients’ over-optimism—they complicate joint decisions about the end of life.

Good communication, not just about outcome, is crucial. Too often patients are not told about the burden of treatment despite guidelines and research evidence that this does influence their decisions.

Doctors have a duty to keep abreast of new treatments and their potential. Non-invasive ventilation can extend options. However, a quarter of doctors did not discuss these in neuromuscular disease, believing that suffering would be prolonged, according to one survey—unhelpful when other studies show that such patients’ quality of life is consistently underestimated. Nevertheless, assisted ventilation can be maleficent, and doctors should respect competent patients’ wishes to refuse treatment or ask it to be withdrawn. “Living wills” are a way of patients recording their wishes and doctors must abide by them.

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