

APM Perspectives

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Why Are Peer Review Outcomes Less Favorable for Clinical Science than for Basic Science Grant Applications?

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For decades, concerns have arisen over the robustness of the clinical research enterprise and the erosion of the cadre of new and experienced clinical investigators.¹⁻⁸ In 1996, the director of the National Institutes of Health (NIH) responded to these concerns by impaneling a group of experienced clinical investigators and teaching hospital administrators to recommend policy changes regarding clinical research.⁹ Subsequently, NIH implemented a number of the panel's recommendations, including increased support of clinical research training programs and the establishment of NIH-sponsored educational debt relief programs for clinical investigators.^{10,11} Re-engineering the clinical research enterprise is a major theme of the NIH Roadmap for Medical Research, launched in 2003.¹²

Despite these initiatives in support of clinical research, clinical investigators often perceive that clinical research grant applications may be disadvantaged in the NIH peer review process. Several reports have indicated that priority scores and funding rates are lower for clinical than for nonclinical applications.^{8,13-15} Comparable differences between clinical and nonclinical applications were observed in applications reviewed in 1994 and 2004. Anecdotally, it has been suggested that these differences reflect inherent limitations of clinical studies, for example, clinical studies are more difficult

to control and it is difficult to determine causality from the results.

Based on an analysis of the relationship of review outcomes in 2004 to study section assignment and the professional backgrounds of study section members, we previously reported that the assignment of priority scores for clinical and nonclinical applications did not differ for reviewers with or without experience conducting clinical research.¹⁵ The less favorable review outcomes for clinical applications also were not accounted for by the "density" of clinical applications reviewed in a study section or by the greater requested costs for clinical research.¹⁵ Our preliminary observations, based on data from 2 funding cycles, suggested that human subject concerns contributed to the overall less favorable review outcomes for clinical applications.¹⁴

We undertook an analysis to further evaluate potential explanations for the difference in peer review outcomes between clinical and nonclinical applications. Specifically, we focused on the impact of the following: rates of submission and outcomes of amended and competing renewal applications submitted by new and established investigators, and human subject protection concerns raised at the time of review.

METHODS

Data were derived from the Consolidated Grant Applications File maintained by the NIH Office of Extramural Research. The Center for Scientific Review (CSR)

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reviews approximately 70% of the applications submitted to NIH, with the balance being reviewed by the institutes and centers within NIH. The data set included R01 (standard research grant) applications reviewed by CSR for the 12 review rounds beginning October 2000 and ending May 2004.

Consistent with the definition proposed by an NIH Director's Panel on Clinical Research, an inclusive definition of clinical research was used. A research application is defined as clinical when the principal investigator (PI) indicates involvement of human subjects in the proposed research by checking "yes" on page 1 of the grant application form in response to the involvement of human subjects query. This definition of clinical research captures research on mechanisms of disease, therapeutic interventions, clinical trials, development of technologies, epidemiological and behavioral studies and outcomes, and health services research. Research involving the collection or study of publicly available or existing deidentified data, documents, records, pathological specimens, or diagnostic specimens was not considered clinical research (NIH Exemption 4 code).

The NIH defines human subject concerns as any potential or actual unacceptable risk(s) or inadequate protection against risk(s) to human subjects identified in any portion of the application. NIH staff and study section members use codes to identify concerns with human subject protections. Study section members are advised to factor human subject concerns in their assignment of a priority score.

Review outcomes were evaluated both in aggregate and separately for "new" and "experienced" investigators. This distinction is based on the individual's having served or not served, as PI on a Public Health Service-supported research project. Individuals classified as new investigators may have served as PI on a small grant (R03), an Academic Research Enhancement Award (R15), an exploratory development grant (R21), or certain mentored research career development awards (K01, K08, and K12).

Applications reviewed by NIH receive a priority score, which reflects a scientific review group's evaluation of the scientific and technical merit of the appli-

cation. Using incremental units of 0.1, individual members "vote" scores from 1.0 (highest merit) to 5.0 (lowest merit). If an application is deemed to be "non-competitive" (in the lower half, qualitatively, of applications reviewed by the study section) by unanimous agreement of the study section, it will not be fully discussed at the study section meeting and will not receive a priority score. Because of the variability of scoring behaviors among study sections, to provide cross-study section and longitudinal comparisons, R01 applications within each CSR study section are assigned a percentile rank according to priority scores given in the current and previous two review rounds. As with priority scores, the lower the numerical value of the percentile, the greater the relative merit of the application. Applications that do not receive a priority score are included within a study section's percentile rankings. This analysis focuses on the results of the scientific peer review, as reflected by the percentile rank.

