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Defining Compliance, Serious Noncompliance, and Continuing Noncompliance in IRB Policies

By Robert S Bienkowski

Introduction

Institutions conducting research involving human subjects and operating under either the Common Rule or FDA regulations for protection of human research subjects are required to have "written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of…any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB…"[1] The terms *noncompliance*, *serious noncompliance,* and *continuing noncompliance* are not defined in the regulations, and there is no regulatory requirement that an institution define them in their written procedures. However, a determination of serious or continuing noncompliance can adversely affect an investigator's (and the institution's) reputation, so it is fair and prudent that an institutional entity charged with evaluating such allegations and making determinations[2] have clear definitions of the terms — fair because the investigator has a reasonable expectation of knowing the rules, and prudent because a determination based on undefined terms may not be sustainable if an investigator contests the decision.

There are, however, significant variations in the definitions currently used by different IRBs, so persons or committees reviewing allegations based on the same set of facts but using different definitions can arrive at different conclusions. Furthermore, some definitions allude to forms of noncompliance covered by regulations beyond the IRB's scope of responsibility, authority and expertise, which can lead to bungled investigations. The purpose of this study was to assess variations in the definitions, evaluate how broadly applicable they are to different kinds of noncompliance, and recommend definitions that address potential deficiencies.

Methodology

Institutional Policies

A Google search conducted in September and October 2013 using the terms *irb, compliance*, *serious noncompliance,* and *continuing noncompliance* yielded policies from institutions classified as research universities, colleges, academic medical centers, community hospitals, and "other," which included Veterans Affairs medical centers, free-standing research institutes, and central IRBs. The first set was a testing set (n=70), which was used to analyze policies and definitions in detail and search for commonly used word strings and themes. The second set was a confirmatory set (n=68), which was used to validate the themes identified in the first set. The number of policies analyzed in this paper (138) was relatively low compared to the more than 3500 IRBs registered in the United States because very few institutions have posted their operating policies and procedures online.

Throughout this paper, the term *noncompliance* means research compliance committed by an investigator or a member of a research team. Definitions of institutional noncompliance, that is, noncompliance committed by an IRB member or staff, or by persons with responsibility for administering or supporting an institutional human research protection program, were tabulated but not analyzed.

Themes

Themes were identified by reducing candidate word strings to their simplest form (e.g., by dropping two-letter words), considering variants with similar meanings, and repeating the process until most definitions in the set included at least one theme.[3] (The process converged rapidly.) The very few definitions that did not include one of the common themes were coded separately and not included in the analysis.

In general, definitions of noncompliance and serious noncompliance were very short. It was easy to identify themes based on key words and simple word strings. Definitions of continuing noncompliance were usually longer and more complex, making it more difficult to identify individual themes on first reading. To address this problem, each phrase in each definition was analyzed, tagged and indexed, and the index recorded in a spreadsheet. The various entries were then sorted and analyzed for identical or similar key words, word strings, and concepts. The key words, word strings, and concepts were grouped thematically, and then the definitions were coded according to which themes they contained. Many definitions contained two or more themes.

Statistical Analysis

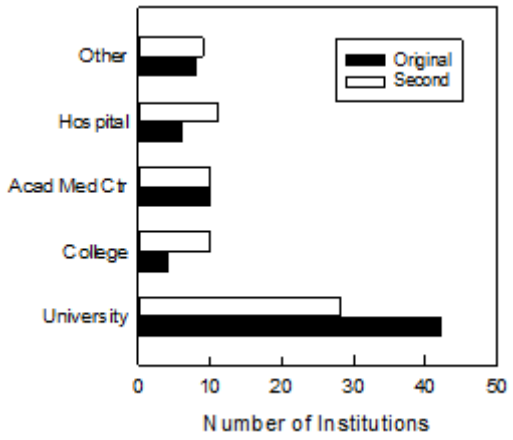
To validate the methodology, the distribution of categories of institutions and distributions of various themes in noncompliance policies in the first and second sets were compared statistically using the chi-squared method. Calculations were not adjusted for multiple comparisons.

Results

Institutional Representation

The first set of institutions appears over-weighted for research universities, but the distributions among the five categories in the testing and confirmatory sets do not differ significantly. (Figure 1; p = 0.14)

Figure 1. Types of institutions whose policies were examined



Original (testing) set, n=70; Second (confirmatory) set, n=68. The difference between the distributions is not statistically significant.

