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Conflicts among Multinational Ethical and Scientific Standards for Clinical Trials of Therapeutic Interventions

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Context

There has been a growing concern over establishing norms that ensure the ethically acceptable and scientifically sound conduct of clinical trials. Among the leading norms internationally are the World Medical Association's Declaration of Helsinki, guidelines by the Council for International Organizations of Medical Sciences (CIOMS), the International Conference on Harmonization's standards for industry (ICH), and the CONSORT group's reporting norms (Consolidated Standards of Reporting Trials), in addition to the influential U.S. Federal Common Rule, Food and Drug Administration's (FDA) body of regulations, and information sheets by the Department of Health and Human Services. There are also many norms published at more local levels by official agencies and professional groups.

Any account of international standards should cover both scientific and ethical norms at once — the two are conceptually intertwined. Recent sources recognize that "[s]cientifically unsound research on human subjects is unethical in that it exposes research subjects to risks without possible benefit."[1] Normative guidance for conducting simultaneously valid and ethical trials have not been as comprehensive as they could be, which may contribute to evaluations of the high number of methodologically suspect trials.[2]

This combination of motivations to gather standards from many countries, in ethics and methods, led us to a search and review which identified nearly 6,000 consolidated standards and created a taxonomic order for the standards, improving our ability to identify

overlooked or underappreciated issues.[3] Though we are not the first to coalesce current standards into a single source,[4] the comparative detail of our taxonomic framework, along with the integration of ethical and science standards, makes our system uniquely useful.

What would have been an immense cognitive task — the comparison of conflicts across many nations' ethical and scientific trial standards — now involves comparison of standards within a relatively manageable and organized system. The purpose of this paper is to present an important aspect of that comparison: topics of conflict and discrepancy within the corpus of official trial standards, taken as an international whole, in substantive ethical and scientific areas central to clinical trials.

Methods

The methods for compiling the compendium, along with a list of all source documents, have been reported elsewhere.[5] However, certain features of the prior phases of our research deserve emphasis, as they are relevant to the compendium's comprehensiveness for seeking conflicts. Table 1 provides additional details.

Document Search Strategies

Using the website ClinicalTrials.gov, we selected the 31 countries hosting the greatest number of active trials. By multi-researcher redundant search strategies, we identified officially endorsed documents from the source countries and their geopolitical alliances. The specialized areas of stem cell, gamete, embryonic, fetal, and genetics research, though obviously controversial, were omitted for scope and likely merit specialty projects of their own. Our resources also only permitted English-language documents (or documents available in English translation by the issuer) to be featured.

Extracting Standards

It was not feasible to review all 1,004 documents found in our search for normative statements, so a sample was taken. First, a set of 50 "core" documents were selected at the outset for extraction, based on the influence and comprehensiveness of the documents. All documents with titles relating to surgery or device trials were also included (N = 39), due to our motivation to combat the generally overlooked trial issues specific to surgery. The remaining documents were sampled at 5% (n = 55) for a total of 144 documents.

Methods for defining and individuating particular normative statements have been given elsewhere (see also Table 1).[6]

Organizing and Consolidating Standards

The team developed a broad organizational scheme *a priori*, initially specifying only major genus and sub-genus rankings for standards. As more standards were added to the compendium, genus boundaries were altered and subcategories were added based on the ideas found in the standards themselves, including the addition of the major genus, *Post-Trial Standards*. Hence, the final taxonomic scheme was empirically informed. The full taxonomy may be found in an appendix to our previous publication.[7]

With the organization refined into manageable sections, standards could be reviewed for inter-relationships. Separate extraction of each document resulted in 14,882 individual normative directives; duplicates and logical equivalents were combined into single, consolidated entries. Procedural standards and broadly platitudinous statements were discarded. Also, topics specific to particular vulnerable population-shave not yet been consolidated or fully reviewed for conflicts due to issues of scope and complexity. We have,

however, included general norms about vulnerability (not type-specific) and topics of emergency research and incapacitated adults (these being highly relevant to our study's emphasis on surgical trials).

These exclusions left 5,905 finalized standards, divided into: *Initiation*, 1,401 standards, eight divisions; *Design,* 1,870 standards,16 divisions; *Conduct,* 1,473 standards, eight divisions; *Analyzing and Reporting Results,* 993 standards, four divisions; and *Post-Trial Standards*, 168 standards, five divisions.

Identifying Conflicts

For the current project, two experienced clinical investigators, one specializing in ethics (BAB) and the other in methods (NPW), engaged in a redundant review of each of the five divisions of the compendium. The raters met to compare notes on perceived conflicts. A research assistant who had contributed to the compendium's creation was present for all meetings and was responsible for record-keeping, aiding in conflictidentification, and double-checking standards against the context of their original source document(s) before officially recording a conflict.

The organizational structure of the compendium might have failed to place conflicting standards in close proximity, creating the danger of overlooking obvious contradictions. To alleviate this danger, any standard which violated the raters' common-sense understanding of trial practice was flagged and set aside in a shorter list so that it would be kept in mind while later sections were reviewed. Whenever entire subcategories in different major sections of the taxonomy seemed likely to bear relation to one another, they too were reread and compared.

The raters distinguished between different levels of conflicts; these working definitions can be found in Table 2 and include *direct conflicts* (DC), which are impossible to satisfy at once, and *potential conflicts* (PC), which may only clash in certain circumstances. For example, we found one set of standards supporting the view that "[r]espect for participants in other countries requires having due regard for their beliefs, customs and cultural heritage, and for local laws."[8] Another set requires that the sponsor be "no less stringent" ethically than what is required in the sponsor's own country.[9] These ideals only conflict when a host culture *forbids* conduct required by the sponsor (for example, a patriarch-leader requires not only that his consent be sought for including women of his community as subjects, which is permitted by both standards, but also that the women's consent *not* be sought in addition to his own, which is forbidden by the second set of standards). This possibility signifies a relationship between standards which is somewhat problematic but not broadly contradictory, and so it motivated the use of "potential conflict" as a rating.

The team found some lines which contradicted a large range of other standards or even the basis of entire subcategories. In these cases, rather than itemize the individual conflicts, we labeled the problem-line as an *outlier*, since it violated what is otherwise an unproblematic consensus. These outliers are found in the Appendix.

An additional category, *exception* or *specification*, was used when re-checking source context to ensure that conflicts were genuine. When two standards are presented out of context, a rule originally meant to be a general, all-things-equal statement may seem to conflict with a more specific exception or special case. Lines were specifically double-checked for indications of any acceptable, "general vs. specific" relationship (e.g., by document subheadings indicating exceptions vs. general rules as part of a document's organization).

Some conflicts were excluded as procedural rather than substantive. For example, the U.K.'s standard operating procedures for research ethics committees gives a three-day maximum on reporting urgent safety measures taken in a trial;[10] the U.S. FDA requires five day notification for similar safety-related protocol deviations.[11] Though the time-frames are in direct conflict, both sources agree on the basic ethical point that urgent safety-related events and actions should be quickly reported to the reseach ethics committee (REC) or institutional review board (IRB). We found that regulatory agencies seldom agreed on the exact time frame for expedited reporting for safety/conduct information, but they agreed on types of occurrences that warrant quick notifications, and the conventional definitions of "expedited" never differed beyond a week for a given kind of notification. This disagreement is about administration, and though logistically significant, it does not impact the ethical or scientific quality of a trial. This case also illustrates that two standards which individually contain ethically substantive ideas (i.e., produce urgent safety reports rapidly) may come into conflict in ways which are not as substantive, and so an exclusion criterion for procedural conflicts, as distinct from the earlier exclusion criterion for individual procedural standards, was deemed warranted. Other procedural conflicts are listed in Table 3 and the Appendix for reference, to further illustrate our judgments of substantive topics vs. procedural ones.