PERSPECTIVES VIEWPOINTS

- Clinical investigators often perceive that clinical research grant applications are disadvantaged in the NIH peer review process.
- The study focuses on the impact of rates of submission and outcomes of amended and competing renewal applications.
- The current data suggest that nearly all of the difference in review outcomes for clinical and nonclinical applications is due to a failure to adequately address human subject protection requirements and to a lower rate of submission of competing continuation applications by clinical applicants.

RESULTS

From October 2000 through May 2004, CSR reviewed 92,922 R01 applications; 62,735 (67.5%) were considered nonclinical applications and 30,187 (32.5%) were considered clinical applications. Figure 1 displays the cumulative percent plotted against percentile data for the clinical and nonclinical applications. Only those applications scoring at the 30th percentile are displayed. In aggregate, 20% of all applications will receive percentile scores of 20.0 or better; 30% will score 30.0 or better, and so on. This "reference" line is displayed in Figure 1 and subsequent figures. Applica-

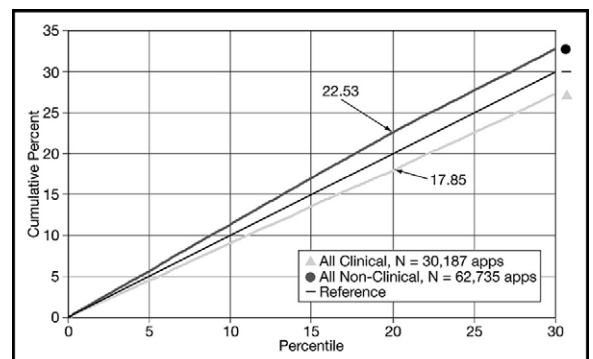


Figure 1 Cumulative percents of clinical and nonclinical R01 grant applications scoring within the 30th percentile.

tions with better outcomes are depicted above the reference line, and applications with less favorable outcomes are depicted below the reference line. There was a modest difference in outcomes for clinical versus nonclinical applications: 17.8% of all clinical R01 applications versus 22.5% of all nonclinical R01 applications received a percentile rank of 20.0 or better.

Of all R01 clinical applications, 14.8% were noted by reviewers to have human subject concerns (Table 1). Initial applications (A0) from new investigators consistently had the highest percent (19.2%) of applications with human subject concerns. Applications of experienced investigators, whether submitting a new application or a competing renewal, also had high percents of human subject concerns, ranging from 9.4% to 15.6% of applications. The percent of new investigator Type 1 applications (new applications) with human subject concerns decreased on resubmission.

For the subset of clinical applications without human subject concerns, 19% had a percentile rank of 20.0 or better (Figure 2). In contrast, for the subset in which reviewers identified human subject concerns, only 10% received a percentile rank of 20.0 or better. Thus, approximately one-half of the observed differences in peer review outcomes for clinical versus basic research applications can be attributed to applicants failing to adequately address human subject concerns in their applications.

Overall, Type 1 applications, whether from new or established investigators, did not score as well as competing renewal (Type 2) applications (Figure 3). Initial Type 1 R01 applications from new investigators did not score as well as initial Type 1 applications from established investigators. This pattern persisted for the first (A1) and second (A2) resubmissions, although the differences narrowed on resubmission. Nonclinical R01 Type 1 and Type 2 applications from new and experi-

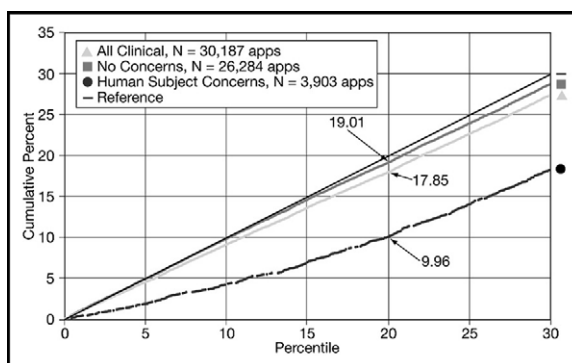


Figure 2 Cumulative percents of clinical R01 grant applications with and without human subject concerns scoring within the 30th percentile.

enced investigators did better than clinical applications on the A0 submission. However, the differences between clinical and nonclinical applications for each category of investigator and application (new vs established and Type 1 vs Type 2) were reduced with the A1 application and disappeared with the A2.