Definitions of Noncompliance

Analysis of definitions of noncompliance revealed three distinct themes:

- **N1.** Noncompliance with federal, state and local laws and regulations governing human subjects research.
- **N2.** Noncompliance with institutional policies governing human subjects research.
- **N3.** Noncompliance with specific directives or determinations of the IRB.

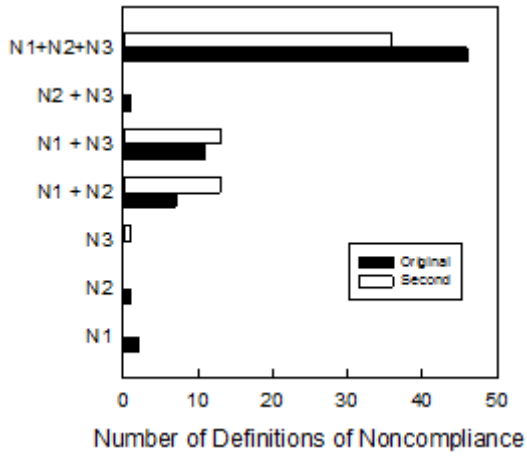
All three themes (N1+N2+N3) appear in the definition published by AAHRPP.[4] However, some institutions use only two themes and a very small number use only one. Omission of theme N3 from a small but not negligible set of definitions is puzzling, given the role of the IRB in making determinations of noncompliance and that this provision appears explicitly in the regulations.[1]

The distribution of themes in the two sets does not differ significantly. (Figure 2; $p > 0.2$) The appearance of the same themes in approximately the same frequencies in definitions of noncompliance in the testing and confirmatory sets (as well as in the definitions of serious and continuing noncompliance discussed below) supports the validity of the methodology.

Several institutions amplify their definitions with statements such as: *Noncompliance may range from minor to serious, be unintentional or willful, and may occur once or several times*.

Two policies in the first set and three in the second set do not have definitions of noncompliance (at least in the documents that defined serious and continuing noncompliance). The gravity of this omission is unclear, but it seems illogical to define serious noncompliance or continuing noncompliance (let alone make determinations) without a clear definition of the underlying concept. Although the sample is small, the finding that five institutions out of a total of 138 do not define noncompliance suggests that 2 to 8% of all institutional policies lack this definition.[5]

Figure 2. Distribution of themes in definitions of noncompliance



N1: Noncompliance with federal, state and local laws and regulations
N2: Noncompliance with institutional policies
N3: Noncompliance with specific directives or determinations of the IRB

The difference between the distributions is not statistically different. However, data for N1, N2, N3 and N1+N3 were not included in the calculation because the samples were too small for a valid calculation.

Definitions of Serious Noncompliance

Three major themes emerged from the analysis of definitions of serious noncompliance in the testing set, and these themes were also present in the confirmatory set:

- **S1**: Serious noncompliance consists of *noncompliance that adversely affects the rights or welfare of subjects.* (FDA considers "noncompliance that adversely affects the rights and welfare of human subjects" to be a grounds for disqualifying an IRB.[6]) S1 is essentially the succinct and comprehensive statement contained in the Huron Toolkit,[7] which was freely available for several years. It should be noted that, although this theme contains two distinct elements, rights and welfare, they are always stated together.
- **S2** considers only increased risks to subjects. (One variant speaks of causing harm, which is a much more stringent requirement than increasing risks.)
- **S3** considers only decreased benefits. S3 never appears alone; it is always stated with S1 or S2

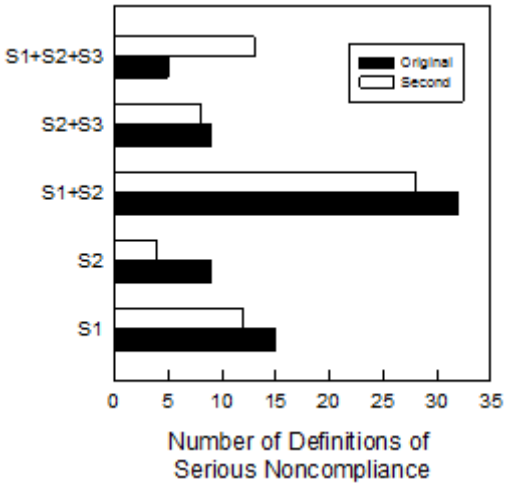
The distributions of S1, S2 and S3 in the original and confirmatory sets were not significantly different. (Figure 3; $p = 0.20$)

