Evaluation of Peer Review of Human Subjects Protections in NIH Research Grant Applications

Executive Summary

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Executive Summary

Research supported by the National Institutes of Health (NIH) that involves human subjects must comply with federal regulations (45 CFR 46) and policies designed to ensure adequate protections for research participants. Human subjects are defined as living individuals about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information. Investigators applying for NIH funding must indicate whether the proposed research involves human subjects and, if so, whether or not the research falls into one or more of the six categories of human subjects research that is exempt from regulation (Table A). For human subjects research that is not exempt, the Protection of Human Subjects section of applications must address risks to subjects, adequacy of protection against these risks, potential benefits of the research, and the importance of the knowledge to be gained.

Table A. Categories of Human Subjects Research Exempt From Regulations

Category	Description[a]
E1	Research is conducted in an educational setting and involves normal educational practices.
E2	Research uses cognitive, diagnostic, aptitude, or achievement tests; interviews; or observations of public behavior, unless subjects are identifiable and disclosure would place them at risk. (Note: Most research involving children is not eligible for E2.)
E3	Research uses cognitive, diagnostic, aptitude, or achievement tests; interviews; or observations of public behavior and is not exempt under E2 if the subjects are public officials or candidates or the law requires that confidentiality be maintained.
E4	Research involves the collection or study of existing data, documents, records, or pathological or diagnostic specimens, if these sources are publicly available or the information is recorded so subjects cannot be identified.
E5	Research involves research and demonstration projects to study public benefit or service programs.
E6	Research evaluates taste and food quality or consumer acceptance of certain foods.

[a] Complete descriptions of categories can be found in 45 CFR 46 Subpart A §101(b).

At NIH, the regulatory requirement to assess human subjects protections in extramural research grant applications is integrated with the NIH peer review process. Peer reviewers on NIH Scientific Review Groups (SRGs) determine if an application's designation of human subjects is correct (i.e., either not human subjects research, exempt human subjects research, or non-exempt human subjects research) and rate the overall acceptability of the Protection of Human Subjects section of the application. If one or more issues are inadequately addressed and/or if a claimed exemption is not adequately justified, the application is rated as unacceptable and reviewers provide written comments describing their concerns. Applications that are rated as unacceptable because of human subjects issues cannot be funded until investigators submit a written resolution of SRG identified concerns. This resolution must be reviewed and approved by the NIH Office of Extramural Research (OER) and the funding NIH Institute or Center (IC).

Purpose of Evaluation

The Human Research Protections Program (HRPP) in the OER Office of Extramural Programs (OEP) provides leadership in policy development, as well as evaluation and administration, of human subjects protections in NIH extramural awards. HRPP also approves the proposed resolutions to SRG concerns in fundable applications and responds to other questions related to human subjects coding of NIH applications and awards; in this capacity, HRPP reviews approximately 1,000 extramural applications

each year and has developed standardized procedures to categorize human subjects concerns identified by peer reviewers (Table B). HRPP constantly monitors its business operations and, as a part of the ongoing effort to evaluate program efficacy, contracted with NOVA Research Company (NOVA) to conduct a comprehensive evaluation of NIH peer review of human subjects protections in research grant applications. The overarching goals of the evaluation were to characterize research grant applications involving human subjects, including outcomes of peer review with respect to human subjects; categorize human subjects concerns identified by peer reviewers; determine what types of human subjects concerns were missed by peer reviewers; assess whether peer reviewers and applicants correctly applied exemptions; and assess the extent to which documentation of human subjects concerns in summary statements complied with NIH standards.

Methods

A team of three NOVA evaluators participated in a one-week training program administered by HRPP staff that included an overview of human subjects research regulations, NIH requirements for description of human subjects protections in grant applications, hands-on practice reviewing grant applications, and instruction on how to code human subjects concerns using the HRPP standard coding scheme (Table B).

