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Regulatory impediments jeopardizing the conduct of clinical trials in Europe funded by the National Institutes of Health

James D Neaton[a], **Abdel Babiker**[b], **Mark Bohnhorst**[c], **Janet Darbyshire**[b], **Eileen Denning**[a], **Arnie Frishman**[c], **Jesper Grarup**[d], **Gregg Larson**[a], and **Jens Lundgren**[e]

[a]Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN, USA

[b]HIV and Infection Group, MRC Clinical Trials Unit, London, UK

[c]Office of the General Counsel, University of Minnesota, Minneapolis, MN, USA

[d]Copenhagen HIV Programme, University of Copenhagen, Copenhagen, Denmark

[e]National University Hospital and University of Copenhagen, Copenhagen HIV Programme, Panum Institute, Copenhagen, Denmark

Abstract

Background—A number of reports have highlighted problems of conducting publicly funded trials in Europe as a consequence of the European Union (EU) Clinical Trials Directive. The impact of the EU Directive on multi-national trials, which include sites in Europe that are funded by the US National Institutes of Health (NIH) have not been described.

Methods—Four problems in the conduct of two international HIV treatment trials funded by NIH in the EU are described: (1) conflicting regulations on the continuing review of protocols by Institutional Review Boards/Research Ethics Committees; (2) US regulations requiring Federalwide Assurances for sites which are only partially funded by NIH; (3) EU guidance on the designation of studies as a trial of an investigational medicinal product; and (4) EU guidance on trial sponsorship and the requirements for insurance and indemnification. Following the description of the problems, recommendations for improving global collaborations are made to the US Office of Human Research Protections, to NIH, and to the EU and its Member States.

Results—A lack of harmonization of regulations at multiple levels caused enrollment in one study to be interrupted for several months and delayed for one year the initiation of another study aimed at obtaining definitive evidence to guide the timing of the initiation of antiretroviral therapy for individuals infected with HIV. The delays and the purchase of insurance resulted in substantial increases in trial costs and caused substantial disruption at clinical sites among staff and study participants.

Limitations—The problems cited and recommendations made pertain to trials funded by NIH and conducted by sites in the EU. There are many other challenges in the conduct of international research, public and private, that global harmonization would alleviate.

Conclusions—Disharmony, at multiple levels, in international regulations and guidelines is stifling publicly funded global research. International scientific organizations and government groups should make the documentation and solution of these problems a priority.

Author for correspondence: James D Neaton, Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN 55414, USA. jim@ccbr.umn.edu.

Introduction

In 2001 the European Parliament and the Council of the European Union (EU) issued a Directive on the approximation of laws, regulations, and administrative provisions of the EU Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use [1]. This Directive aimed to improve the protection of participants in trials and the reliability of trial results by simplifying and harmonizing procedures for the conduct of clinical trials across the EU. It described the role of ethics committees and regulatory authorities and, more generally, provisions that should be in place to ensure good clinical practice. EU Member States were required to transpose the Directive into National laws, regulations, and procedures by May 2003 and to implement them by May 2004.

Over the past few years, there have been several reports indicating that the EU Directive has had an adverse effect on the implementation of noncommercial clinical trials conducted in the EU [2–13]. Some of the problems arise from specific requirements of the Directive including the need for a single trial sponsor for noncommercial trials, for insurance and indemnification, and for processes for adverse event reporting. Other problems relate to the variable manner in which EU Member States have implemented the Directive. In some cases, the problems have significantly increased the cost of noncommercial trials and delayed their implementation [6].

While there have been a number of reports that have highlighted problems conducting trials within Europe as a consequence of the EU Clinical Trials Directive, the impact of the Directive on multinational trials, which include sites in Europe that are funded in total or in part by the US National Institutes of Health (NIH) has not been described. There are also few reports describing the impact of US regulations for NIH-funded trials on the conduct of trials that include sites in Europe. Given the problems the EU Clinical Trials Directive has created for noncommercial trials in Europe, additional problems would be predicted to occur for noncommercial trials conducted in Europe that are funded by NIH. That has been the case as evidenced by the problems we describe in this article.

Based on our experience, neither the US regulations nor the EU Directive were developed with global collaborations in mind. As a consequence, international differences in guidelines have not been considered, noncommercial trial costs have increased, and the answers to critically important research questions that can only be addressed with public funding, and often enhanced by inter-government collaborations, are delayed. We develop this argument by describing four problems (Table 1) that arose in the planning and conduct of two international randomized trials of human immunodeficiency virus (HIV) treatments funded by NIH. One of the trials is funded entirely by NIH and the other trial is funded by NIH and several European governments. Before describing these four problems which were encountered in the two HIV trials, we first describe briefly the US regulations (Common Rule) which govern US funded research, and then the key elements of the EU Clinical Trials Directive.

Common Rule

Regulations and guidelines for the protection of human subjects participating in research in the US evolved over many years. The history is summarized on a website maintained by the Office of NIH History [14]. In the US, a Federal regulation for the protection of human subjects was issued in 1974 that is known as 45 Code of Federal Regulations (CFR) 46 Subpart A. This regulation describes the responsibilities of Institutional Review Boards/ Research Ethics Committees (IRBs/RECs) and other procedures to be followed for US funded research whether it is conducted in the US or elsewhere. In 1991, several other US

government agencies adopted these requirements and they became known as the Common Rule. The elements of the Common Rule relative to this article (problems 1 and 2) are summarized in Table 2.

