



Research Noncompliance among Universities: A Review of the Determination Letters Issued by the Office for Human Research Protections in the 2000s

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The Office of Research Compliance (ORC) takes great pride in overseeing the protection of all human participants in research studies associated with the University of North Carolina at Greensboro (UNCG). As part of ensuring the protection of human subjects, the ORC actively investigates the relevant news and advancements in the field. The ORC provides the applicable information regarding the IRB and protection of human subjects to the faculty, student researchers, and all other research affiliates in order to facilitate greater understanding of sound research practices. Ultimately, the goal of the ORC is to strive towards greater protection and safety of human research participants, while maintaining the integrity of research practices associated with UNCG.

Recently, the ORC has examined the determination letters written by the Office for Human Research Protections (OHRP), a division of the U.S. Department of Health and Human Services (HHS). The OHRP's Division of Compliance Oversight (DCO) is responsible for the review of institutional compliance in the midst of the federal regulations, which govern the protection of human research participants in HHS-sponsored research. Upon receiving allegations of noncompliance with the HHS regulations, the OHRP investigates the allegations. If substantial concerns arise, the OHRP will open up a formal investigation. After the investigation into the issues of non-compliance, the OHRP makes determinations based on the concern, and at times requests a response from the institution under investigation. In some cases, the OHRP requires corrective actions of the institution and the associated researchers. In severe cases, research is stopped altogether until the concerns are resolved and the institutional practices are deemed satisfactory. The DCO reports findings concerning the noncompliance allegations in the form of a determination letter addressed to the institution whose practices are in question. As standard procedure, ten days after the letter is issued, the OHRP posts these letters on their website for viewing. The determination letters available on their website begin with July 2000. (1, 2)

In total, there were approximately 750 determinations letters posted on the website by the OHRP from July 2000 to December 2010 (1, 3). Early in the decade, the total number of letters peaked at nearly 150 letters per year. Whereas in 2010, there were only 16 letters posted, which indicates a significant decline in the number of determination letters over the last 10 years (see Figure 1). In 1979, the Belmont Report was released stating the basic ethical principles of research and changing the standards of research practices in America. (4) This established national standards for the ethical treatment of human research subjects. Even though the guidance documents were in place, the process of increasing public awareness took time and researchers needed to adjust to repercussions for non-compliance. Possible causes for the decrease in determination letters over the past 10 years are unclear and heavily debated in the research compliance community.

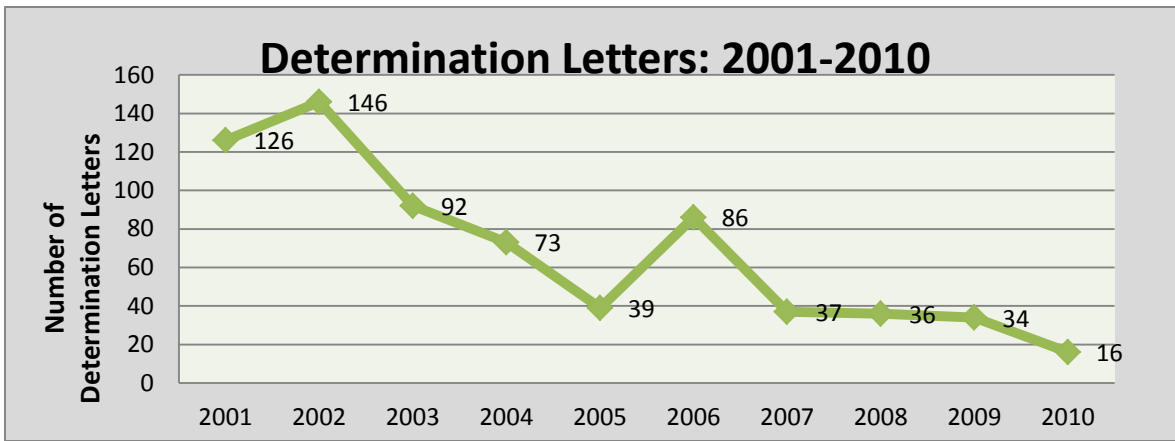


Figure 1: Total of Determination Letters from 2001 to 2010. (The determination letters from 2000 were excluded because of a partial year.)

There are a variety of different institutions addressed within the determination letters, including: social-behavioral universities, universities with medical schools, hospitals, health centers, clinic foundations, cancer centers, councils of science and technology, and the National Institutes of Health (NIH). For the relevance of this evaluation, only the social behavioral and medical universities were further examined from 2000 to 2010, which totaled 485 determination letters. Approximately 57% of the 485 letters included social-behavioral institutions; therefore 43% were from medical sites (medical schools and university affiliated health centers, research clinics, or hospitals) (3).