Table B. HRPP Human Subjects Concerns Coding Scheme

- Confidentiality
- Data and Safety Monitoring Plan/Board
- Human subjects section
  - *Human subjects section exemptions: inadequate justifications*
  - *Human subjects section: missing/inadequate/incomplete*
- Informed consent
  - *Informed consent: assent/parental permission*
  - *Informed consent: missing/inadequately addressed*
  - *Informed consent: other*
- Recruitment
  - *Recruitment: compensation*
  - *Recruitment: inappropriate setting/privacy*
  - *Recruitment: missing/inadequately addressed*
  - *Recruitment: undue influence/coercive*
- Risks: incidental findings/referrals
- Risks: physical/clinical
- Risks: psychological/suicidal
- Other risks
  - *Risks/benefits: inappropriate*
  - *Risks: protections/other*
- Sources of data/specimens
  - *Sources of data/specimens: code interpretation error*
  - *Sources of data/specimens: missing/inadequately discussed*
- Other concerns
  - *Financial conflict of interest*
  - *Gene analysis concerns*
  - *Justice issues*
  - *Vulnerable subjects involvement: lack justifications*
  - *Other*
- No valid concern
  - *No valid human subjects concerns*
  - *No concern provided*

The evaluation included competing extramural research grant applications submitted to NIH in fiscal years (FY) 2011, 2012, or 2013 and peer reviewed by NIH SRGs. Application data, including data on outcomes of peer review of human subjects protections, were retrieved from the NIH Query, View, Report (QVR) tool. Descriptive analyses of applications involving human subjects by variables of interest (Task 1) informed selection of samples for subsequent components of the evaluation. Statistical analyses, primarily chi-square tests, were conducted to assess differences in peer review outcomes related to variables of interest and also to inform the sampling procedures for subsequent tasks. For Task 2, NOVA evaluators reviewed summary statements of a sample of unawarded applications rated by SRG as unacceptable for human subjects and coded the concerns noted by peer reviewers using the

coding scheme developed by HRPP. Data for this sample were weighted to better represent the population from which the sample was drawn. These weighted data then were combined with human subjects concerns data provided by HRPP for all awarded applications originally rated as unacceptable by SRGs. For Task 3, NOVA evaluators reviewed a sample of applications originally rated as acceptable by SRGs (both exempt and non-exempt human subjects research) and associated summary statements and assigned each application a human subjects code based on this review (not human subjects research; acceptable exempt human subjects research, including the specific exemption that applied; acceptable non-exempt human subjects research; or unacceptable). For applications rated by NOVA as unacceptable, human subjects concerns were coded using the coding scheme used for Task 2. Differences in NOVA- and SRG-assigned human subjects codes were analyzed. Task 4 involved analysis of documentation of human subjects concerns in the summary statements for the unawarded applications rated as unacceptable for human subjects that were reviewed for Task 2.

Results

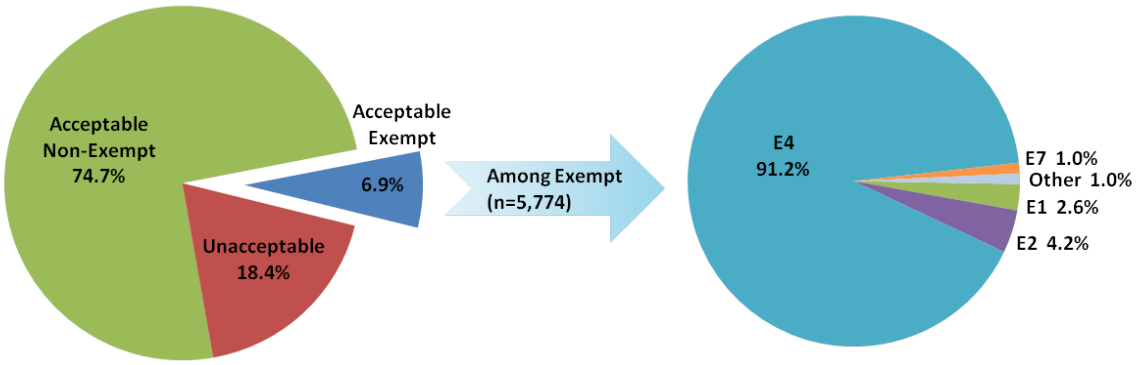
Task 1: Descriptive Analysis of Outcomes of Peer Review of Human Subjects

Of more than 215,000 research grant applications peer reviewed by NIH in FY2011-2013, 83,403 (38.7%) involved human subjects. Awarded applications were slightly less likely to involve human subjects than applications that were not awarded (36.8% versus 39.2%). The percentages of applications involving human subjects varied by NIH Institute and Center, ranging from a low of 7.9 percent to a high of 91.5 percent of applications. Nine of 26 ICs administered applications in which more than 50 percent involved human subjects. Human subjects involvement also varied by grant mechanism. Cooperative Agreements (U applications) and Research Program Projects and Centers (P applications) were most likely to involve human subjects (66.8% and 65.6%, respectively), while applications for Research-Related Programs (S applications) were least likely (7.3%). Among Research Project Grants (R applications), 38.3 percent involved human subjects.