Table 2 compares submission rates for all clinical versus all nonclinical R01 applications by investigator category (new vs experienced), application type (Type 1 vs Type 2), and application submission category (A0 vs A1 or A2 revisions). Overall, 33.9% of clinical applications were submitted by new investigators, compared with 29.5% of nonclinical applications. Additionally, investigators conducting clinical research were less likely to submit a competing renewal application than those conducting nonclinical research (20.0% vs 28.3%). Resubmissions (A1 and A2) of competing renewal (Type 2) applications from clinical investigators also represent a smaller percentage of all clinical applications (8.0%) compared with Type 2 nonclinical applications (10.6%). Thus,

Table 1 Percent of R01 Clinical Applications with Human Subject Concerns

PI/App	Type	Number of Clinical Applications	Human Subjects Code Concerns
New/T1	A0	7382	19.2%
	A1	2761	13.4%
	A2	690	10.9%
Established/T1	A0	8446	15.6%
	A1	3775	14.0%
	A2	1086	14.1%
Established/T2	A0	3625	9.4%
	A1	1825	10.4%
	A2	597	13.4%
Total		30,187	14.8%

PI = principal investigator; A0 = initial application; A1 = first revision; A2 = second revision of application; T1 = new application; T2 = competing renewal application.

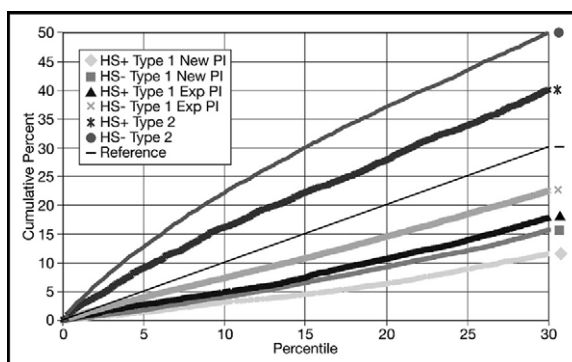


Figure 3 Cumulative percents of R01 grant applications by type (Type 1 [new] vs Type 2 [competitive renewal]), clinical [HS+]* vs nonclinical [HS] and by principal investigator status (new vs experienced) scoring within the 30th percentile. *HS+ = involving human subjects; HS- = not involving human subjects.

Table 2 Rate of Submission of Initial and Revised Applications

Application Type	Investigator	Percent Clinical Applications	Percent Nonclinical Applications	Percent Difference
Type 1A0	New	24.5	20	22.5
Type 1A1	New	9.1	7.6	19.7
Type 1A2	New	2.3	1.9	21.1
Type 1A0	Exp	28	27.4	2.2
Type 1A1	Exp	12.5	11.4	9.6
Type 1A2	Exp	3.6	3.4	5.9
Type 2A0		12	17.7	-32.2
Type 2A1		6	7.9	-24.1
Type 2A2		2	2.7	-25.9
Total		100.0	100.0	

PI = principal investigator; A0 = initial application; A1 = first revision; A2 = second revision of application; T1 = new application; T2 = competing renewal application.

not only are clinical investigators less likely to submit a Type 2 application, they are less likely to submit a revised application for a competing renewal.

Because different subsets of applications (for example, Type 1 vs Type 2, initial vs revised) have different peer review outcomes, differences in the proportions of applications within each subset affect the overall review outcome. Two values influence the aggregate percentages of clinical and nonclinical applications scoring within the 20th percentile: the percent of applications in each of the 9 subsets in Table 2 with a percentile rank of 20.0 or better; and the percent of each subset relative to the total. By modeling the impact of the differences in submission rates of the various types of applications, we have estimated that the lower rate of submission of competing clinical applications contributes to approximately one half of the aggregate difference in peer review outcomes between clinical and nonclinical applications.

DISCUSSION

The present study, based on data from 12 review council rounds, confirms and extends preliminary observations that clinical grant applications, in aggregate, do not fare as well in peer review as nonclinical applications.^{7,13-15} The current data suggest that nearly all of the difference in review outcomes for clinical and nonclinical applications is due to 2 separate factors: a failure of 14.8% of clinical applicants to adequately address the human subject protection requirements for research proposals and a lower rate of submission of competing continuation applications by clinical applicants. Each of these 2 factors accounts for approximately half of the difference in review outcomes between clinical and nonclinical applications.

The increasing complexity of federal regulations dealing with the ethical conduct of clinical research is a challenge for the clinical investigator.¹⁶ Even some

experienced funded clinical researchers proposing continuation of their research have difficulty documenting adequate protections for human subjects. Applications cited for having human subject concerns do not necessarily mean that the science is less meritorious. Human subject concerns raised at the time of review can reflect inadequate explanation by the investigator in the protection of human subjects section of the application. Conceivably, instructions for completing this section of the application may require further clarification. However, we cannot exclude the possibility that these applications also might be weaker for reasons other than inadequate documentation of human protections. Nevertheless, there can be value in providing more rigorous training for both emerging and experienced clinical investigators regarding the utilization of human subjects. The message to applicants is that failure to provide complete information about the plans to protect human subjects may result in a less favorable priority score and could adversely affect the likelihood of funding.