While US regulations [45 CFR 46.101(h)] state that for research in foreign countries, 'if a department head or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy.' To date, no procedure for determining the equivalence of human subjects' protection in clinical research in other countries to those in the US has been approved by the Office for Human Research Protections (OHRP).

EU clinical trials directive

There are three elements of the EU Clinical Trials Directive that are relevant to the problems presented in this article (Table 3). The first two elements are related. According to the Directive, for example in the International Conference on Harmonization [15], the sponsor is 'an individual, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.' The sponsor does not need to be located in an EU Member State, but it has to have a legal representative in the EU. The sponsor may delegate any or all of the trial-related tasks/duties and functions to an individual, institution, or organization. However, there still must be an overall sponsor for the trial that assumes ultimate responsibility for compliance with the Directive and the conduct of the trial.

The Directive also states that the trial cannot be undertaken unless 'provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor.' In simple terms, indemnity is a promise to cover another party's liability. Insurance is a commercially available contractual mechanism for addressing the financial implications of liability.

The EU Directive goes on to state that before a trial commences, RECs must consider 'any insurance or indemnity to cover the liability of the investigator and sponsor' and 'the arrangement for indemnity or compensation in the event of injury or death due to the trial.' The Directive does not state who should provide the indemnity or compensation or the breadth of liability coverage. The expectation, in most cases, is that the sponsor would pay for the liability coverage. As previously noted, the manner in which the Directive has been implemented by EU Member States varies. Goudsmit *et al.* [16] described the variability with which the Member States implemented the insurance and indemnification requirements. Some countries required insurance of varying amounts, some did not, and some were silent on the requirements. The experience of German investigators in having to acquire insurance to supplement that provided by the sponsor, the London School of Hygiene and Tropical Medicine, for a large multinational trial illustrates the lack of harmonization in insurance requirements and the difficulty for investigators in acquiring insurance [17]. Unlike other countries participating in the trial from the EU, the indemnity insurance purchased by the sponsor did not meet with limits required by federal German drug law. The German investigators had significant difficulty in finding insurance coverage that met the limits, and the only German coverage they were able to find limited the number of participants that could be covered and requested unacceptably high premium costs for surgical risks not associated with the treatment under study.

In general, sponsor responsibilities, in terms of civil (e.g., compensation for damages to a study participant) or criminal law (e.g., fines, debarment, and/or imprisonment for violation of national laws and regulations), are not governed by the Directive. For these responsibilities, laws of the individual Member States apply [18] and the laws vary.

An investigational medicinal product (IMP) is defined in the Directive as ‘a pharmaceutical form of active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization, but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.’ For trials with an IMP, the treatments must be provided to participants in the study free of charge, although some countries have provided waivers to this requirement. IMPs may be subject to importation regulations and expedited adverse event reporting requirements.

INSIGHT HIV trials

The problems discussed in this article arose in two HIV treatment trials conducted by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), a network funded by the Division of Acquired Immune Deficiency Syndrome (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), NIH. INSIGHT includes many sites in the US and over 200 international sites. About 100 of the non-US sites are in Europe. Sites in 16 EU Member States have participated in INSIGHT studies.

Until recently, NIH has been the funder and sponsor of trials conducted by INSIGHT. As sponsor, and as is typical of many NIH-funded trials, a number of sponsor responsibilities related to trial management and quality assurance have been delegated to coordinating centers they fund.

One of the trials, Study of Aldesleukin With and Without Antiretroviral Therapy, (STALWART), used as a case example, was ongoing when the regulatory issue that is described as Problem 1 occurred. STALWART is funded by NIH and was initiated in 2005. The trial is studying the use of an approved drug for a new indication and is therefore being carried out under an US FDA Investigational New Drug (IND) application. The other trial, Strategic Timing of AntiRetroviral Treatment (START), was close to initiation in 2008, following more than a year of planning. START is a strategic trial on the optimal timing of initiation of antiretroviral therapy, that uses approved antiretroviral drugs and is not being carried out under a US IND. START is funded primarily by NIH; however, several European governments are also providing support for the trial.

Problem 1: Continuing reviews and equivalent protections

In several INSIGHT trials, European countries have requested an exemption from OHRP to the regulations in 45 CFR 46 section 109(e) concerning continuing review. In STALWART, the UK requested an exemption.

US policy in 45 CFR 46 section 108(b) states: ‘An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and research.’ The policy also states that the IRB shall ‘review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas.’

Thus, based on this US regulation, continuing reviews of protocols for long-term clinical trials must be reviewed at least annually by the majority of the IRB members even if there have been no protocol amendments. This regulation differs in other countries. For example, in the UK, the chair of the central ethics committee initially conducts the continuing review of a study and may decide, based on that review, that it does not require a full-board review

(e.g., there have been no protocol amendments and a Data and Safety Monitoring Committee has indicated that there were no safety concerns) [19].

The EU Clinical Trials Directive states that for multi-center trials carried out by more than one Member State ‘a single opinion shall be given for each Member State concerned by the clinical trial.’ [1] As codified into law in the various countries, this most often results in a single ethics committee that is part of the Member State government establishing procedures, rather than the institution holding the Federalwide Assurance (FWA). A central ethics committee may determine that they are not subject to the requirements of the FWA. Although a central ethics committee must be registered with OHRP, it does not mean that the central ethics committee reviews research in accordance with the requirements of the Department of Health and Human Services (DHHS) Protection of Human Subjects regulations [20].