Outcomes of peer review with respect to human subjects are summarized in Figure A. Among research grant applications involving human subjects, SRGs rated 74.7 percent as acceptable non-exempt, 6.9 percent as acceptable exempt, and 18.4 percent as unacceptable. More than 90 percent of acceptable exempt applications were assigned exemption 4 (research that involves collection or study of existing documents, records, or specimens, if those sources are publicly available or if the information is recorded by investigators in a way to ensure that subjects cannot be identified). Exemptions 1, 2, and 7 each comprised between 1 and 5 percent of assigned exemptions while exemptions 3, 5, and 6 were only rarely applied.[1]

[1] E7 is an NIH administrative code for applications that propose more than one category of exempt research.

Figure A. NIH Research Grant Applications Involving Human Subjects by Human Subjects Rating (N=83,403)

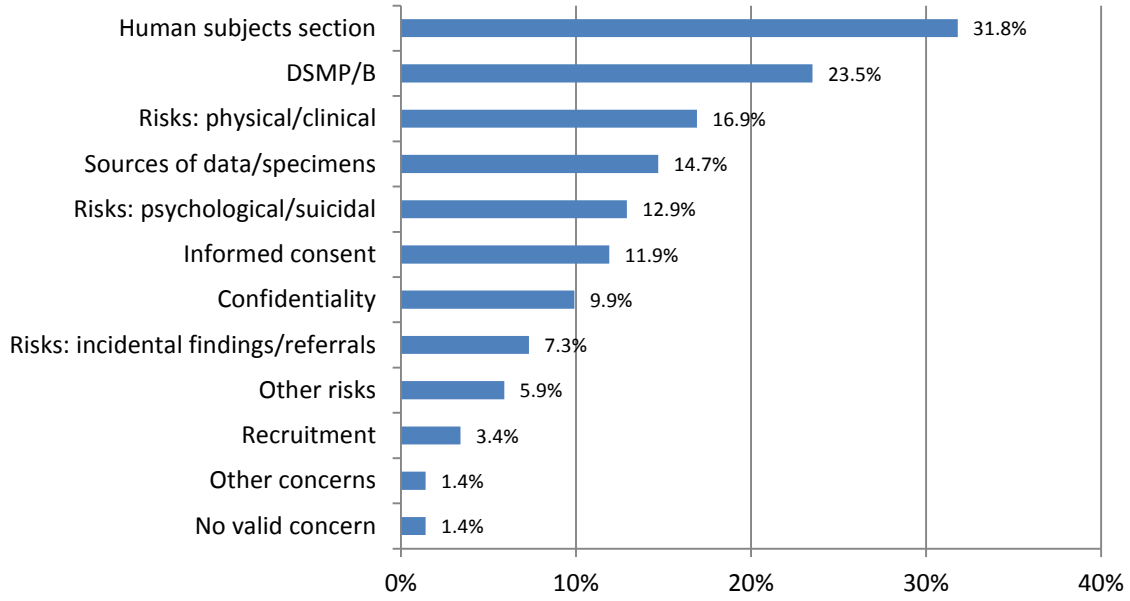


Peer review outcomes also were analyzed (primarily chi-square tests) with respect to application, organization, investigator, and SRG characteristics, as well as by scientific discipline/area. Results of these analyses informed selection of samples for subsequent components of the evaluation.

Task 2: Analysis of Human Subjects Concerns Identified by Peer Reviewers

Specific human subjects concerns identified by peer reviewers for applications rated by SRGs as unacceptable with respect to human subjects protection are shown in Figure B (N_w indicates the sample includes weighted data; see Methods). The most common concern—identified for nearly one-third of unacceptable applications—related to an SRG determination that the application had general deficiencies in the Protection of Human Subjects section. Peer reviewers also indicated that nearly one-quarter of unacceptable applications did not provide an adequate description of a required Data and Safety Monitoring Plan or Board (DSMP/B). There were some notable differences in the types of concerns identified in awarded compared with unawarded applications, illustrating the value of supplementing the data HRPP maintains on awarded applications with information about unawarded applications. The percentage of unawarded applications with concerns related to DSMP/B was about twice that of awarded applications with DSMP/B concerns (25.0% vs. 12.8%). A similar discrepancy existed for applications with concerns related to incidental findings/referrals (7.8% vs. 3.6%). Reviewers also were more likely to identify concerns related to psychological risks in unawarded applications. On the other hand, nearly 14 percent of awarded applications were flagged because of reviewer concerns about "other risks" (e.g., social, legal) compared with just under 5 percent of unawarded applications. Human subjects concerns identified by peer reviewers also were analyzed by application, investigator, and SRG characteristics, as well as by scientific discipline/area.