Findings

We found 15 substantive topics of conflict (including the potential conflict of "respect for customs" used above for illustration of definitions), with one related outlier worth mentioning. See Table 3 for the list of all topics involving conflicts, and the Appendix for conflicts and outliers not commented on here.

Conflict 1: Inclusion of Vulnerable Subjects

There are two related conflicts dealing with vulnerable populations (children, the mentally disabled or incompetent, the underprivileged, prisoners, etc.). The first is about their inclusion in general, while the second focuses on inclusion in non-therapeutic trials (Conflict 2 below). For the general conflict: an important set of documents places the burden of "special justification" on the investigator before conducting research on vulnerable subjects.[12] Subjects "should be the least vulnerable necessary to accomplish the purposes of the research."[13] By the 2001 European Clinical Trials Directive, mentally impaired adults incapable of consent should be included "on an even more restrictive basis" than children.[14] This restrictive tendency hinders the potential *benefits* of trial enrollment, and so our documents also express counter-values against over-protection: "Vulnerable subjects should not be precluded from studies solely on the basis of their vulnerability,"[15] and, particularly, "It is important that research involving people who lack capacity can be carried out."[16] More generally, "investigators and IRBs must be careful not to *overprotect* vulnerable populations so that they are excluded from participating in research in which they wish to participate."[17]

We label this as a potential conflict, only dealing with the tension of very general values, well known in the ethics literature.[18] It is necessary to walk the line between protective and inclusive considerations successfully, but do we succeed? The next conflict suggests that a clearly articulated consensus is lacking.

Conflict 2: Non-Therapeutic Research for Vulnerable Populations

Authorities remain divided on how to handle vulnerable populations in trials "in which there is no anticipated direct clinical benefit to the subject."[19] One position denies that including

vulnerable populations (sometimes more narrowly: incapacitated adults) is ever proper in these situations:

> In the event that the patient is unable to give his informed consent, the patient may nevertheless be included in a trial which is linked to the treatment of illness, if...the investigator judges that it may be of benefit to the patient.[20]

> Phase 1 trials cannot include adults unable to consent for themselves, as one of the requirements... is that there are grounds for expecting that administering the investigational medicinal product will produce a benefit to the subject.[21]

In contrast, a more permissive collection of standards offers one or more common exceptions — the population must be essential to the trial objective, indirect benefits to the subject/population are anticipated, risk is minimized (low, routine, minor, etc.), and surrogate consent is provided.[22] The permissive group also contains an internal dispute. CIOMS tolerates "slight or minor increases above minimal risk (where minimal risk means risk no more likely and not greater than the risk attached to routine medical or psychological examination)" when "there is an overriding scientific or medical rationale" approved by committee.[23] However, the Oviedo Protocol holds that non-therapeutic research on a person without the capacity to consent requires that "additional potential benefits of the research shall not be used to justify an increased level of risk or burden" above minimal risk.[24] Similarly, for unconscious subjects, the NHMRC requires "minimally invasive research," constricting the use of non-therapeutic surgical trials.[25]

Multiple sources contain some variant of the statement that vulnerable subjects' interests should "always prevail over those of science and society".[26] Taken literally, the statement is on the far restrictive end of the spectrum — there is no reason to engage in non-therapeutic research from the standpoint of the individual patient's health without accounting for the indirect benefit of improving medical knowledge for the population. Taken more loosely, the statement is vague, and its values are better expressed by more specific standards of protections and exceptions. The problematic statement is part of a larger genus, though, which is worth exploring briefly, as a related outlier found during the conflict search.

Related Outlier: "The Subject Takes Precedence"

The more general idea that any subject (not merely vulnerable ones) "takes precedence over science and society" is repeated as an introductory statement in many key trial guidance documents, including ICH's E6, the Declaration of Helsinki, and European policies.[27] A more preferable wording may be found in the OHRP's IRB Guidebook:

> In research where no direct benefits to the subject are anticipated, the IRB must evaluate whether the risks presented by procedures performed solely to obtain generalizable knowledge are ethically acceptable. There should be a limit to the risks society (through the government and research institutions) asks individuals to accept for the benefit of others, but IRBs should not be overprotective.[28]

A "limit" can be specified by criteria which can be consulted (e.g., specified requirements of minimal risk, acceptable risk-benefit ratio, and other protective standards); "precedence" is qualitative, and it does not transition well to the complexities and specifics in balancing individual risks against social benefits. Sources using the "precedence" formulation still appreciate these complexities (by specifying them in later sections or related documents), but the details and general values seem disjointed when stated in this manner.

Conflict 3: Completion Bonuses to Subjects

The Royal College of Physicians (RCP) and the FDA agree that, when subjects are paid for a study, payment should be proportional to participation rather than deliverable or reliant

upon full completion.[29] However, the RCP goes on to say, flatly, "Completion bonuses are unethical."[30] The FDA, does not consider a full restriction necessary:

> While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable to FDA, providing that such incentive is not coercive. The IRB should determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn.[31]

We interpret this as a direct conflict regarding the permissibility of completion bonuses, preserving an enduring tension on the significance of research incentives in general.[32]

Conflict 4: Subject Treatment or Compensation for Injury

We expected issues of treatment and compensation for research-related injury to vary, reflecting the more general differences between nations with private health care systems and those with public health care. Actual conflict was surprisingly subtle and localized. International European law leaves it to each nation to decide who is responsible,[33] though sponsors and investigators are expected to have indemnity insurance.[34] The U.K. and some individual European nations place the responsibility for treatment or compensation squarely with the sponsor,[35] as does Australia.[36] In cases where the conduct of the trial complied with the protocol submitted in the application to the regulatory agency, Hungary does place responsibility on the regulatory authority.[37] CIOMS follows the European influence, placing responsibility on the sponsor, particularly for externally conducted research;[38] ICH merely cautions sponsors to consult their nation's "applicable regulatory requirement(s)."[39]

The most unique statement found was from South African regulations, which permitted that, when an intervention is withdrawn for its adverse events:

> ...[A]ppropriate therapy to manage the adverse drug effects should be made available within the study framework at no cost to the patient, by referral to the local health service, or through the patient's medical insurance, unless exceptions have been agreed upon by all parties.[40]

Even mentioning the patient's insurance (as opposed to the sponsor's) clashes with the U.K.'s National Health Service and bio-industry associations, which hold this case no different than one in which the sponsor is held liable by default:

> Where there is an adverse reaction to a medicinal product under trial and injury is caused by a procedure adopted to deal with that adverse reaction, compensation should be paid for such injury as if it were caused directly by the medicinal product under trial.[41]

Given liability discrepancies, U.K.-South African trials would require particularly careful compensation agreements prior to trial launching.

None of the United States sources spoke directly on this issue, though there are implied standards on compensation within informed consent regulations:

> No informed consent...may include any exculpatory language through which the subject...is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.[42]

If the research involves "more than minimal risk," the consent should also include:

> ...an explanation as to whether any compensation and...whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.[43]

These standards leave open the exact compensatory body, when compensation is warranted, and guidance when trial injuries are not attributable to negligence.