Procedures

The determination letters posted by OHRP provide great insight into the current research practices and patterns of compliance issues across the nation. For this reason, a total of 485 determination letters were analyzed, which spanned nearly 2,400 pages. The selection of letters included the first available letters via the website from July 2000 until Dec 2010. With some variation, the determination letters included information regarding the allegations of noncompliance, comments on the corrective actions employed by the institutions, lists of any other issues of noncompliance that arose during the investigation, suggestions for improvement, and required actions for resolution of the compliance concern. (3).

Upon review, it was noted that there are similarities among the infractions across the research sites. It was necessary to sort the qualitative information and to organize the infractions across the pool of letters. The OHRP posted a list of categorized determinations of noncompliance on their website (5). The list includes nine categorized groups of non-compliance issues, including: Initial and Continuing Review, Expedited Review Procedures, Reporting of Unanticipated Problems and Noncompliance, IRB review of Protocol Changes, Application of Exemptions, Informed Consent, IRB Membership and Staff, IRB Documentation and Procedures, and Other. There are a total of 51 specific determinations listed among the nine categories proposed by the OHRP. (5) In the current investigation, this list was used to categorize the infractions found in the letters. There were a few infractions that did not properly fit into one of the 51 named categories. For greater accuracy and clarity, there were 5 additional determinations that were added under the Other Category according to the OHRP list. Therefore, the final list included 56 specific infractions. Each of the determination letters was read electronically and information was gathered into an electronic database. From the letters, the following factors were considered: specific infractions, the suspension of specific Principal Investigator’s (PI) studies, the termination of studies, the OHRP required institution-wide suspension, and any actions required of the institution by the OHRP.

Results

The 485 letters were reviewed and classified based on the determination(s) of noncompliance stated in the letters. Roughly 21% of the letters included a single infraction, while 79% of the letters included multiple infractions. There were a total of 1707 determined infractions listed among the 485 letters. From the 56 possible categories of infractions, there were 15 infractions that occurred frequently and compromised roughly 75% of all 1707 infractions (See Figure 2). The most commonly listed infraction in the determination letters was *Inadequate Informed Consent Document lacking basic elements*. This infraction was listed among nearly 50% of the 485 letters that were examined. The next infraction occurring in 25% of all 485 letters examined was *IRB lacks sufficient information to make determinations required for approval*. At 23.7%, this was followed by *Lack of appropriate written IRB policies and procedures*. The subsequent frequently occurring infractions can be found in Figure 2. (3,5)

Figure 2: Top 15 Infractions that occurred most frequently out of 485 letters.

Infraction	Percentage of Occurrence
Inadequate Informed Consent Document lacking basic elements	49.9%
IRB lacks sufficient information to make determinations required for approval	25.2%
Lack of appropriate written IRB policies and procedures	23.7%
Failure of investigator to obtain legally effective Informed Consent or of the IRB to appropriately waive Informed consent requirement	22.1%
Research conducted without IRB review or approval	19.9%
Enrollment procedures did not minimize possibility of coercion	18.1%
Changes to research initiated without IRB approval	17.3%
Failure to minimize risks to subjects	17.1%
Failure to conduct continuing review at least once per year	14.4%
Failure to report unanticipated problems, noncompliance, suspensions, and terminations to IRB, institutional officials, and OHRP	12.8%
Informed Consent Language too complex	11.8%
Failure to document informed consent or of the IRB to appropriately waive the required documents	10.7%
Inadequate IRB Minutes	10.3%
Failure of IRB to make required findings when reviewing research involving children	8.0%
Inadequate continuing review	7.2%

As stated within the determination letters, 40% of the letters required no additional involvement of the OHRP in the matter, and therefore indicated that the allegation was not sustained or the response from the institution was appropriate and of a satisfactory standard for the protection of human subjects. On the other hand, sometimes the OHRP listed required actions in the letters and requested a response from the institution. In nearly 50% of the letters where a response was required, the institutional compliance office was able to address the required actions sufficiently on the first attempt. Less than 10% of the letters required multiple correspondences in order to adequately address the compliance concern stated in the first determination letter.