The position of DHHS on equivalent protections for continuing review was stated in the Federal Register in July 2006:

> ‘Some regulated institutions may have been confused by the fact that several national and international procedural standards are listed on the FWA for international (non-US) institutions, and interpreted this to mean that non-US institutions have a choice of whether or not the requirements of 45 CFR part 46 must be met for HHS-conducted or -supported research conducted by their institutions… for example, if a non-US institution selects a procedural standard on its FWA that does not explicitly require continuing review by an institutional review board (IRB) at least annually, the institution still must ensure than an IRB designated under the FWA conducts continuing review of nonexempt human subjects research supported by HHS at intervals appropriate to the degree of risk, but no less than once per year…to date, the Secretary has not made any determinations that other procedures provide equivalent protections to those afforded by HHS regulations.’

Because of the regulations set forth in 45 CFR 46 and because INSIGHT includes many sites that did not have FWAs prior to joining the network, the NIAID requested that continuing reviews and the manner in which they were conducted (e.g., full-board or chair) be tracked centrally by INSIGHT and reported to them. In June 2007, following NIH receipt of a report from INSIGHT on REC approvals, that noted continuing reviews in the UK were not done by the full ethics committee, enrollment of participants in STALWART at five UK sites was ordered to halt.

The UK's position was stated by a representative of the Department of Health in an e-mail in December 2006, before enrollment was halted, as follows: ‘The applicable statutory instruments which have validity in the UK are the Medicines for Human Use (Clinical Trials) Regulations 2004 and their 2006 Amendment…In the UK, our mechanisms for delivering the robust governance of research are configured differently from the United States IRB arrangements.’ The Department of Health representative goes on to point out that research ethics committees are not equivalent to IRBs and that the US FDA recognizes the differences and provides waivers to sponsors wishing to conduct trials outside the US.

During the summer of 2007, NIH officials discussed the halting of enrollment in the UK trial with OHRP. There were also ongoing discussions between the UK Department of Health and OHRP. In August 2007, OHRP informed the NIH Office of the Director not to take further action (e.g., closing other sites/protocols sponsored by NIH to enrollment) based solely on the continuing review issue.

In September 2007 the order to stop enrollment was lifted. However, DHHS and OHRP have still not issued a ruling on whether they view the UK practice as an 'equivalent protection.' So, while there was a temporary fix to this problem and enrollment in STALWART was initiated again after a three month lapse, a long-term solution has still not been found.

Problem 2: Requirements for Federalwide Assurances for studies jointly funded by NIH and other governments

Trials evaluating HIV treatment strategies with clinical outcomes require large sample sizes and long follow-up. Even when trials are efficiently conducted, such studies can be expensive because of the number of study participants and the required follow-up. To conduct these studies, NIH has encouraged INSIGHT to seek co-funding from other governments. Even when other governments provide financial support for the sites in their country to participate in international trials, policies in 45 CFR 46 have to be considered if the NIH is providing some support to the coordinating center for the trial.

Several governments are providing support for the START study. For example, the Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS) in France supports the participation of 11 clinical sites that will enroll and follow study participants. The ANRS is the second largest government funder after NIH for HIV research. Thus, they are a natural organization for INSIGHT (and NIH) to collaborate with on strategic trials of HIV treatments – trials that require large amounts of public funding and little incentive for pharmaceutical companies to carry out.

For the proposed trial, sites in France will collect data according to the same protocol as sites funded by NIAID and other governments. The sites will submit all data to the INSIGHT Statistical and Data Management Center in the US which is funded by NIAID. The ANRS inquired whether the 11 sites they were supporting needed FWAs. Most had them but did not want to renew them upon expiration. OHRP was asked about the requirement for FWAs for the French sites and the following response was provided:

> 'We've discussed the question you posed about whether NIAID's collaboration with institutions in France to conduct a clinical trial would make the study HHS-supported at the French institutions. Based on your description of NIAID's involvement in the study at issue, we believe that the French institutions would be receiving HHS support, since a NIAID-supported contractor will be labeling, holding, and distributing the study drug to institutions in France to carry out the clinical trial. Although we understand that the drug is being donated by a pharmaceutical company, we believe that NIAID's role in providing the study drugs to the French institutions would make the study HHS-supported.'
>
> 'However, you mentioned that the institutions in France may be able to obtain the drug from another source other than NIAID. If this were done, then we do not believe that the study would be HHS-supported, provided that NIAID's involvement was limited to the following:
>
> - NIAID will be involved in the development of the protocol;
> - NIAID will be involved in study monitoring;
> - NIAID-supported contractor will be analyzing study data, but will not provide analyses that will determine subject eligibility, study group assignment, or any other aspect of the conduct of the protocol with respect to subjects at the foreign institution;

- NIAID (perhaps through a contractor) will provide data collection forms to the study sites in France that will be used to provide study data to a NIAID-supported contractor in the US that will be analyzing study data; and
- NIAID-supported contractor will provide training to investigators in France regarding the implementation of the protocol.'

The third bullet above required some clarification because it implied that random treatment assignments could not be provided via INSIGHT (the 'contractor'). OHRP cited guidance provided to the National Cancer Institute that stated that an FWA was needed if 'foreign institution(s) sends specimens or data collected as part of the protocol to a central laboratory or data management center for processing or analysis that will be funded or conducted by HHS, and the results of the assays or tests performed on the specimens or from the analysis of the data will be used to determine subject eligibility, study group assignment, or other aspect of the conduct of the study with respect to the involvement of subjects at the foreign institution(s).'