Conflict 5: Representing the Investigational Arm to Subjects

Maintaining the distinction between therapy and research in the consent process is an important goal. The FDA and OHRP remind IRBs that consent documents should not represent the investigational product as safe and/or effective, or otherwise exaggerate the benefit of the product.[44] However, an OHRP guide, while tackling the equally difficult topic of explaining randomization to subjects, possibly undercuts this point:

> Merely telling [subjects] that the assignment to treatment will be done randomly, mathematically, or by lottery may not be sufficient. Instead, more of an explanation should be given. In a two-arm trial, for example, subjects should be told that there is a 50 percent chance of receiving one of two treatments *thought to be beneficial* for patients with their particular kind of disease; that one is the standard treatment and the other is the experimental treatment; that the experimental treatment is *thought to be at least as good* as the standard treatment; and that their physician will not be the person who decides which treatment they receive.[45]

In an attempt to handle the challenge of explaining experimental procedure, this guide forgets how naïve subjects can be regarding therapeutic misconception, a major problem in the ethics of research consent.[46] As a result, OHRP's advice stands in potential conflict with other cautions about consent. Phrases like “thought to be beneficial” and “thought to be at least as good as,” to the medically trained eye, refer to equipoise or tentative pre-clinical results, not a claim of unproven effectiveness, but it may not be reasonable to assume that subjects will perceive such a subtle distinction in their consent forms. Patients could come to the conclusion, based on this randomization section, that their physician will give them the treatment which is beneficial, contrary to whatever appears under the heading of the test treatment itself. The RCP suggests different language:

> In randomized trials, patients should be told...that they will...be given either the standard treatment or one which may prove to be better or worse,... and...that their treatment will be chosen by chance (random allocation).[47]

Patients told their treatment “may prove to be better *or worse*” are given a more sustained picture of the equipoise behind the research.

Conflict 6: Pre-Randomization

The ethical acceptability of randomizing subjects prior to consent (pre-randomization), such as the method proposed by Marvin Zelen, is a controversial topic in peer-reviewed literature,[48] and there are also potential conflicts in more officially endorsed standards. The IRB Guidebook requires as much explanation as possible, prior to randomization, in the consent process: “Ethical considerations demand that subjects be informed when their assignment will be random,” which includes the method and “probability of assignment to the various groups.”[49] The tense here indicates that subjects may not be randomized before being informed of the allocation method. However, the RCP expresses a cautiously lenient perspective, telling review committees that they may make exceptions:

> We note the complexity of these debates. Pre-randomisation without consent is infrequently used, should never be used unless there are plausible harms to be avoided and the reasons should be explicitly examined by the REC.[50]

The RCP does not itemize what sorts of avoidable harms an REC should find relevant. Other standards (including regulations) do not broach the topic even as directly as this, and so do not yet offer resolution or clear guidance to the debate. It is more common to find brief statements within consent checklists, e.g.: “In broad terms, investigators must inform their subjects regarding: i. The study's rationale and methods, including randomization, when relevant....”[51] Notice the unexplained phrase, “when relevant,” which is ambiguous between the possibility of Zelen-like exception on one hand, and cases of non-random allocation schemes on the other.

Conflict 7: Placebo Control Groups

There is a long history of tension between the scientific usefulness of placebo control and the ethical value of beneficence, which resists the idea of giving patients false-therapies. Debates in ethical literature motivated several revisions of the Declaration of Helsinki to clarify the topic.[52] What has been officially codified? We found greater clarity in the latest versions of control group standards, leaning in the direction of tolerating placebo use within commonly formulated conditions, but the voices are not entirely univocal.

The strongest verbiage comes from the Italian National Bioethics Committee, contributing an opinion for the drafting of the (then in-process) Oviedo Protocol Article 23. The stance was not wholly adopted in the final Protocol, but the Italian Committee retains their commentary online (apparently as currently endorsed). They contend that:

> ...[T]he use of placebo treatment when alternative treatment of proven effectiveness exists is a violation of the ethical code and is not in the interests of the patient. This cannot even be justified by reference to the interests of science and society.[53]

Australia's NHMRC re-iterates a similarly restrictive opinion, allowing placebos only in cases of clear equipoise:

> The use of a placebo alone or the incorporation of a non-treatment control group...is ethically unacceptable in a controlled clinical trial where...other available treatment has already been clearly shown to be effective....[54]

This opinion may be appealing on ethical grounds (why should the subject be denied proven therapy?) and on scientific grounds (the only interesting hypothesis is whether new drugs are better or at least non-inferior to established treatments). Both grounds are disputed widely by regulators and professional societies. In terms of ethics, exceptions favoring placebo use are endorsed under acceptable risk-benefit ratios and minimal risk by regulations in the U.S., Europe, and South Africa, along with CIOMS, the RCP, the Oviedo Protocol's finalized Article 23(3), and the most recent revision of Helsinki.[55] Scientifically, it is recognized that an equivalence or non-inferiority trial may not be able to answer important questions unless a placebo is involved at least second-hand (from a relevantly similar trial) to preserve statistical assay sensitivity.[56] The FDA actively encourages placebo use in these instances:

> ...[I]t is critical to review the evidence that harm would result from denial of active treatment, because alternative study designs, especially active-control studies, may not be informative, exposing subjects to risk but without being able to collect useful information.[57]

> If possible, use of a third (placebo or lower dose) arm, so that a treatment difference can be shown, is a desirable strategy in equivalence trials.[58]

Even within this placebo-tolerant group, there is noteworthy imprecision. These standards do not have an established, common lexicon for expressing the minimal-risk requirement. South Africa requires that “participants will not be harmed,”[59] which may or may not be more stringent than the European/American ban on “unacceptable risk or burden,”[60] while

CIOMS requires that risks be "minor and short-lived,"[61] and Helsinki bans "risk of serious or irreversible harm."[62] More standardized terms could avoid potential problems arising from subtle semantic differences.

Conflict 8: Underpowered Studies

ICH reiterates that "individual clinical trials should always be large enough to satisfy their objectives."[63] On this view, underpowered studies fall prey to the overarching principle that scientifically invalid studies are *ipso facto* unethical.

The Royal College of Physicians, however, holds that "an underpowered study is not necessarily unethical,...and in rare conditions, an underpowered study may be better than no study at all."[64] Examples include pilot studies, student projects, and small but similarly designed studies that contribute to a "global effort" or to helpful meta-analyses.[65]

We would be inclined to interpret ICH as referring most narrowly to Phase III efficacy trials, given the context, but even this reading does not dissolve the direct conflict. The RCP's point about global research programs, especially those struggling to help rare conditions, contradicts ICH's representation of individually powered trials that always provide "a reliable answer to the questions addressed."[66]

Conflict 9: Efficacy Stopping Rule

The U.S. National Cancer Institute (NCI) potentially conflicts with the Declaration of Helsinki and ICH statistical guidelines regarding the forcefulness of an efficacy stopping rule. NCI states:

> If participants are experiencing unexpected and severe side effects, or there is clear evidence that the risks are outweighing the benefits, then the IRB and the Data Safety Monitoring Board will recommend that the trial be stopped early. In other cases, a trial *might be stopped* because it is going particularly well. If there is clear evidence early-on that a new treatment or intervention is effective, then the trial *may be halted* so that it can be made widely available right away.[67]

Stopping to halt an arm on evidence of failure is given stronger, more mandatory language than stopping to halt an arm on evidence of success. Helsinki and ICH make no such distinction. In the words of Helsinki, "Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results."[68] Of course, depending on the trial arms, these cases could be two sides of the same coin — the success of one treatment renders the other totally obsolete, in which case the stopping rules should be symmetrical in force. Conversely, it may be that efficacy is not the only trial goal, so that the efficacy of one intervention does not automatically make it the only defensible choice over the comparator in terms of safety or cost-effectiveness; these considerations favor the asymmetry portrayed by NCI.