Theme S1 seems sufficient to cover all eventualities that an IRB might encounter when considering allegations of serious noncompliance. In contrast, a definition of serious noncompliance based only on increased risk to subjects (S2) or only on increased risk and decreased benefit (S2+S3) may not be adequate to determine even egregious violations of subject rights, as articulated in the Belmont Report.[8] For example, withholding information that might influence a person's decision to continue participating in a research study would

violate the principle of autonomy, and employing recruitment procedures that take advantage of individuals' vulnerabilities would violate the principle of justice, but neither would necessarily increase risks or decrease benefits. On the other hand, definitions that combine S1 with S2 or S3 are unnecessarily complex because S2 (increased risks) and S3 (decreased benefits) are covered by the welfare provision of S1.

Several definitions include examples of noncompliance that are always considered serious, such as substantive modifications to IRB-approved research without IRB approval, conducting non-exempt human subjects research without IRB review and approval or without appropriate informed consent, and not following the approved protocol. These examples are based on guidance from the Office for Human Research Protections (OHRP) in public presentations or responses from OHRP staff to specific queries.[9] Each example meets the definition of serious noncompliance covered by theme S1.

Figure 3. Distribution of themes in definitions of serious noncompliance



S1: Adversely affects rights or welfare of research subjects
S2: Increases risks to subjects
S3: Decreases potential benefits for subjects

There is no statistically significant difference between the distributions.

Definitions of Continuing Noncompliance

Three major themes emerged from analysis of the definitions of continuing noncompliance and they reflect different meanings of the word *continuing*.

- **C1** is *persistent failure to adhere to the laws, regulations or policies governing human research.*

This definition, which appears, for example, in the VA Handbook,[10] covers a pattern of noncompliance that ranges from trivial to serious, so an IRB employing this definition alone would have to justify why persistent noncompliance of a very minor nature justifies a finding that is reportable to federal oversight agencies. The terms *continuing* and *persistent* are largely synonymous, but *persistent* implies willfulness, a concept that will be discussed below.

- **C2** is *a pattern of noncompliance that, if allowed to continue, is likely to increase risk to subjects.*

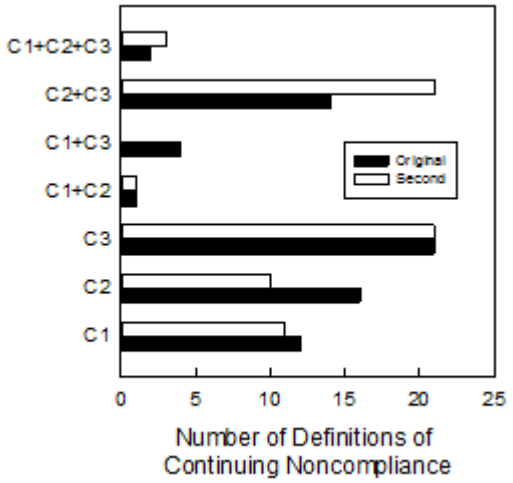
Here, *pattern of noncompliance* means a set of noncompliant actions that do not individually meet the criteria for serious noncompliance, and *continue* indicates that the actions occurred over a period of time, perhaps up to when the matter was brought to the IRB's attention. Not allowing the pattern to continue might consist of suspending approval for all or part of a protocol (which, in itself, would be reportable according to the Common Rule and FDA regulations) or mandating corrective action. In either case, it is the recognition of the likelihood of increased risk to subjects that triggers the determination of continuing noncompliance.

- **C3** is *a pattern of noncompliance that continues to occur after a report of noncompliance and a corrective action plan have been reviewed and approved by the IRB.*

In this case, the IRB might have reviewed reports of noncompliance that were not serious and not even alarming enough to require suspension of approval. As used here, *continuing* connotes recurrence of the noncompliance *after* the IRB-mandated corrective action. It is the recurrence that is reportable as continuing noncompliance, not the original pattern of noncompliance. Several definitions include *failure to respond to a request to resolve an episode of noncompliance*, and this was coded as C3.

The distribution of themes C1, C2 and C3 in institutional policies is shown in Figure 4. There is no difference between the testing and confirmatory sets ($p > 0.05$). Note that 21 definitions contained two or more themes and were essentially compound definitions. When each is used alone, C2 and C3 are too limited because they cover different circumstances. To illustrate the problem, consider the following scenarios, involving two complex, FDA-regulated protocols that present the same levels of risk and are approved at the same time. At continuing review, each protocol has enrolled approximately 100 participants.