To avoid the sites in France having to secure and maintain FWAs, INSIGHT agreed to randomize participants in France using an algorithm defined by INSIGHT, but not implemented by INSIGHT.

This example demonstrates the complexity of defining whether the US government is providing 'support' for a trial and thus whether institutions participating in a study require an FWA according to OHRP regulations. More importantly, it illustrates that even when a foreign government agrees to provide substantial support for the conduct of a clinical trial, its rules for the protection of human subjects are superseded by US requirements. This may not be acceptable to the foreign government.

Problem 3: Designation of a study as a clinical trial of an IMP

Each EU Member State makes a designation of the study as a clinical trial of an IMP or not. IMP studies must be recorded in the EudraCT database and have more regulatory requirements than non-IMP studies. In START, Denmark designated the study as a non-IMP study while other European countries designated START as an IMP study. In the UK, for example, the competent authority stated that the trial was to be designated as an IMP study because it 'may provide new information on a therapy which will be used to inform future clinical practice.' As this interpretation reflects, most clinical trials involving drugs, approved or not, would be considered IMP studies by the UK and possibly most other EU Member States.

In contrast, NIH determined that an IND would not be needed in START since the trial is investigating treatment strategies on the timing of use of HIV drugs in their approved indication and is not a trial of a specific drug or regimen (any approved regimen designated as 'preferred' by US HIV treatment guidelines may be used) [21]. NIH and INSIGHT also determined that since serious adverse events were collected in the START study for both treatment groups, irrespective of use of antiretroviral therapy, and randomized treatment comparisons were to be reported to an independent Data and Safety Monitoring Board (DSMB) at least annually, that the protocol could simply indicate that serious adverse events for a specific drug should be reported to national and international regulatory authorities according to local requirements and that MedWatch reports should be submitted to the FDA by US sites. In other words, INSIGHT and NIH judged that having the DSMB review treatment comparisons of major clinical outcomes, including adverse events, on a regular basis best ensured the safety of trial participants. The DSMB would send a report to each

IRB/REC following their review. This general approach to safety is consistent with other recent recommendations [22].

However, as a consequence of some European countries' designating START an IMP study, the sponsor, through its legal representative in Europe, was obligated to ensure that all relevant information about suspected unexpected serious adverse reactions (SUSARs) is recorded and reported to the central and/or concerned EU Member State authorities and ethics committees as appropriate and in compliance with requirements for expedited reporting. Furthermore, the sponsor had to ensure that investigators recognized their responsibility for reporting of serious adverse reactions and had to set up a system to allow the pharmaceutical companies providing study drugs (Marketing Authorization Holders) to report serious adverse reactions according to their obligations.

Thus, even though all of the drugs to be used in START are approved, being used within the indication for which they are approved, and not the focus of the experimental comparison (the drugs are used for a strategic comparison on the timing of initiation of treatment), expedited reporting procedures had to be established for suspected adverse events judged to be serious, unexpected, and related to specific drugs.

Problem 4: Trial sponsorship, insurance, and indemnification

The EU Directive increased the responsibilities of the trial sponsor in a number of ways. Of particular importance to the START trial, the Directive requires that the sponsor secure liability coverage for the trial; specifically, the Directive requires that ‘provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor.’ [see Article 3(f)] [1] Table 4 defines indemnification and insurance and gives examples as they pertain to clinical trials. As evidenced from this table, the distinction as to whether the sponsor must provide both indemnification and insurance or only insurance is important.

Precisely what insurance coverage is required is not clear. The EU directive does not address how much ‘provision’ must be made and does not specify whether ‘indemnity’ must also be promised, if an adequate level of ‘insurance’ has been purchased. Before a trial commences, ethics committees must consider ‘any insurance or indemnity to cover the liability of the investigator and sponsor’ and ‘the arrangement for indemnity or compensation in the event of injury or death due to the trial.’ (see Article 6) [1]. The Directive does not state who should provide the liability coverage and does not harmonize requirements across Member States. Thus, they vary by country [1]. Baeyens [4] noted that this raised the possibility that in countries without specific regulations concerning insurance requirements, ethics committees might impose their own insurance conditions on sponsors. This occurred in START. Goudsmit [16] cautioned that possible gaps in insurance coverage resulting from inconsistent standards across Member States could leave sponsors and research institutions ‘dangerously exposed to significant financial consequences.’

While sponsor responsibilities generally can be shared among different groups, the Directive requires that ultimate responsibility for the trial lies with the sponsor, which must be a singular entity [see Article 2(e)] [1]. As a consequence of the variable manner in which Member States have translated the Directive into law, some Member States, like the UK, permit shared sponsorship. Others do not.

Conceivably the ‘liability of the sponsor’ under the EU Directive is limitless, since the sponsor ultimately is responsible for everything. As previously noted, however, the Directive itself does not create legal liabilities; rather, the laws of each of the EU Member States in which a trial is conducted (16 Member States for INSIGHT) determine the civil (and possibly criminal) liability of a sponsor. Thus, a Member State might impose liability

on a collaborating group regardless of its status as sponsor, and it might or might not impose liability on a sponsor for wrongdoing of another individual or group within the study.