Conflict 10: Number of Trials Needed to Establish Superiority

We found two standards in potential conflict regarding trial number. The first, from the OHRP IRB Guidebook, is an endorsement of a standard proposed by Benjamin Freedman,[69] that a randomized clinical trial "must be designed such that its 'successful completion will show which [of the therapies] is superior.'"[70] This standard's inclusion in the Guide is not simply a poorly-worded attempt to establish that trials should be valid and duly powered; various types of equipoise are under discussion in this section (not only for superiority trials), and the requirement's suggestion that one trial should be sufficient is given in too universal a context (especially when one considers planned, multi-trial programs); it is

certainly inapplicable to Phase I-II studies, for example, and is at least problematic to apply for equivalence or non-inferiority trials.

On the other hand, there is a well-known FDA standard by which at least *two* trials are necessary before superiority evidence is deemed sufficient.[71] The two-trial standard potentially creates too stringent a requirement in the possible event that a study *does* manage to resolve equipoise with a single trial design (i.e., satisfying the Freedman standard).

In a U.S. Guidance for Rheumatoid Arthritis Trials co-produced by the FDA, a more active rationale is given for the two-trial standard:

> Because the persuasiveness of trials showing a difference is, in general, much greater than that of equivalence trials, it is highly desirable for a claim to be convincingly demonstrated in at least one trial showing superiority of the test agent over placebo or active control. If a claim of superiority over a specific comparator is sought, rather than just straightforward efficacy, the claim should be substantiated by two adequate and well-controlled trials showing superiority.[72]

In this case, the two-trial standard for superiority appears to derive from the greater difficulty in establishing superiority hypotheses compared to equivalence or non-inferiority. However, we found no corroborating claims in our other sources (including ICH's design and statistical standards) from which a specifically *two*-trial standard could be derived. It is also unlikely that the authors advocate separating a placebo-controlled trial from an active-controlled one to establish superiority. While this would establish the need for *two* trials at minimum, no reason is given for why a single trial could not incorporate placebo and active comparator arms (which the FDA otherwise advocates for equivalence trials; see Placebo Conflict above).

An anonymous reviewer of this article has suggested two resolutions. First, the FDA standard makes sense in the context of new test therapies, which require more verification when safety mixes with efficacy concerns, while the Freedman standard makes more sense in reference to superiority tests for established therapies (e.g., when safety data has been confirmed and the current hypothesis focuses on efficacy only). Second, the FDA guidance is quite negotiable in practice, with Phase III often waived based on data or context. If this is the case, then the unspoken exceptions would help clarify the rule with more official emphasis. Since these interpretations are consistent with both standards, but not overtly or helpfully expressed by them, we have accordingly downgraded this case from “direct” to “potential” confict.

Conflict 11: Sponsor Role in Data Analysis

Given the possibility of a commercial sponsor's vested interests in the outcome of a trial, the Royal Austral-asian College of Physicians (RACP) holds that, “with multi-[center] trials, it is desirable that analysis of the results... are undertaken by a committee of the investigators independent of the sponsoring company,”[73] to protect trial results from claims of biased interpretation. However, the U.S. FDA holds that “for a multi-center investigation, ... the sponsor and/or lead investigators will be responsible for analyzing the results of the overall investigation....”[74]

We have rated this as a potential conflict due to the fairly flexible terms used (“desirable” does not imply a requirement in every case). It is clear, though, that while the RACP holds sponsor involvement to be undesirable, the FDA does not.

As an additional potential conflict with both standards above, the World Federation of Neurosurgical Societies (WFNS) submits the following standard: “Investigators are

responsible to ensure that data analysis...is objective [and] free of commercial input, influence, or bias."[75] The most straightforward way to satisfy this investigator obligation is, among other important conflict of interest measures, to make sponsor involvement in data analysis not only undesirable (in the semi-lenient terms of the RACP), but prohibited (contrary to the FDA). However, the WFNS does not explicitly ban sponsor involvement, and because of the possibility of non-commercial sponsorship or investigator-sponsorship, this line only conflicts indirectly with the other two standards. The theme of controversial sponsor roles continues in the next standard.

Conflict 12: Sponsor Role in Producing the Integrated Full Regulatory Report of Indivdual Trials

National regulatory agencies require the submission of a trial report considerably more comprehensive than a published article. ICH guidelines call this the Integrated Full Report (a comprehensive report "of an individual study of any therapeutic, prophylactic or diagnostic agent...conducted in patients").[76] Sweden requires that the sponsor and investigator create the report "in collaboration."[77] CIOMS suggests, more specifically, that protocols should include "a mandatory obligation [of the sponsor] to prepare with, and submit to, the principal investigators the draft of the text reporting the results," especially for industrial sponsors.[78]

A French regulation on medical device trials, on the other hand, requires that the sponsor draw up the final report, with no word on investigator collaboration.[79] Without the added requirement of collaboration, this regulation stands in potential conflict with guidelines designed to include the investigator in the reporting process.

Conflict 13: Appropriate Staff to Obtain Consent

When investigators serve as treating physicians for patients, special considerations arise for the appropriateness of the physician-investigator to be the research recruiter and obtain consent. There are three positions on this topic. The first, by both American and South African regulations, assumes that the investigator obtains informed consent from the subjects.[80] The second view, from an Australian research society, holds:

> The actual granting of consent should be to someone other than the clinician primarily responsible for [the patient's] care.... When clinicians suggest to patients the possibility of involvement in studies in which they are investigators, independent professionals should be available to...undertake formal recruitment into the study.[81]

A third, slightly less committal position by the actual Australian government states that whenever there is a physician-investigator, "it should be considered whether" a separate consent-taker is appropriate (which does *not* imply separation in all cases).[82]

Separation prevents the subject from being influenced by real or imagined coercive circumstances, due to the "unequal or dependent relationship" that may exist between caregiver and patient.[83] Also, since the investigator is a caregiver, separation may help minimize therapeutic misconception.[84] Though clarifying the dual nature of a physician-investigator's role is important, it remains open which particular staffing and training schemes should be mandated.

Conflict 14: Qualifications of Investigators

Determining the qualifications of investigators and staff is an important pre-trial concern, especially for the supervisor position of Principal Investigator. Any confusion over what it takes to be a PI is notable. The American Society of Hospital Pharmacists (ASHP) argues

that “research, to be meaningful and productive in terms of a pharmacy's needs and goals in organized health care settings, must include the participation of pharmacists practicing in those settings,” and they conclude, “it is appropriate for pharmacists to function as principal investigators in research projects.”[85] This is in direct conflict with ICH, Finnish, and Swedish regulations identifying only registered physicians and dentists as principal investigators.[86]

Within the general consensus that PIs should, of course, be health care professionals and well-trained for whatever tasks the trial requires, and given the previously noted reality of international trial-conduct, it is bizarre that regulators should be so attached to the particular certification definitions at their own national levels. While there should be a check to ensure PI qualification (a purpose for which credentialing is designed), it is also important not to set up unnecessary barriers to research. Not only does the ASHP make a salient point about pharmaceutical PIs, but similar issues may be raised for allowing the role of PI to other non-M.D. health professionals (e.g., U.S. mid-level practitioners such as physician assistants or nurse practitioners, etc.), particularly if the trial circumstances would benefit from the differences in perspective or specialty.

Conclusions

Trends in Results

As the survey of conflicts presented above shows, many conflicts might only be potential conflicts, dependent upon interpretation or circumstance, though the source documents were not without direct contradictions in fundamental ethical and scientific issues (e.g., Completion Bonuses, Underpowered Studies). Also, while some conflicts involved standards related to trial initiation (Qualifications of Investigators), conduct (Efficacy Stopping Rules), or reporting (Identifiable Data in Trial Reports, Sponsor Role in Producing the Report, etc.), the majority of conflicts involved trial design (see Table 4).