Some of the letters stated required actions set forth by the OHRP. Based on the situation of noncompliance and the population at hand, at times the institutional compliance office was required to

either suspend or close a research project. In 11.9% of the determination letters, the researchers' studies were suspended until the issues of noncompliance were resolved. As indicated in the content of the letters, the suspensions were often initiated by the institutional authorities, and therefore it cannot be determined whether the suspensions would have been ultimately required by the OHRP. Also, the results indicated that only 4% of the letters included the termination of a researcher's study. In approximately 7.6% of the letters, research was shut down or suspended across the university as a whole. (3)

In order to further examine the relationship between infractions and suspension, statistical analyses were performed. Specifically, the binary dependent variable was examined using a probit nonlinear regression model. The estimates of the marginal effect of each infraction on the likelihood of research study suspension were obtained. The results indicate that infraction 3, 5, 18, 28, 29, 38, and 52 are all significant ($p < .10$) (6,7). These infractions are respectively: *IRB lacks sufficient information to make determinations required for approval; Members present at convened IRB Meetings Lacked the Expertise to Make Determinations Required for Approval; Failure to report unanticipated problems, noncompliance, suspensions, and terminations to IRB, institutional officials, and OHRP; Inadequate Informed Consent Document lack of additional elements; Informed Consent Document Language too complex; Lack of Professional Competence to Review Specific Research Activities; Absence of General Safeguards for research involving vulnerable subjects.* Infractions 5, 18, 29, and 52 all have negative marginal effects, but the magnitude is relatively small to those infractions with positive marginal effects.(7)

University-Wide Suspensions

University-wide suspensions occurred in 7.6% of all 485 determination letters examined. This subgroup of university-wide suspensions was further analyzed in order to gain insight into the relationship between the infractions and the likelihood of a university-wide suspension. As seen in Figure 3, there were 10 infractions that occurred more often. Over 41% of all letters that resulted in a university-wide suspension cited *Inadequate informed consent document lacking basic elements.* Also, 41% of the letters that resulted in university-wide suspension were found to include *Lack of appropriate IRB policies and procedures.* (5)

Figure 3: Infractions that occurred most frequently among the letters with university-wide suspensions.

Type of Infraction	Percentage of Occurrence
Inadequate Informed Consent Document lacking basic elements	41.38%
Lack of appropriate written IRB policies and procedures	41.38%
IRB lacks sufficient information to make determinations required for approval	27.59%
Enrollment procedures did not minimize possibility of coercion	24.14%
Inadequate IRB Minutes	24.14%
Changes to research initiated without IRB approval	20.69%
IRB members with conflicting interest participated in IRB Review of Research	17.24%
Failure to conduct continuing review at least once per year	17.24%
IRB Chairperson and Members lack sufficient Understanding of HHS Regulations	17.24%
Failure of IRB to make required findings when reviewing research involving children	17.24%

Next, a regression analysis was performed for whether the research was shut down across the university on whether a particular infraction was committed at the institution (7). There were a number of infractions that were dropped from the analysis due to infrequency of occurrence, leaving a total 35 infractions. The results indicated that infractions 17, 25, 27, 38, 44, and 46 are all significant ($p < .05$) (6). The corresponding infractions are: *Expedited Review Conducted by Someone Other than an IRB Member*; *Failure to Document Informed Consent or of the IRB to Appropriately Waive the Requirements to Document Informed Consent*; *Inadequate Informed Consent Document lacking basic elements*; *Lack of IRB Professional Competence to Review Specific Research Activities*; *Failure of the IRB to determine that criteria for IRB approval are satisfied*; *Failure of IRB to Make required findings when reviewing research involving prisoners*.(4) Infractions 17, 38, and 44 all had positive effects, whereas 25, 27, and 46 had negative effects.(7)

Discussion

The examination of the infractions and the consequences set forth by the OHRP yielded significant findings that are relevant to research entities across the U.S. On a smaller scale, there is a university office that oversees research compliance and serves to oversee both the researcher conduct and the IRB committees. As a result, an infraction found within a determination letter could be the result of noncompliance from any of these associated divisions. It is important to consider the direct audience or responsible persons of the infraction when applying the information in a preventative manner. Therefore, it is also important to consider the origination of the infraction when examining the results.

The first regression analysis examined the relationship between specific infractions and the likelihood of a researcher's study being suspended. There were significant results for infractions 3, 5, 18, 28, 29, 38, 52. The positive marginal effects were found in infraction 3, 28, and 38, which are respectively: *IRB lacks sufficient information to make determinations required for approval*; *Inadequate Informed Consent Document (lack of additional elements)*; and *Lack of IRB Professional Competence to Review Specific Research Activities*. (5) This indicates that particular infractions were associated with an increased likelihood of a researcher's study being suspended when all else was held equal. When looking at the origins of the infractions, it appears that these infractions are associated with the IRB competence in the review process. However, these infractions could also be the result of researcher's withholding relevant information from the IRB conducting the review process.