In many cases, the sponsor is the funder. That has typically been the case for trials funded by NIH and by the pharmaceutical industry. However, this is not a requirement of the EU Directive [see Article 2(e)) [1], and often is not the case for publicly financed trials in Europe.

During over one year of trial planning for START, all parties understood that NIH would sponsor the trial. However, when it was recognized that the trial would be subject to the regulatory requirements of the EU Directive, NIH reconsidered its position on sponsorship. The possibility of open-ended indemnification requirements led NIH, the funder of the START trial, to state that they could not 'sponsor' trials conducted in the EU, at least not in any Member States that required trial indemnification. Following is a communication INSIGHT leadership received from NIAID in July 2008:

> 'After further internal discussions with NIH Office of General Counsel and the NIAID Office of Global Research, NIAID (DAIDS) has been advised not to serve as a sponsor (i.e., register as a Sponsor with competent authorities of EU Member States or with EudraVigilance) for clinical trials conducted in the EU, particularly if the national regulations of an EU Member State require the sponsor to indemnify or provide insurance for research-related injury, due to the limitations imposed by the US Anti-Deficiency Act.'

According to the Anti-Deficiency Act, in the absence of specific authority conferred by another statute, it is unlawful for a US government official to 'make or authorize an expenditure or obligation exceeding an amount available in an appropriation or fund for the expenditure or obligation.' [23]. Since NIH does not have statutory authority to agree to indemnify where the amount of the government's liability is indefinite, indeterminate, or potentially unlimited, the NIH Counsel judged sponsoring a clinical trial was no longer possible in EU Member States that required indemnification.

We do not know how many trials funded by NIH are being carried out by EU Member States, nor is it clear how other NIH-funded groups have dealt with this recommendation by the NIH Counsel. As a consequence of NIH's decision not to sponsor START, NIH asked the grant recipient for START, the University of Minnesota, to assume sponsorship for the trial. To our knowledge, there is no precedent for a US university serving as the sponsor of an NIH-funded multi-center, multi-national trial such as START. Most state universities, for example, are subject to state constitutional restrictions comparable to the Anti-Deficiency Act and therefore would have been barred as a matter of state law from accepting an open-ended liability. Consideration of the matter required several meetings among University Vice Presidents, START investigators, University risk management officials, and the University General Counsel. The University's counsel were not convinced that NIH Counsel was correctly interpreting the Anti-Deficiency Act and they requested NIH Counsel to reconsider the matter. After a teleconference in November 2008, it was clear that NIH was not going to change its position. NIH asserted that serving as regulatory sponsor would violate the Anti-Deficiency Act in some jurisdictions; hence would not agree to be sponsor. In December 2008, nearly 5 months after the NIH notified the University that NIH could not serve as the trial sponsor, the University agreed to serve as the sponsor of START.

As noted previously, and typical of many NIH-sponsored trials, the University was already carrying out many of the responsibilities of a trial sponsor. However, in previous INSIGHT trials carried out with NIH support, the University did not assume legal responsibilities of the sponsor, and therefore did not assume potential sponsor liabilities for damages caused by

other investigators in the trial or for damages caused to trial participants that were not the fault of any party. The change in the University's role in START created a potential problem. The University understood from NIH's decision to decline sponsorship that there were jurisdictions in the EU for which it would be exposed to unlimited liability as sponsor. Other than limited insurance, the University's primary source of liability protection is the Minnesota Tort Claims Act [24]. This Act covers wrongdoings of State and University employees and establishes a financial limit on claims; it is applicable for claims in Minnesota (in principle it should be applicable in other states that apply principles of comity among states). It is not adequate liability coverage for an international trial.

NIH and INSIGHT considered the requirement for insurance by sites in some European countries, and NIH determined that the purchase of insurance for the sites in the EU that required insurance in order to have ethics committee approval of the protocol was an allowable direct cost. Limits required per claim and in aggregate for multiple claims in the trial varied by country and are summarized in Table 5.

The cost for this insurance was $178,479. It covers the estimated number of participants to be enrolled in the first year (about one-third of total enrollment planned by the specified country) and their follow-up to the end of the trial (5 years). The cost of this insurance is about 4% of the total trial budget for the first year.

The limits set by each country appear arbitrary. For example, in Greece the total study insurance is the limit per claim times the number of participants estimated to be randomized. While trial insurance is required by Greek law, the determination of the amount required is left to interpretation of the ethics committee.

Following the decision to serve as sponsor, responsibility for negotiations of clinical trial agreements with six pharmaceutical companies that are donating drug switched from NIH to the University of Minnesota. The negotiations concerning insurance and indemnification provisions were time-consuming. The pharmaceutical companies were willing to assume responsibility for the provision of defective product to INSIGHT; the University was willing to agree that the companies would not be responsible for harm to study participants resulting from an investigator not following the START protocol. However, none of the parties was willing to assume responsibility for unexpected adverse events that might occur on one or more of the drugs. While everyone felt the risk of a lawsuit was very low, as the drugs to be used were approved, the University was concerned about its unknown liability in the role it was asked to play and felt that even if a lawsuit were brought against a pharmaceutical company, the University might well also be named as a defendant and in such event would likely incur substantial legal fees. Ultimately, after 6 months of negotiation, the University made a decision to purchase additional insurance. NIH would not pay for this insurance. Thus, it was purchased with University funds.