We anticipated but did not find conflicts on a number of controversial topics, e.g., the ethics of “sham surgery” placebos,[87] the statistical appropriateness of composite endpoints,[88] and recent challenges to the connection between monetary incentives and coercion.[89] This may indicate that some controversies, though lively in peer-reviewed literature, may not have settled down sufficiently to be featured in officially endorsed regulations or professional position papers.

Limitations

Our compendium contains standards drawn from several documents in a process that isolated individual normative statements from their original paragraphs, possibly losing valuable context clues. By checking up on the contexts behind each potential conflict, we hope to have alleviated this concern. On the other hand, the original extraction method may better reflect actual IRB, regulator, and trialist practice of using bulky source documents as reference tools only rather than as whole works, in effect isolating specific sections out of context for their own operational guidebooks and institutional manuals. If the latter is the case, then the fact that certain lines even require extensive checking for clarity is an even more pressing concern regarding the usability of official trial standards.

Secondly, the cut-off date for document searching for the compendium, November 14, 2008, may not reflect more recent developments. This could have biased our presentation of current dissension either way, depending on whether the body of endorsed standards has become more or less contradictory over time.

Due to limitations in the ability to manage the large bulk of search results, not all documents found were extracted for the compendium; this, coupled with the exclusion of genetic specialties and special populations already mentioned, suggests that our collection of substantive conflicts is not comprehensive of all specialty trials, but only represents divergences in the norms for the most general clinical trial issues. Similar research devoted to these specialized areas is needed and would prove valuable in identifying conflict and clarity issues.

Implications

Overall, finding only a small handful of conflicts amid nearly 6,000 consolidated standards is a tremendously encouraging result, despite the limitations above. International researchers can be assured that for most general trial norms, regulators and professionals are on the same page across several political borders, diffusing concern over globalization of trial conduct. One hypothesis for this achievement of consensus lies in the existence of trans-national guideline issuers available for individual nations around the globe to consult (e.g., ICH, EU legislation, WMA's Declaration of Helsinki, etc.). Another hypothesis is that official guidance documents do not wish to make a stand on matters of great dissension until better consensus has already appeared in peer-reviewed literature; judgment is left to individual institutions in these cases. It does appear that when global entities do wish to take an official stand, that stand is effectively distributed, critiqued, refined, and accepted (as in the Oviedo Protocol and its rounds of national feedback).[90] As long as ethical and scientific researchers are committed to staying on top of the issues, it seems that official conflicts, though present and substantive, remain manageable in number and can easily be targeted for further discourse (very recently, U.S. regulators have even proposed to increase harmonization within U.S. Common Rule implementation).[91]

It is fortunate that the quantity of conflicts is manageable, since it is of great importance to manage each one, especially given their important quality. The majority of conflicts featured here involve trial design, which affects not only how trialists draft protocols, but also how regulatory, ethical, and scientific reviewers make determinations about those protocols. As we have categorized them, “design” standards encompass fundamental issues of scientific validity and its ethical implications (e.g., Conflicts 8 and 10), obligations to the subject during recruitment and consent (Conflicts 3, 5, 6, and 13), and difficult questions of risk and benefit for vulnerable groups (Conflicts 1-2). The consequences of trialists working from inconsistent design standards are therefore directly related to both the ethical and scientific quality of trials around the globe.

Why design conflicts are more prominent than initiation, conduct, analysis, or interpretation could admit of a number of interpretations. First, this result may validate the efforts of the CONSORT group, the International Committee of Journal Editors (ICMJE), and other groups specifically targeting consensus in trial reporting, and likewise for efforts made towards uniform, institutionalized guidance in trial launching and conduct (e.g., standards for prior and continual review by independent ethical boards, maintaining standards for trialist qualifications, expedited safety reporting, etc.). However, controversies surrounding trial design prove that the devil is still in the (designing) details and must be dealt with. If our speculation is correct, that means increasing the multi-national efforts targeting trial design issues specifically to develop consensus in just these areas, as CONSORT and ICMJE have done for reporting.

The character of each conflict is also noteworthy. The prevalence of potential conflict over direct conflict is arguably another positive result, indicating that *direct* dissension is very small at the level of finalized policy, even in a wide survey of documents. This is also arguably a negative result, revealing an extensive lack of clarity in policy standards, which

can be as obstructive to trialists as outright contradiction, and potentially harder to arbitrate. A great challenge to consensus standard-making, even when multiple nations concur on the "spirit" of the law, is to ensure the letter is precise enough to avoid interpretive problems such as those encountered in Conflicts 2, 5, and 7. No particular nation seems stronger than another in this regard (the U.S. IRB Guide is clearer on Conflict 2, but the U.K.'s Royal College of Physicians is preferred in Conflict 5), but hopefully when each of our source documents come up for review, a call for clarity will be heard. The U.S. IRB Guide, for example, has recently noted that the 1993 version could use an errata document to update its portrayal of federal regulations.[92] This would be a timely occasion to reflect upon the way regulations are summarized for use by independent reviewers.

We hope to have diagnosed some of the difficulties inherent in following, applying, and enforcing the current standards for clinical trials as they are officially endorsed. We will be pleased if our work can guide future philosophical and legal debates at the level of peer-reviewed discourse and stimulate greater organization within official codes, with the eventual result that some of the contradictions can be remedied, ambiguities clarified, and greater international consensus achieved.

Acknowledgments

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Appendix

Conflicting Standards and Outliers Not Discussed in Text

DC = "Direct Conflict," PC = "Potential Conflict." See commentary for interpretation of the nature of the conflict.

Standard numbers refer to consolidated standards by our team's taxonomy; verbiage may be a hybrid of equivalent standards from multiple sources.

Procedural Only

Who Registers a Trial

1.6.100.500.0 Before beginning the clinical phase of the research, researchers should register clinical trials in a publicly accessible register.[1]

PC

1.6.100.600.0 The investigator shall not register the clinical trial on any publicly accessible clinical trials registry, as this is the sponsor's responsibility.[2]

Commentary: The term "researcher" is commonly used to refer to an investigator. On this interpretation, the first line requires the investigator to register the trial, but the second prohibits the investigator from interfering with the sponsor's means of handling the responsibility. At best, holding both lines in their original verbiage results in a lack of clarity.

Meaning of Prior Trial Registration

1.6.100.200.0 Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.[3]

DC

1.6.100.400.0 Unless it is an exploratory clinical trial, the sponsor shall submit the clinical trial for listing in a free, publicly accessible clinical trial registry within 21 days of initiation of patient enrolment.[4]

Commentary: The first line requires registration before enrollment begins while the second establishing a three week grace period.

Regulatory Agencies' Access to Identifiable Data

2.7.4900.300.c Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations that the monitor(s), the auditor(s), the research ethics committee, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access. If any other entity, such as the sponsor of the study, may gain access to the study records, the subjects should be so informed.[5]

2.7.4900.300.d Study subjects should be informed during the informed consent process that regulatory authorities may inspect study records, including individual subject medical records.[6]

2.7.4900.300.e Subjects participating in studies involving investigational drugs must be told that the relevant regulatory authority may have access to their medical records as they pertain to the study.[7]

2.7.4900.300.f Absolute protection of confidentiality by regulatory authorities should not be promised or implied. Consent documents should neither state nor imply that regulatory authorities need clearance or permission from the subject for access to records identifying the subjects.[8]

PC

2.7.4900.300.g The patients shall be informed and give written consent for particulars which relate to the trial and which within the medical services may become the object of secrecy to be examined by personnel from the sponsor and foreign authority for medicinal product control in connection with quality control and quality assurance. A proviso entailing that the particulars will not be passed on shall be made.[9]

2.7.4900.300.h The person participating in a trial must consent to the scrutiny of personal information during inspection by competent authorities and properly authorized persons, provided that such personal information is treated as strictly confidential and is not made publicly available.[10]

PC

2.14.100.300.b The sponsor shall not disclose the identity of clinical trial subjects to third parties without prior written consent of the clinical trial subject, unless in relation to a claim or proceeding brought by the clinical trial subject in connection with the clinical trial.[11]

2.14.100.310.0 Personal data shall not be disclosed to the sponsor save where this is required to satisfy the requirements of the protocol or for the purpose of monitoring or

adverse event reporting, or in relation to a claim or proceeding brought by the clinical trial subject in connection with the clinical trial.[12]

Commentary: Confidentiality standards, and related standards on informed consent information regarding confidentiality, are unclear regarding the degree of access to identifiable information a subject can expect regulatory agencies, monitors, and ethics committees to have. The first set of standards imply full, direct access; the second set provide for limitations on the ability of the authority to disseminate materials further (2.7.4900.300.g was particularly hard to interpret, though, both in and out of its original context); the third set may be interpreted as restricting the sponsor from disseminating data to authorities ("third parties") without a stronger form of consent than may be implied by the other standards.