Figure 4. Distribution of themes in definitions of continuing noncompliance



C1: Persistent failure to adhere to the laws, regulations or policies governing human research.
C2: A pattern of non-compliance that, if allowed to continue, is likely to increase risk to subjects
C3: A pattern of noncompliance that continues to occur after a report of noncompliance and a corrective action plan have been reviewed and approved by the IRB

There is no statistically significant difference between the distributions. (However, the data at C1+C2 were not included because the sample was too small for a valid calculation.)

In the first scenario, an investigator reports 10 deviations involving different participants: two instances of using the wrong version of the consent form, four instances of consent forms signed but not dated by participants, one follow-up visit scheduled out of window by a coordinator, two different failures to order required blood tests, and one telephone follow-up call missed by a coordinator. The site monitor did not consider any of these deviations to be serious but did recommend that the investigator pay greater attention to detail. Most IRBs would probably find that none of these deviations meets the criteria for serious noncompliance. However, an IRB using C2 could determine that this set of deviations constitutes a pattern that would likely lead to an increase in risk to subjects, require corrective action, and make a determination of continuing noncompliance. In contrast, an IRB using only C3 could not make a determination of continuing noncompliance.

In the second scenario, an investigator reports 10 instances of consent forms that were signed but not dated. Again, neither IRB considers these deviations as meeting the criterion for serious noncompliance,[11] but both require corrective action plans. A report six months later reveals that two of 10 new consent documents are undated. An IRB using C2 might conclude that, for practical purposes, the pattern of noncompliance has ended. In contrast, an IRB using C3 might conclude that any recurrences after the corrective action meet its criterion for continuing noncompliance.

In summary, both C2 and C3 are required to cover all cases of continuing noncompliance, but C1 is not.

Other Matters

"Willfully" and "Knowingly"

Most definitions are silent on the issue of whether an investigator willfully or knowingly committed noncompliance. However, some address the matter explicitly and state that noncompliance can be either intentional or unintentional and committed knowingly or not. Inclusion of "willfully" or "knowingly" in a definition is problematic because it suggests that an IRB might not make a finding of serious noncompliance when someone unintentionally or unknowingly disregards federal regulations, institutional policies, or IRB directives. In addition, it gives the IRB the difficult task of assessing the investigator's state of mind and what the investigator knew or did not know, and it might give investigators an incentive to not know the rules. In contrast, an IRB using a definition that is either silent about investigator intentions and knowledge or explicitly discounts them as mitigating factors would probably make a determination of noncompliance. (According to OHRP, serious noncompliance can occur either knowingly or unknowingly.[9]) It is the act (or acts) itself that constitutes the noncompliance, not the investigator's intentions. Similarly, for purposes of determining noncompliance, knowledge of the rules is irrelevant. However, the intentions and knowledge of the investigator may be taken into account when developing corrective action plans.

Determination of Noncompliance

Some definitions explicitly state that the IRB chair or convened IRB has the authority to determine, for example, that a pattern of acts constitutes continuing noncompliance. The process for determining noncompliance is a separate procedural issue that should not clutter the definition of noncompliance.

Research Integrity and Research Misconduct

Actions that compromise the integrity of research or research data appear 25 times in both sets of definitions of serious noncompliance and 15 times in both sets of definitions of continuing noncompliance. Compromising research or data integrity is usually interpreted as equivalent to either research misconduct or investigator misconduct. Office of Research Integrity regulations define research misconduct as fabrication of data, falsification of data, or plagiary.[12] FDA guidance and other publications define investigator misconduct as falsification of data submitted in support of an application to FDA.[13, 14] However, misconduct does not necessarily constitute noncompliance with regulations governing human subjects protections. For example, fabricating subjects is clearly misconduct, but protecting imaginary people is beyond the IRB's purview. Indeed, the role of an institution's human research protection program in evaluating issues involving integrity of research data or misconduct *per se* is not defined in the Common Rule or in FDA regulations or guidance. To the extent that an allegation of misconduct affects the rights or welfare of study participants, it can be evaluated by the IRB as an allegation of serious or continuing noncompliance. This is not to say, however, that an IRB investigation of noncompliance should be conducted in isolation. Other institutional offices may also have regulatory obligations to investigate the matter, and federal oversight agencies may have to be involved at different stages of the inquiries. An investigation involving noncompliance with multiple institutional policies and different sets of federal regulations can be very challenging because the policies and regulations are not always consistent and may, in fact, be in conflict.[15]

Institutional Noncompliance

Several definitions of serious and continuing noncompliance refer to actions that compromise the integrity of the human research protection program. Although not stated explicitly in most policies, these references are probably meant to address institutional noncompliance, which is a very different from individual noncompliance and should be addressed by different procedures.