In other NIH-funded and sponsored trials, NIH negotiated the clinical trial agreements with pharmaceutical companies, and as part of that negotiation, developed mutually agreed-upon language concerning insurance and indemnification. That language typically stated that the pharmaceutical company would hold harmless NIH and its respective agents (e.g., site investigators) for any liabilities or lawsuits resulting from claims made concerning the study drug provided the claim was not caused by gross negligence or misconduct. This language was not agreeable to pharmaceutical companies for START. Negotiations between six pharmaceutical companies and the University of Minnesota over the issues of insurance and indemnification were complicated, difficult, and protracted. It required many months to finalize all of the agreements.

Discussion

We have described four problems encountered in the conduct of noncommercial trials in Europe that are funded in total or in part by NIH. Broadly speaking, these problems arose because regulations concerning the protection of human subjects participating in research are not harmonized either within Europe or between Europe and the US, and because the implementation of the EU Directive requires sponsors to provide liability coverage for trial investigators. This disharmony, at multiple levels, caused enrollment in one study to be interrupted for several months and delayed for one year the initiation of another study aimed at obtaining definitive evidence to guide the timing of the initiation of antiretroviral therapy for individuals infected with HIV. It resulted in substantial increases in trial costs for the primary funder (NIH) and the sponsor (University of Minnesota). More importantly, the delays caused substantial disruption at clinical sites among staff and study participants. Site staff had already participated in training for the study and the delays necessitated that training be repeated at several locations. Study participants had already been contacted, but with the delay in initiation of the study many were no longer eligible. All had to be asked to wait for screening for a period of time that was uncertain.

We have focused on only a few examples of the disharmony in international guidelines and regulations. There are many others (e.g., drug formulation and importation). The disharmony is stifling precisely the type of research that needs to be carried out worldwide – trials comparing different strategic approaches to treatment, trials that will inform clinical decision-making guidelines, and improve health outcomes. Since this research may involve several approved treatments and not be aimed at drug approval, it is research which pharmaceutical companies are not likely to fund.

The US American Recovery and Reinvestment Act provided a large boost in funding for comparative effectiveness research. Such research is defined as research that ‘compares treatments and strategies to improve health.’ [25]. The trials described in this article being carried out by INSIGHT are examples of comparative effectiveness research. A recent review article examined mechanisms for conducting comparative effectiveness research in four developed countries, Britain, France, Germany, and Australia, with the goal of informing US work in this area. The authors state three ingredients for success: (1) strong political endorsement; (2) engagement with stakeholders; and (3) a demonstrable commitment to quality and evidence-based practices [26]. Our experience suggests that they have overlooked an important fourth ingredient – worldwide harmonization and simplification of regulations concerning the conduct of clinical research.

An increasing number of trials are being done outside the United States [27]. NIH is also funding more studies in foreign countries. There are many advantages to collaborative multi-national studies. Governments should be supporting these collaborative efforts both by co-funding comparative effectiveness studies and by working toward harmonizing and simplifying regulations. We should be doing more of these types of trials, not fewer. However, such trials are getting harder to do. Several authors have described the regulatory challenges in conducting trials in the US [28–31]. As the examples described in this article illustrate, the challenges faced by investigators doing clinical trials in one country are compounded when the trials are multinational. US regulations and the EU Clinical Trials Directive are threatening the conduct of multi-national, publicly funded trials.

What can be done? The solution to these problems cannot be left to the academic community. For example, asking the university community to accept the sponsor role for NIH-funded trials in Europe is not a solution. This problem needs to be resolved on a government-to-government basis – between the US government and the EU Member States.

We give several recommendations to government organizations below that would improve global collaborations for publicly funded (noncommercial) trials. Others have also made many recommendations. We recognize the political challenges of implementing these recommendations. However, we are encouraged by the fact that NIH has formed a working group in the Director's Office to review barriers to collaboration on both sides of the Atlantic and meetings with the European legal and regulatory community are already taking place.

Recommendations for OHRP

Establish a mechanism for defining and approving equivalent protections

Different groups have addressed the assessment of equivalent protections. In a 2003 report, a working group proposed five steps in determining equivalent protections [32]:

1. Articulation of the specific protections embodied in 45 CFR 46.
2. Assessment of the protections provided by the institution's procedures.
3. Comparison of the protections provided by the institution's procedures with those provided by 45 CFR 46 and determination of equivalence, or not.
4. Approval of the relevant US department or agency head for the substitution of the institutional procedures in lieu of the procedures of 45 CFR 46.
5. Assurance from the institution that the substituted procedures (those of the institution) will be followed in the conduct of human subjects research funded by the US DHHS.

Although these proposals for assessing equivalent protections have not been implemented, we feel they are rational and could greatly facilitate international clinical trials. In the EU, since a single national ethics committee typically determines how ethics committees at different institutions within the Member State operate, it is critical that discussions of equivalent protections be at a national, not an institutional, level.

The problems of conflicting procedural requirements for continuing review as well as the challenges of determining whether trials only partially funded by the NIH require FWAs – problems 1 and 2 in this article – would be addressed if equivalent protections were determined for the regulations under which the trials were being performed. Ideally, this determination would be by an international body, not a single entity in the US.

Convene an international panel with the aim of harmonizing and simplifying international regulations concerning the participation of human subjects in research

As part of OHRP's assessment of equivalent protections, we also recommend that they convene an international group that compares regulations across countries and makes recommendations for multi-national trials. The review could result in more harmonized, simpler regulations as well as guidelines to follow for multi-national research efforts. The very fact that an international review group was formed would attest to the importance of global research.