Protocol Change Approval Process, Including Verbal Disputes

3.5.1000.400.0 An application of amendments identified as substantial should be submitted to the Ethics Committee that gave the initial favorable opinion.[13]

3.5.1100.100.0 An application of amendments identified as substantial should be submitted to the regulatory authority.[14]

PC

3.5.1000.50.0 A sponsor must obtain research ethics committee approval prior to implementing a change to an investigational plan.[15]

3.5.1000.100.0 All study amendments must be notified to and approved by the research ethics committee.[16]

3.5.1000.200.0 No change to the protocol may be made without consideration and approval by the committee.[17]

3.5.1000.300.0 As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to the research ethics committee for review and approval/favorable opinion.[18]

3.5.1100.150.0 As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to the regulatory authority(ies) if required.[19]

Commentary: There appears to be a discrepancy in lines requiring approval for protocol changes in only some cases (first set, distinguishing "substantial" from "minor") and lines which seem to require any amendment (substantial or not), as well as other changes besides protocol amendments, to be approved.

Possible confusion is also likely due to variation in definitions. There is no standardized way to refer to changes requiring independent approval (through IRB/REC and/or governmental regulatory supervision) as opposed to changes which do not. "Substantial" vs. "minor" amendment, in some cases of U.K. usage, encapsulates the difference between changes requiring review and changes which do not, respectively.[20] In all other documents, this distinction is made less formally, and various terms are used ("modification," "amendment," "change") without built-in connotations regarding required review-level.

Data Management in the Face of Systems Upgrades

3.7.600.100.0 Recognizing that computer products may be discontinued or supplanted by newer (possibly incompatible) systems, it is nonetheless vital that sponsors retain the ability to retrieve and review the data recorded by the older systems.[21]

PC

3.7.600.150.0 All versions of application software, operating systems, and software development tools involved in processing of data or records should be available as long as data or records associated with these versions are required to be retained.[22]

Commentary: The first standard merely requires that sponsors confirm that, after systems upgrade, data will remain cross-version compatible. The second standard is more conservative, requiring that backup copies of old program versions remain present at a trial site throughout trial retention periods (according to other compendium standards, this time period can range several years beyond analysis and publication of data; see below). This equivocation is found within a single document and is therefore best interpreted as an imprecision in policy rather than divergent policies.

Mandatory Sample Retention after the Trial

5.2.400.125.0 Reference samples from each manufacturing batch shall be kept by the manufacturer for at least two years after the clinical trial has been terminated, or for at least one year after the final expiry date has passed if this occurs at a later date.[23]

PC

5.2.400.150.0 To the extent stability permits, samples should be retained by the sponsor either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period. [24]

Commentary: This is a regulatory difference, expressing different methods for enacting the overall standard to retain pharmaceutical samples. See also the next entry:

Mandatory Archiving Period After the Trial

Note: Our team deemed the subcategory of standards dealing with mandatory archiving to contain subtle conflicts throughout the whole section, not easily divided into discrete conflicts. Different regulatory environments range from 2 to 20 years of post-trial mandatory archiving periods (plus some less quantitative criteria).

5.2.500.100.0 Accurate and complete records of research data should be maintained until there has been sufficient time for critical review.[25]

5.2.500.150.0 The medical files of trial subjects shall be retained in accordance with the maximum period of time permitted by the hospital, institution or private practice.[26]

5.2.500.200.0 Data from original research should be retained for a reasonable period of time, particularly for data that is used to substantiate a claim, or to prove or disprove a hypothesis.[27]

5.2.500.250.0 Where a trial is using materials of biological origin, or other materials where there is limited experience of their long-term use, records should be preserved for long enough to enable participants to be traced in case evidence emerges of late or long-term effects.[28] 5.2.500.275.0 The sponsor should inform the investigator(s) and institution(s) in

writing of the need for record retention and again when the trial-related records are no longer needed.[29]

5.2.500.300.0 Essential documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor.[30]

5.2.500.400.0 An investigator shall retain records required to be maintained for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the relevant regulatory authority is notified.[31]

5.2.500.500.0 An investigator shall maintain the records required during the investigation and for a period of 2 years after the latter of the following two dates: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.[32]

5.2.500.550.0 A sponsor shall maintain the records required during the investigation and for a period of 2 years after the latter of the following two dates: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.[33]

5.2.500.600.0 The sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.[34]

5.2.500.650.0 A sponsor shall retain the records and reports required for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the relevant authority has been so notified.[35]

5.2.500.700.0 Protection of human subjects regulations require institutions to retain records of research ethics committee activities and certain other records frequently held by investigators for at least 3 years after completion of the research.[36]

5.2.500.800.0 The investigator shall retain the essential documents relating to a clinical trial for at least 5 years after its completion, or for a longer period where so required by applicable requirements or an agreement between the sponsor and the investigator.[37]

5.2.500.900.0 The sponsor shall retain the essential documents relating to a clinical trial for at least 5 years after its completion, or for a longer period where so required by applicable requirements or an agreement between the sponsor and the investigator.[38]

5.2.500.1000.0 For clinical trial data a minimum archiving period of 10 years is specified for investigators.[39]

5.2.500.1100.0 The investigator shall store and maintain the documentation of the clinical evaluation of the medical device including the final report for the period of 10 years.[40]

5.2.500.1200.0 For clinical trial data a minimum archiving period of 10 years is specified for sponsors.[41]

5.2.500.1300.0 It shall be ensured that source data is available at the trial site for at least 15 years after the final report is available.[42]

5.2.500.1400.0 All procedures and all records, located with all those who are or have been involved in the conduct of a trial, shall be available for at least 15 years after the final report is available.[43]

5.2.500.1500.0 Any documents and records related to the clinical investigation shall be safe-kept for at least 20 years after the clinical investigation completion.[44]

OUTLIERS AND OUTLIER CONFLICTS

Investigators Choosing Consultees (Surrogates)

2.7.550.300.0 Where there is no-one who meets the conditions for a consultee for a person who lacks capacity to consent, the researcher must nominate a person to be the consulted.[45]

Commentary: Consultees (a U.K. term for those charged with providing surrogate consent and consultation on behalf of the subject; cf. U.S. “legal representative”) are chosen based on criteria related to subjects’ known wishes and relationships. This line is generally problematic by giving someone interested in the research project arbitrary decision-making power to determine the consultee when other conditions fail. Though this system is not without boundaries (e.g., the consultee “must be involved in the person's care” and “must be interested in the person's welfare” and “must not be a professional or paid care worker”), a more independent process, in keeping with both U.S. practice and the spirit of other highly structured U.K.-norms on “qualifying relationships,” would seem in order.[46]