Figure B. Human Subjects Concerns Identified by Peer Reviewers in Applications Originally Rated as Unacceptable



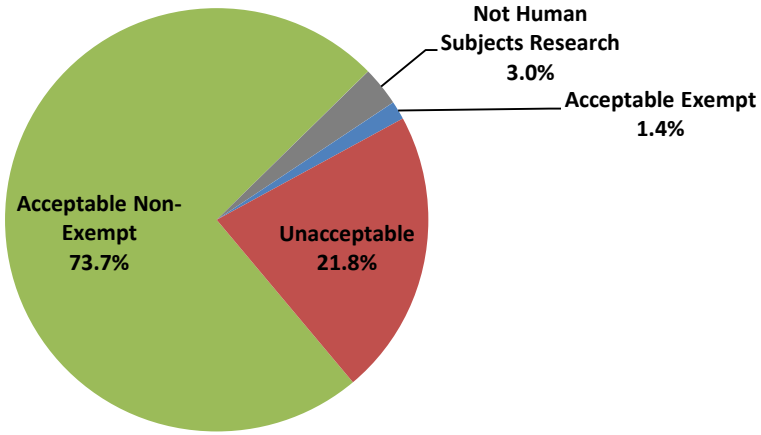
Task 3: Evaluation of Accuracy of Peer-Review Assessment and Coding of Human Subjects Concerns

Task 3 of this evaluation assessed the accuracy of peer review of human subjects protections for applications coded by SRGs as acceptable non-exempt and acceptable exempt.

Acceptable Non-Exempt Applications

The goal of the evaluation of acceptable non-exempt applications was to determine the types of human subjects concerns missed by peer reviewers. NOVA evaluators reviewed 495 applications rated by SRGs as acceptable non-exempt human subjects research and determined which human subject code they thought should have been applied to each application. (No SRG-assigned codes were changed in NIH systems as part of this evaluation.) Figure C provides an overview of human subjects codes assigned to these applications by NOVA. NOVA evaluators agreed with the SRG codes for nearly three-quarters of applications. NOVA evaluators determined that a small number of applications were either not human subjects research (3%) or exempt (1.4%) and identified concerns in about one in five applications (21.8%). When NOVA evaluators identified human subjects concerns missed by SRGs, they designated the application as unacceptable. The distribution of human subjects codes assigned by NOVA evaluators was investigated by several application, investigator, and SRG characteristics, as well as by clinical trial status and scientific discipline/area.

Figure C. Summary of Human Subjects Codes Assigned by NOVA to Applications Rated by SRGs as Acceptable Non-Exempt (N=495)

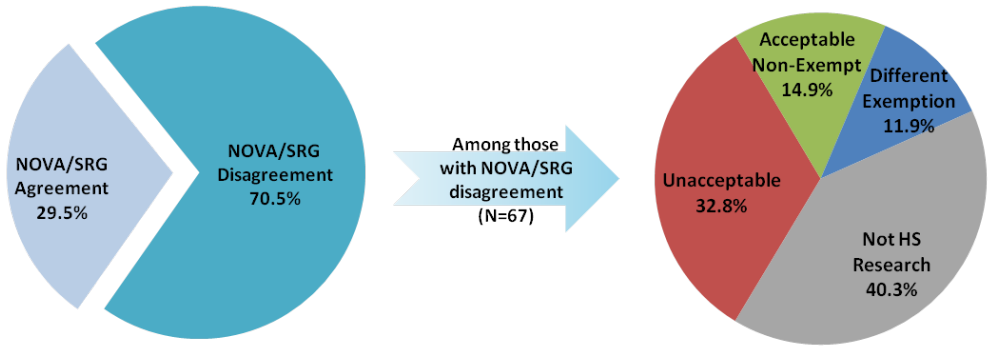


Among applications rated by NOVA evaluators as unacceptable with respect to human subjects protections, the most common concern related to general deficiencies in the Protection of Human Subjects section: NOVA evaluators had concerns about the human subjects sections of nearly 30 percent of the applications they determined to be unacceptable. About one in six applications determined by NOVA evaluators to be unacceptable were flagged because of concerns related to each of the following: informed consent, psychological/suicide risks, physical/clinical risks, and DSMP/B issues. Slightly fewer applications rated by NOVA as unacceptable (13.9%) were flagged because of concerns about incidental findings and/or referrals. Concerns related to other categories—including confidentiality, recruitment, sources of data/specimens, and other risks—were identified for fewer than 8 percent of applications rated as unacceptable by NOVA evaluators.