Recommendations for the NIH

NIH/HHS Office of the General Counsel should have dedicated EU Directive expertise

A 2008 report by the Delegation of the European Commission to the United States indicated that in fiscal year 2006 NIH funded 251 awards to Member States in the EU [33]. It is not clear how many of these awards were for clinical trials; however, the number of NIH awards is likely greater than this statistic indicates since some awards are likely through

subcontracts with academic institutions in the US (e.g., such as the STALWART and START studies). The problems cited in this article require extensive knowledge of the EU Directive and how the Directive is implemented by different Member States. It is not reasonable to expect individual US academic institutions to master this information or keep abreast of changes. With dedicated expertise, NIH/DHHS could consider if there are alternatives that would allow NIH to serve as clinical trial sponsor without having the responsibility for an indeterminate level of liability in EU Member States. For example:

- Determining if co-sponsorship agreements are possible with certain EU Member States;
- Identifying which EU Member States currently do not require an indemnity beyond the insurance levels specified by law or RECs;
- Clarifying whether EU Member States would ever entertain a suit against the US (e.g., NIH) for sponsoring a noncommercial trial.

Create a database of problems caused by conflicting regulations and examples of how challenges of NIH-funded research in the EU have been resolved

NIH Office of the Director should consider the establishment of a database documenting the experience of the NIH Institutes in addressing international compliance issues, regulations that influence those problems, resolution tactics (either temporary or permanent), impact on the trials, and whether changes to regulations or processes, both within the US or other nations, was required. The database would be a valuable resource for NIH if the same issues arise in multiple NIH Institutes and for US universities if NIH were to continue to request that universities take on the sponsor role. To this point, little information has been shared because there is no common source of information.

Recommendations for the EU and Member States

Reassess and harmonize the insurance and indemnification requirements for publicly financed trials

The NIH should not have to bear the total cost for liability coverage for trials that they fund in Europe. These trials benefit the public health missions of all countries, and in part, if not entirely, the cost of liability coverage should be the responsibility of the participating country, e.g., ministries of health or public health systems. The European Science Foundation also recognizes that insurance and indemnification requirements of certain nations are obstacles to publicly funded multi-national research. In a recent report they focus on the ‘insurance’ side of this and cite several recommendations including a not-for-profit insurance organization for clinical trials [35]. This recommendation, if implemented, would likely have a significant effect on insurance costs since this is not only repetitious coverage but also premiums that are far too high given the risks and the claims history for trials. If insurance costs were lower, public funders may be much more willing to contribute toward them.

Given the high cost of insurance and the amount of money that is therefore being directed away from direct research costs, we support the recommendations regarding insurance by the European Science Foundation [34]. We also recommend that the EU establish a web site with the insurance requirements of each country, the rationale for the requirements, and circumstances in which national organizations will cover the cost of insurance. Investigators and funders who are interested in international collaborations and are trying to identify locations for future trials would use this information. Such a web site would highlight discordant requirements and might be an additional impetus for Member States to reduce costs and to the EU to strive to harmonize those requirements.

The European Science Foundation report notes that problems stemming from the EU Directive are international and need to be addressed beyond the EU [34]. As the problems outlined in this report illustrate, to help facilitate trials funded by NIH in the EU, the unintended consequence of the term ‘indemnity’ as it affects US public bodies as well ‘insurance’ needs to be addressed.

We recommend that the EU and its Member States address the ambiguity regarding what if any ‘indemnity’ is required beyond the insurance limits specified by a Member State (in general legislation) or by an ethics committee (additional for a particular trial). It is not clear why any additional indemnity is required for publicly sponsored, noncommercial trials.

The EU and Member States should also consider clarifying that the doctrine of international sovereign immunity will protect NIH from suit in Member States' courts for noncommercial clinical trials that are sponsored and funded by NIH. Such trials should be considered governmental, not proprietary, functions; and government agencies sponsoring or participating in such trials should be subject to suit only in their own courts and under their own laws, not in each of the numerous jurisdictions of collaborating countries. US law provides generous sovereign immunity protections for foreign governments, and EU jurisdictions should reciprocate. This approach eliminates the need for NIH to develop expertise regarding the varying and often changing laws of liability and indemnity in the various Member States. Rather, US law would be applied in US courts. If an NIH employee had been the cause of harm to a study participant, the participant could obtain relief under the Federal Tort Claims Act, which provides reasonable compensation for harms caused by US government employees. If some other party had been the cause of harm, an injured party could seek redress from that party. If a participant suffered harm that was not attributable to the fault of any party, compensation would be available from the no-fault insurance for the trial. If a government failed to require sufficient no-fault coverage for its citizens, the injured citizen-participant might be able to seek compensation from his/her own government (which in the EU is typically already covering most medical costs and providing wage replacement for disability), but recourse should not be sought from NIH (which did not cause the harm and was not responsible for the level of no-fault coverage for that Member State).