At the same time, there were negative marginal effects found within this regression analysis for infractions 5, 18, 29, and 52, which are respectively: *Members present at convened IRB Meetings Lacked the Expertise to Make Determinations Required for Approval*; *Failure to report unanticipated problems, noncompliance, suspensions, and terminations to the IRB office, institutional officials, and the OHRP*; *Informed Consent document Language is too complex*; *Absence of General Safeguards for research involving vulnerable subjects*.(5) If these infractions were present, the likelihood of research study suspension was significantly less. The relationship between the variables and the negative marginal effects are unclear. However, it does appear that other factors may have contributed to the variables. For example, in infraction 18 the factor of time wasn't determined among the analysis. If an issue of noncompliance occurred and was not reported to the OHRP, the study may have been completed before the OHRP became aware of the issue. Therefore, the study was at a lower risk for being suspended or closed. Also, there is the possibility that the study was suspended by the university compliance officials prior to the OHRP becoming aware of the study. It appears that for this reason, the infraction was less likely to be suspended.

The next analysis examined the relationship between infractions and the likelihood of university-wide research suspension, which included a small sample of the total letters. The results indicated that infractions 17, 38, and 44 all had positive effects, which are respectively: *Expedited Review Conducted by Someone Other than an IRB Member*; *Lack of IRB Professional Competence to Review Specific Research Activities*; and *Failure of the IRB to determine that criteria for IRB approval are satisfied*. (5) These specific infractions were associated with an increased likelihood of research being shut down across the university. Upon further examination, it appears that each of these infractions is noncompliance from the IRB or research compliance office and not a result of direct action of a single researcher. These infractions are evidence that there may be foundational concerns with the structure and function of the IRB. Structural issues such as these led the OHRP to be concerned with the research oversight at the university and requested that a university-wide suspension was necessary.

There were also significant negative effects from the second analysis that are of interest. Particularly, infractions 25, 27, and 46 displayed significant results indicating that the presence of a particular infraction within a determination letter decreased the likelihood of university-wide research suspension. These infractions are respectively: *Failure to Document Informed Consent or of the IRB to Appropriately Waive the Requirements to Document Informed Consent*; *Inadequate Informed Consent Document lacking basic elements*; and *Failure of IRB to make required findings when reviewing research involving prisoners*. (5) It is important to consider to volume of such protocols that are connected to the infractions listed above. The amount of research that would include a waiver of informed consent documentation or research involving prisoners is only a small percentage of the research that takes place. It seems appropriate that research across the entire university would not be shut down by the OHRP with concerns in such minimal areas. Further investigation into the specific details of the determination letters for each of these infractions would be required for clarification on the relationship between infractions and university-wide suspension.

Overall, it is important to note that the group of letters that included a university-wide suspension represents a small portion of the total letters. Out of the 485 determination letters that were posted over the last decade, approximately 94% resulted without the requirement for suspension or closing of studies not directly associated with a particular PI. Of the studies that did include a partial or full suspension of research at the university, the universities were able to address the issues of noncompliance in a relatively short period of time and improve the standards of compliance to a suitable level for the protection of human subjects.

Future examination into the OHRP determination letters should consider the connections between variables. The current results do provide insight into the common infractions that surface in the midst of an OHRP examination. Also, it is important to note some of the qualitative pieces within the determination letter analysis. For one, the manner in which the OHRP responded within the letters to the university whose practices was in question. Upon notification of the noncompliance concern, the OHRP made it a point to evaluate the validity of the reported concern and the relevance of the initial response of the university compliance office in relation to the specific issue. Often, the determination letters included positive words that recognized the efforts of university personnel towards the protection of the human research subjects, along with suggestions for improvement.

Conclusion

Listed above, there are a number of notable findings that are applicable for researchers, the IRB, the institutional official, or other research compliance university personnel. Generally, it is the duty of the institutional official and the research compliance personnel to oversee the actions of both the IRB and the researchers. As seen in the infractions listed above, there are concerns for all of these entities.

There were infractions that listed structural or procedural concerns, as well as, committee member competencies that apply directly to the IRB. In this case, it would be the responsibility of the university research compliance personnel and the IRB to ensure proper training and diversity among committee members. On the other side, there were infractions that resulted from researchers not following the stipulations of the approved protocol or withholding relevant information from the IRB. The determination letters clearly reveal that it is not the sole responsibility of the research compliance office and institutional official to ensure the protection of human subjects. Rather, the responsibility also lies with the IRB and the research investigators. It is imperative that the communication lines between the research compliance office, the IRB, and the researchers remain fluid to ensure greater unity with research practices at universities. In addition, it is important to spread awareness of the common issues of research noncompliance, as well as the associated consequences of noncompliance that affect the research participants, principal investigators, other researchers, the IRB, the research compliance office, and the university at large. Increased awareness will help create unity among the associated research branches on an individual university level, and ultimately solidify greater protection for human research participants across the nation.

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