Fullest Possible Information in Consent

2.7.2550.175.0 Particular care should be taken to ensure that potential participants have the fullest possible information about the proposed study.[47]

Commentary: The wording of this standard is clearly misleading when one considers the common and often necessary measure of blinding the subject to treatment; as a practicality issue, including irrelevant technical details for layperson subjects, even when this does not threaten validity, is likely to reduce the subject's overall understanding. All other standards are more careful to define relevant information as a function of voluntary consent. Examples (emphasis added):

2.7.2550.200.0 The informed consent and any other written information given to participants should provide *adequate* information for the participant *to make an informed decision about participating*.[48]

2.7.2550.200.a Those patients whom the responsible investigator assesses as being capable of being included in a clinical drug trial shall receive such information on the trial that they can voluntarily decide whether they wish to take part or not.[49]

Informing Subjects of Post-Trial Access to Results

2.7.5730.50.0 Before requesting an individual's consent to participate in research, the investigator must provide information that, after the completion of the study, subjects will be informed of the findings of the research in general and individual subjects will be informed of any finding that relates to their particular health status.[50]

Commentary: The language of this consent standard assumes that the subject will have access to the "findings of the research in general," but standards directly referring to subject rights to post-trial access of results only ensure access to results relevant to subject health needs (with certain exceptions permitted). CIOMS provides a much safer consent norm (emphasis added):

2.7.5730.75.0 Investigators should inform subjects *of what* information gained from the study will be passed along to them.[51]

Dictating the Risk-Benefit Ratio

2.7.4850.100.0 Human subjects participating in clinical research programs should be assured that the potential benefit of the research outweighs the risks.[52]

Commentary: Though not technically contrary to other standards requiring that subjects be informed of risks and benefits, this is the only standard that allows the consent information to represent benefits as *outweighing* the risks. Including such a statement has the potential to undermine a key purpose of any medical consent — allowing the subject to deliberate on the risks and benefits by his/her own particular values and risk-taking preferences, without paternalistic pressure from the medical/trial staff. Ethics committee approval of the risk-benefit ratio is not the only such judgment to consider in trial ethics.

Informing Subjects of the Content of Committee Approval

2.7.3300.100.0 The information given to persons being asked to participate in a research project or to those being asked to authorize participation of a person in a research project shall include the opinion of the research ethics committee.[53]

2.7.3300.200.0 Before requesting an individual's consent to participate in research, the investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of the written information given approval/favorable opinion by the research ethics committee.[54]

Commentary: Although subjects are routinely told of the *fact* of ethics committee approval, our lead investigators could not recall ever being called on to include documentation or details of that approval in the consent materials. This may reflect the nature of experience of our research team (American), vs. the mostly European-centered sources of these standards (contributors include the Council of Europe Bioethics Division, CIOMS, ICH, and European Commission). Hence, this outlier may point to an implicit conflict or omission of U.S. practice versus international standards rather than a "fluke" or poorly worded standard, as in the other outliers.

Debriefing as a Means of Negating Harms

2.7.6000.300.b In some circumstances of debriefing subjects who have been deceived, the verbal description of the nature of the investigation would not be sufficient to eliminate all possibility of harmful after-effects; for example, an experiment in which negative mood was

induced requires the induction of a happy mood state before the participant leaves the experimental setting.[55]

Commentary: This standard relates to debriefing subjects in cases where research required deception or incomplete disclosure. It presupposes that one purpose of debriefing is to "eliminate all possibility of harmful after-effects," but aside from offering one example, it does not explore the force of this presupposition, including what kinds of harms require recompense (minor discomfort, temporary anxiety, etc.), or what to do when a form of commensurable recompense is not feasible. Debriefing is a practice designed to offset the original lack of consent and, in some cases, to allow subjects the opportunity to retract their data; it is not necessarily well-suited as a tool for compensating subjects and is noticeably absent in the standards directly related to that topic.

Ignoring the Reality of Crossover, Drop-out, and Withdrawal

2.9.400.500.0 After assignment has been revealed, the participants themselves should not be able to alter the assignment.[56]

Commentary: Crossover, though scientifically undesirable, is a factor in any trial reflecting the ethical requirement that subjects' voluntary consent be maintained throughout the trial, not just initially. Taken broadly, this standard would also ignore the reality of subjects dropping out and withdrawing, insofar as that "alters the assignment" on the basis of the same ethical value. Though the idea of subject withdrawal as an inalienable right has come under fire in peer-reviewed literature, we did not find evidence of this challenge at the level of official endorsement.[57]

Stringent Constraints on High-Risk Trials, with a Self-Experimentation Exception

2.11.100.800.0 No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.[58]

Commentary: Taken flatly as stated in the Nuremberg Code, the first half of this standard contradicts the common and necessary conduct of trials investigating serious illnesses for which death or high morbidity is the reliable endpoint (albeit under certain ethical constraints and conditions, e.g., data monitoring). The exception clause is not the sort of consideration found in more recent standards, but it does represent a fascination with self-experimentation found in early research ethics case studies and scholarship.[59]

Physician Equipoise vs. Clinical Equipoise

2.11.200.400.0 Participating physicians have a primary responsibility to their patients and must provide for individual patients what they consider to be the best medical care, combining medical research with medical care only if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.[60]

Commentary: Though physicians should not be expected to ignore their conscience or Hippocratic Oath, generalizing this line could suggest a *de facto* constraint on research proposals stronger that those suggested by other standards. Physician equipoise is importantly different from *clinical* equipoise used in the regulatory contexts. A research proposal based on clinical equipoise appeals to lack of consensus between physicians, regardless of the strength of their individual convictions; a restriction based on physician equipoise is stronger and would allow only for trials on topics for which a feasible number of physicians lack confidence individually. A possible tension between ethics and science

may also be implied: it is ethically more satisfying for physicians in equipoise to recruit for research, by the logic of this outlier, but scientifically confounding variables may be introduced by such a systematic preference for subject recruitment.

Variant Wordings on Risk-Benefit Ratio

2.13.100.150.0 The risk of study participation relative to benefits should be low or nonexistent.[61]

2.13.100.500.a Individual investigators must consider whether the discomfort and inconvenience, or maybe risks, to which patients are to be exposed are reasonable, taking into account the nature of the project, the patient population to be studied, and the likely benefits.[62]

Commentary: The overwhelming preference in diction when discussing risk-benefit ratios is that the risk must be “reasonable” in relation to the benefits. The phrase “low or nonexistent” in Std. 150 could be taken to imply stronger criteria. In Std. 500.a, the use of the phrase “maybe risks” is anomalous — all other sources take risks (i.e., of potential harm) as seriously as any actual harm when interpreting what is reasonable.

Time-Frame for Expedited Reporting

3.2.1800.400.0 All adverse events that qualify for expedited reporting must be reported to the research ethics committee within the protocol-designated time-frame.[63]

Commentary: All other sources (including the U.S., U.K., and Europe) establish the time-frame for expedited reporting as a point of official regulation; it is not up to the protocol authors to decide that time-frame.

Blinded Data Monitoring Committee

3.2.2200.75.0 When reporting SUSARs (Suspected Unexpected Serious Adverse Reactions), the blind should be maintained for persons responsible for the analysis and interpretation of results, e.g. the Data Monitoring Committee, and for staff working on separate trials.[64]

Commentary: Review of unblinded data is standard practice for DMCs. When there are investigators, direct sponsor-employees, or other individuals sitting in on a DMC meeting for whom maintaining the blind is relevant, the meeting is often divided into an “open” session (blinded), and a “closed” session (unblined, when blinded personnel are not present). There is an entire taxonomic division of trial standards devoted to the appropriate use, composition, and conduct of DMCs based on the fact that they may be unblinded (11 subcategories with 144 consolidated standards).