Establish procedures that permit delegation of responsibilities to multiple trial sponsors

The University of Minnesota as the sole sponsor for START carries all of the sponsor's responsibility for the START trial. But the prospect of multiple sponsors may encourage more involvement on the part of collaborators because they would share responsibilities. For instance, the Division of AIDS at NIH had certain responsibilities they wanted to maintain for the START study, but the University of Minnesota and the NIH Office of the General Counsel had to determine if these duties could remain with the Division of AIDS if they were not serving as sponsor and were also unable or unwilling to defend or indemnify the University of Minnesota if it were sued (as sponsor) for the actions of the Division of AIDS. With the prospect of multiple sponsors, each being responsible for its own acts, these duties could be more easily divided. The European Science Foundation has also called for the sponsorship of multi-national trials to be addressed in modifications to the EU Guidance [34]. While the focus of the Foundation's recommendation is pan-European sponsorship, improved guidance for US and other global partnerships is needed.

The EU may already be addressing elements of this proposal. A recent document from the EU Commission indicates that a number of parties may agree in writing to form an organization in which different groups take responsibility for different tasks and duties [18]. Documentation of experiences with this approach among different academic groups is needed.

Harmonize EU Member State designation of a study as an 'IMP' trial

Randomized trials vary considerably in terms of potential risks to study participants and in knowledge about the treatments to be used. A recent public consultation sponsored by the EU notes this [11]. Better cooperation among Member States and/or central assessment of IMP designation, particularly for publicly sponsored trials is needed. We recommend that a single entity in the EU make this designation, using guidelines agreed upon by Member States, and that the guidelines be regularly reviewed.

Summary

In summary, publicly funded trials are critical to provide an evidence base for the prevention and treatment of diseases. Often these trials are aimed at understanding the optimal use of products which already have marketing authorizations. Frequently, to obtain reliable evidence, large clinical trials are needed. Such trials should have the same level of quality and credibility and offer the same level of human subject's protection as commercial trials. These trials could be more efficiently carried out by academic groups across many countries, while still maintaining high standards for data quality and the safety of study participants, if regulations were harmonized and simplified.

We have described four problems in the conduct of clinical trials in the EU that are funded by NIH. There are many other problems encountered in the conduct of both publically and privately sponsored research. Through the presentation of these case examples we hope that others are encouraged to describe problems they have faced and that governments and international scientific organizations are motivated to rapidly address the problems of conducting multi-national research. It is time to look beyond national boundaries and harmonize regulations so that the untapped potential of publicly funded international research can be realized.

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Table 1

Four problems that arose in international trials funded by the National Institutes of Health

1	Conflicting regulations on the continuing review of protocols by Institutional Review Boards/Research Ethics Committees.
2	US regulations requiring Federalwide Assurances for sites which are only partially funded by NIH.
3	EU guidance on the designation of studies as a trial of an investigational medicinal product.
4	EU guidance on trial sponsorship and the requirements for insurance and indemnification.

Table 2
Elements of the Common Rule relevant to the problems listed in Table 1

- Institutions participating in NIH-funded research must complete a Federalwide Assurance (FWA) indicating compliance with US regulations, specifically requirements set forth in 45 Code of Federal Regulations 46.
- FWAs are required whether the institution is in the US or elsewhere. Local regulations apply but US regulations supersede them.
- FWAs specify requirements for Institutional Review Board/Research Ethics Committee membership and procedures for review of research.
- Department or agency heads may approve substitution of foreign procedures.

Table 3

Elements of European Union Clinical Trials Directive relevant to the problems listed in Table 1

• Trial sponsor responsibilities.
• Requirements for trial insurance and indemnification.
• Definition of an investigational medicinal product.

Table 4
Indemnification and insurance: definitions and examples

Indemnification

- Indemnification is a promise to cover another party's liability. For example, a promise by one party (e.g., sponsor) in a relationship to cover the liability of another party (e.g., site) for an expense that arises from a transaction (e.g., injuries suffered by a study participant as a result of the trial).
- Indemnity promises are often exchanged, with each party agreeing to indemnify the other party to the extent a liability is caused by the actions or omissions of a party. For example, a pharmaceutical company may indemnify if an injury to a study participant is caused by an adverse reaction to their drug; a site indemnifies if an injury was caused by the site's violation of a law, regulation, or the study protocol.
- The extent of a liability (and of a corresponding indemnity) is determined by the applicable law for the jurisdiction where a trial is conducted.

Insurance

- Insurance is a commercially available contractual mechanism for addressing the financial implications of liability. Insurance is a type of ‘indemnity’ contract, in which a third party, which is not a party to a transaction, agrees to cover liabilities of those who are parties to the transaction.
- Insurance could cover a party's (e.g., sponsor's) own liability and also a party's agreement to indemnify another party (e.g., site) for its liability.
- Insurance can cover losses for which no party is ‘liable’ in the sense that no party is really at fault. In the EU, as a condition of conducting a trial, many jurisdictions require a level of such no-fault insurance to cover injuries to participants. No-fault insurance focuses on assuring that the injured party is compensated and can avoid delays and legal expenses associated with disputes about who was at fault or which party should indemnify the other party, and by how much.

Table 5
Insurance requirements for START study by country

Country	No. of participants (sites)	Limit per claim	Limit per study
Belgium	30 (2)	EUR 500,000	EUR 5,000,000
Greece	45 (3)	EUR 200,000	EUR 9,000,000
Italy	15 (1)	EUR 1,500,000	EUR 5,000,000
Poland	15 (1)	EUR 1,000,000	EUR 1,000,000
Spain	75 (5)	EUR 500,000	EUR 2,500,000
Switzerland	45 (3)	CHF 1,200,000	CHF 10,000,000

EUR = Euro = 1.3 Dollar on 15 May 2010; CHF = Swiss franc = 0.90 Dollar on 15 May 2010.