The percentage of A0 submissions for Type 2 clinical applications was less than that for nonclinical applications. Similarly, Dickler et al⁸ recently reported that clinical researchers with an MD degree only are more likely than nonclinical researchers to leave the R01 grant applicant pool, although this assertion was not true for individuals with both the MD and PhD degree. Potential factors that may contribute to the attrition of clinical investigators include the total time required for clinical research training; a paucity of clinical research mentors; the slow pace of clinical research and its impact on academic promotion and subsequent competitiveness for renewal grant applications; financial indebtedness of medical school graduates; and stable, attractive alternative career options.¹⁷ The clinical research enterprise would benefit from an informed, current understanding of the factors driving a lower

submission rate for clinical research Type 2 applications.

Limitations

Several limitations of this report should be noted. The observations are based on an inclusive and admittedly imperfect definition of clinical research. In the future, it would be useful to develop a more accurate mechanism for identifying and tracking review outcomes for specific types of clinical research. This analysis focuses exclusively on R01 applications reviewed by CSR. Applications for clinical research also are reviewed by other NIH institutes and centers, and clinical research also is supported by other funding mechanisms, including contracts. Finally, peer-review outcomes, not funding rates, are the focus of this analysis. However, percentile rank is not the only factor used by NIH's institutes and centers in guiding funding decisions.

CONCLUSION

This analysis is not meant to deemphasize the importance of the composition of review panels and the assignment of applications to appropriate review groups. With the input of the external community, CSR monitors and evaluates the peer review process on an ongoing basis. Although peer review may be imperfect, it should not become the scapegoat for the organizational and cultural barriers to clinical research within medical schools and teaching hospitals, as identified by a recent Association of American Medical Colleges Task Force on Clinical Research.¹⁸

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References

1. Wyngaarden JB. The clinical investigator as an endangered species. *N Engl J Med*. 1979;301(23):1254-1259.

2. Goldstein JL, Brown MS. The clinical investigator: bewitched, bothered, and bewildered—but still beloved. *J Clin Invest*. 1997;99(12):2803-2812.
3. Campbell EG, Weissman JS, Moy E, Blumenthal D. Status of clinical research in academic health centers: views from the research leadership. *JAMA*. 2001;286(7):800-806.
4. Nathan DG. Educational debt relief for clinical investigators—a vote of confidence. *N Engl J Med*. 2002;346(5):372-374.
5. Nathan DG. Careers in translational clinical research—historical perspectives, future challenges. *JAMA*. 2002;287(18):2424-2427.
6. Ley TJ, Rosenberg LE. Removing career obstacles for young physician-scientists—loan-repayment programs. *N Engl J Med*. 2002;346(5):368-373.
7. Sung NS, Crowley WF, Jr, Genel M, et al. Central challenges facing the national clinical research enterprise. *JAMA*. 2003;289(10):1278-1287.
8. Dickler HB, Fang D, Heinig SJ, et al. New physician-investigators receiving National Institutes of Health research project grants: a historical perspective on the “endangered species.” *JAMA*. 2007;297(22):2496-2501.
9. Nathan DG. Clinical research: perceptions, reality, and proposed solutions. *JAMA*. 1998;280(16):1427-1432.
10. Nathan DG, Varmus HE. The National Institutes of Health and clinical research: a progress report. *Nat Med*. 2000;6(11):1201-1204.
11. Nathan DG, Wilson JD. Clinical research and the NIH—a report card. *N Engl J Med*. 2003;349(19):1860-1865.
12. Zerhouni E. Medicine. The NIH roadmap. *Science*. 2003;302(5642):63-72.
13. Williams GH, Wara DW, Carbone P. Funding for patient-oriented research: critical strain on a fundamental linchpin. *JAMA*. 1997;278(3):227-231.
14. Kotchen TA, Lindquist T, Malik K, Ehrenfeld E. NIH peer review of grant applications for clinical research. *JAMA*. 2004;291(7):836-843.
15. Kotchen TA, Lindquist T, Miller Sostek A, et al. Outcomes of National Institutes of Health peer review of clinical grant applications. *J Invest Med*. 2006;54(1):13-19.
16. Mello MM, Studdert DM, Brennan TA. The rise of litigation in human subjects research. *Ann Intern Med*. 2003;139(1):40-45.
17. Wolf M. Clinical research career development: the individual perspective. *Acad Med*. 2002;77(11):1084-1088.
18. Association of American Medical Colleges. *Promoting Translational and Clinical Science: The Critical Role of Medical Schools and Teaching Hospitals. Report of the AAMC's Task Force II on Clinical Research*. Washington, DC: Association of American Medical Colleges; 2006.