Acceptable Exempt Applications

The goal of the analysis of applications rated as acceptable exempt by peer reviewers was to determine whether peer reviewers and applicants understood and applied exemptions in accordance with human subjects regulations. The analysis focused on the four exemptions most commonly assigned to NIH research grant applications (E1, E2, E4, and E7; see Table A). NOVA evaluators reviewed 95 applications rated by SRGs as acceptable exempt human subjects research and determined which human subjects code they thought should have been applied to each application. NOVA selected a code different from what was originally assigned by the SRG for 67 applications (70.5%; Figure D). Of the applications for which NOVA evaluators disagreed with peer reviewers, NOVA rated 40.3 percent as not human subjects research, 14.9 percent as acceptable non-exempt research, and 11.9 percent as acceptable with an exemption other than that originally assigned by the SRG. NOVA reviewers determined that the human subjects sections of 32.8 percent of applications (n=22) were unacceptable. The vast majority of unacceptable ratings assigned by NOVA (n=19) were due to the fact that applications did not adequately describe the sources of their data and/or specimens or clearly delineate whether investigators had access to participant identifiers.

Figure D. Summary of Human Subjects Codes Assigned by NOVA to Applications Rated by SRGs as Acceptable Exempt (N=95)



Task 4: Assessment of Documentation of Human Subjects Concerns in Summary Statements

NIH Scientific Review Officers (SROs) compile a summary statement for each application reviewed by SRGs. The purpose of Task 4 was to assess the extent to which documentation of human subjects concerns in summary statements complied with NIH standards. The analysis focused on the summary statements for the unawarded, unacceptable applications reviewed as part of Task 2 of the evaluation. For unacceptable applications that *are* discussed by the SRG, compliant summary statements must include a human subjects label of unacceptable and a resume that summarizes the SRG discussion and human subjects concerns. For unacceptable applications that *are not* discussed by the SRG, at least one assigned reviewer must have noted a concern related to human subjects protections.

Summary statements of 400 applications rated by SRGs as unacceptable with respect to human subjects were reviewed. Overall, nearly 94 percent of summary statements were compliant with NIH standards for documentation of human subjects concerns. Reviewer critiques in the six noncompliant, not-discussed summary statements did not include a description of concerns related to human subjects protections or provide an explanation for the unacceptable rating. Of the 19 noncompliant summary statements of discussed applications, 15 lacked a resume summarizing human subjects concerns, 2 had an errant label of “acceptable” listed in the resume, and 2 lacked a resume *and* were mislabeled.

Conclusions and Recommendations

This evaluation characterized NIH research grant applications involving human subjects and assessed peer review outcomes based on application, organization, investigator, and SRG characteristics, as well as by scientific discipline/area (Task 1). Human subjects concerns identified by peer reviewers of NIH research grant applications also were tabulated (Task 2). These data may be helpful for future applicants as they prepare their Protection of Human Subjects sections and NIH program staff who may be consulted by applicants during the application preparation process. This evaluation project determined that human subjects protections proposed in NIH grant applications generally are being evaluated appropriately and documented in peer review. However, the evaluation did identify several areas for potential improvement (Task 3). Of note, many of the concerns identified by peer reviewers and NOVA evaluators were due to lack of information or inadequate descriptions of one or more parts of the plan for protection of human subjects. NIH may wish to consider educational efforts and/or changes to the application structure that may increase the likelihood that applicants include all information needed for a comprehensive assessment of the Protection of Human Subjects section. The recent NIH clarification of the definition of a clinical trial may reduce the frequency of concerns related to DSMPs/Bs. In

addition, applicants, peer reviewers, and NIH staff all may benefit from additional guidance on the categories of research that are exempt from human subjects regulation, including clear guidance on handling instances where peer reviewers believe applicants have not chosen the appropriate human subjects designation. The evaluation found that compliance of summary statements with NIH standards related to human subjects is very high (Task 4), though further improvements may be possible by reminding staff that human subjects information must be included in summary statements. The results of the evaluation will inform future HRPP efforts to ensure continued high-quality peer review of human subjects protections in NIH applications through efforts focused on applicants, peer reviewers, NIH program staff, and SROs.