Recommendations

Making a determination of serious or continuing noncompliance is among the most difficult and unpleasant responsibilities facing IRBs. Many IRBs have little experience in making these determinations because allegations of noncompliance that merit substantive review are infrequent, the facts and rules are not always clear cut, reputations are at stake, and professional and personal relationships between IRB members and investigators can be strained.[16] It is important, therefore, that definitions of compliance, serious noncompliance, and continuing noncompliance, which are the basis of any assessment, be clear, reasonable and broad enough to cover the range of problems likely to arise at an institution. This study of noncompliance policies identified definitions that are too narrow or ambiguous to cover even flagrant noncompliance. The following recommendations are offered with the intent of encouraging institutions to review their policies and correct any deficiencies:

> ***Noncompliance*** means not following:
> (1) federal, state and local laws and regulations governing human subjects research;
> (2) institutional policies governing human subjects research; and
> (3) directives or determinations of the Institutional Review Board.

It is important to include all three themes (N1, N2 and N3) because they refer to different levels of authority and responsibility for an institution's human research protection program. However, in certain circumstances, e.g., when a central IRB oversees protocols on behalf of a research site, the second element might require adjustment.

> ***Serious noncompliance*** means noncompliance that adversely affects the rights or welfare of research participants.

Here, the IRB's interpretation of "*adversely"* defines the distinction between what is serious and reportable and what is not. Theme S1 is adequate; themes S2 and S3 are limited, and therefore inadequate, versions of S1.

> ***Continuing noncompliance*** means noncompliant activity that:
> (1) if allowed to continue could reasonably be expected to develop into serious noncompliance; or
> (2) recurs after a report of the activity has been evaluated and corrective action has been mandated.

The first element here is stronger than theme C2 discussed earlier: the phrase *likely to increase risk to subjects* is now replaced with the more general *could reasonably be expected to develop into serious noncompliance.* As well, this phrasing establishes an explicit connection between serious and continuing noncompliance, thus supporting an integrated framework for evaluating allegations.

None of these definitions mention research misconduct, adversely affecting the integrity of research, HIPAA violations, or conflict of interest, which are covered by separate regulations and institutional procedures. If infractions in these areas also meet the definitions of serious or continuing noncompliance, the investigation conducted by the IRB should be coordinated with the appropriate institutional bodies and government agencies.

Acknowledgements

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References & Notes

1. 45 CFR 46.103(5)(i) and 21CFR56.108(b)(2) respectively.
2. The regulations do not specify which officers or persons at an institution should receive or evaluate allegations of noncompliance or make determinations. At many institutions these duties fall to either the IRB or the IRB chair, which will be assumed in this paper. However, other approaches are possible and probably even preferable.
3. Ryan GW, Bernard HR. Techniques to Identify Themes. Field Methods. 2003;15:85-109.
4. Tip Sheet 14. Non-compliance. Association for Accreditation of Human Research Protection Programs.
5. This is the 95% confidence interval for the ratio 5/138.
6. 21CFR56.121(b)(2).
7. Huron Toolkit. Huron Life Sciences; 2009.
8. The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects. 1979.
9. K. Borror, Director, Division of Compliance Oversight, Office for Human Research Protections, personal communication. 2013.
10. VHA Handbook 1058.01 Research Compliance Reporting Requirements.
11. FDA regulations at 21CFR50.27(a) require that consent forms be dated by the research subject; the Common Rule does not.
12. Public Health Service Policies on Research Misconduct, 42CFR93 (2005).
13. Government Accountability Office. Oversight of Clinical Investigators. Action Needed to Improve Timeliness and Enhance Scope of FDA's Debarment and Disqualification Processes for Medical Product Investigators. 2009.
14. Food and Drug Administration. Reporting Information Regarding Falsification of Data. Proposed Rule. Federal Register2010. p. 7412-26.
15. SACHRP Recommendation Regarding Oversight of Research Misconduct and Regulatory Noncompliance. 2012.
16. All good reasons for not assigning the task to the IRB but to another entity within the institution.

Author

Robert Bienkowski, PhD, CIP, is a consultant on clinical research and research compliance. Contact him at 1.607.426.9437 or bienkowski.robert@gmail.com.