Protocol Change and Risk Increase

3.5.1100.1200.0 All requests to the regulatory authority for change or modification to the protocol of a device trial should state a statement to the effect that such change(s) do not increase the risk to either the patient or user.[65]

Commentary: This standard is curiously specific, requiring that no device trial can be changed in such a way that increases the risk. In our taxonomic division devoted to protocol changes (15 subcategories with 49 relevant consolidated standards), there is no other mention of this constraint in either device or medicinal trials; changes that affect the safety profile of the trial may be made (with updated review and approval), and presumably the safety changes of nontrivial interest in these cases are those increasing risk or decreasing benefit.

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155. Referring to Council of Europe Bioethics Division, *supra* note 22.

91. 76 FR 44528.

92. See Penslar, *supra* note 12, main page.

There are two related conflicts dealing with vulnerable populations (children, the mentally disabled or incompetent, the underprivileged, prisoners, etc.). The first is about their inclusion in general, while the second focuses on inclusion in non-therapeutic trials.

There is a long history of tension between the scientific usefulness of placebo control and the ethical value of beneficence, which resists the idea of giving patients false-therapies. Debates in ethical literature motivated several revisions of the Declaration of Helsinki to clarify the topic. What has been officially codified? We found greater clarity in the latest versions of control group standards, leaning in the direction of tolerating placebo use within commonly formulated conditions, but the voices are not entirely univocal.

Overall, finding only a small handful of conflicts amid nearly 6,000 consolidated standards is a tremendously encouraging result. International researchers can be assured that for most general trial norms, regulators and professionals are on the same page across several political borders, diffusing concern over globalization of trial conduct.

Table 1

Methods Notes

Step	Notes and Definitions
Document Search Strategies	**Top countries** were defined as >700 trials underway at the time of access (July 24, 2008); nations had close and continuous numbers down to 700, then the numbers jumped to 516 trials (Greece), so the 700 mark presented itself as a natural cut-off point, yielding 31 nations. **Source documents** were those issued by some combination of national regulatory agencies, inter-agency collaborations, professional medical societies, funding agencies or coalitions, NGOs, and/or government advisory bodies. We defined **officially endorsed** documents as those which were still available and had not been superseded or rescinded as of our search cut-off date of November 14, 2008. As such, all documents represent finalized policy. Norms expressed solely in peer-reviewed journal articles were not used, since this is the expected place to find fluid debate and variety of opinion. By the time of official regulatory and professional endorsement, however, norms are expected to be as standardized and as univocal as possible.
Extracting Standards	**Core documents** are those displaying a comprehensive range of trial guidance topics and/or a high degree of influence. Examples include Council of Europe legislation, E-series documents from the International Conference on Harmonization (ICH), and multiple FDA and OHRP regulations and guidelines.
Organizing and Consolidating Standards	**Procedural** standards were those regarding compliance with conventional administrative systems, with no implications on ethical or scientific guidance. **Platitudes** were defined as statements of value too general to dictate specific actions in trial situations. **Vulnerable/special groups** not fully analyzed at this time include minors, the mentally disabled, the underprivileged, those in subordinate positions, subjects with desperate injury or illnesses (as a subject class), prisoners, and pregnant women or those of child-bearing potential.

Table 2

Working Definitions

Category	Definition
Direct Conflict	Two or more standards are logically contrary or contradictory (cannot both be true or satisfied at once).
Potential Conflict	Two or more standards are contrary, but only under certain trial circumstances or certain readings of vague or ambiguous wording in the standards (may not be satisfied at once in specific but important cases).
Outlier	A standard which conflicts with a large number of other established standards, common trial practices, and apparently unproblematic consensus. Outliers, often due to imprecise wording, were set aside as flukes and are featured in the Appendix for reference; conflicts between outliers and other specific lines were not fully itemized.
Exception/Specification	One standard specifies a case in which another, more general standard does not hold; an innocuous relationship to be distinguished from a conflict. Standards found to bear this relationship were not itemized with the conflicts.

Table 3

List of Topics Involving Conflicts

Discussed in Methods (Example for Definitions)
Local Custom vs. Researcher Standards in Multinational Research
Discussed in Results
1. Inclusion of Vulnerable Subjects
2. Non-therapeutic Research in Vulnerable Populations Related Outlier: “The Subject Takes Precedence”
3. Completion Bonuses to Subjects
4. Subject Treatment or Compensation for Injury
5. Representing the Investigational Arm to Subjects
6. Pre-Randomization
7. Placebo Control Groups
8. Underpowered Studies
9. Efficacy Stopping Rule
10. Number of Trials Needed for Conclusive Evidence
11. Sponsor Role in Data Analysis
12. Sponsor Role in Producing the Integrated Full Regulatory Report of Individual Trials
13. Appropriate Staff to Obtain Consent
14. Qualifications of Investigators
Procedural Only – In Appendix
Who Registers a Trial
Meaning of Prior Trial Registration
Regulatory Agencies’ Access to Identifiable Data
Protocol Change Approval Process, Including Verbal Disputes
Data Management in the Face of Systems Upgrades
Mandatory Sample Retention after the Trial
Mandatory Archiving Period after the Trial

Table 4

Areas of Conflict in Taxonomic Context

Conflict(s)	Taxonomic Area(s) Involved
Qualifications of Investigators	1.7 - Standards Related to Choice of Trial Staff and Centers to be Studied 1.7.200 - Qualifications of Staff - Investigators and Statisticians 1.7.200 - Qualifications of Staff - Investigators and Statisticians
Inclusion of Vulnerable Subjects Non-therapeutic Research in Vulnerable Populations “The Subject Takes Precedence” Outlier	2.5 - Standards Related to Selection of Study Subjects 2.5.400 - Inclusion of Vulnerable Subjects
Appropriate Staff to Obtain Consent	2.7 - Standards Related to Consent 2.7.400 - Appropriate Staff to Obtain Consent
Completion Bonuses to Subjects	2.7.1800 - Undue Inducement and Coercion - Payments and Rewards
Representing the Investigational Arm to Subjects	2.7.4500 - Mandatory Information on Treatment Allocation 2.7.6000 - Limited Disclosure, Deception, and Misleading Statements
Pre-Randomization Placebo Control Groups	2.7.4500 - Mandatory Information on Treatment Allocation 2.9 - Standards Related to Assignment of Subjects to Different Groups 2.9.200 - Allocation Concealment 2.9.400 - Allocation Implementation 2.8 - Standards Related to Choice of Control 2.8.300 - Use of Placebo Controls & & 1.4 - General Standards Related to Protocol Development and Content 1.4.300 - Scientific Background
Under-powered Studies	2.15 - Standards Related to Planned Statistical Analysis 2.15.100 - Sample Size Determination
Subject Treatment or Compensation for Injury	2.16 - Standards Related to Financial Obligations 2.16.100 - Treatment of Research-Related Injury 2.16.300 - Compensation for Research-Related Injury 2.16.600 - Insurance to Cover Subject Losses
Efficacy Stopping Rule	3.4 - Standards Related to Data Monitoring During the Trial and Related Decisions 3.4.800 - Stopping Rules
Number of Trials Needed for Conclusive Evidence	4.2 - Standards for Interpreting or Generalizing Results 4.2.100 - Drawing Conclusions about Clinical Significance
Sponsor Role in Data Analysis	4.1 - Standards for Statistical Analysis of Data 4.1.2000 - Multi-Center Analyses 4.1.2100 - Researcher Role in Data Analysis

Conflict(s)	Taxonomic Area(s) Involved
Sponsor Role in Producing the Full Integrated Regulatory Report of Individual Trials	4.3 - Standards for Reporting Results 4.3.200 - Preparing the Final Report