AIDS Trials Take On Peer Review

Members of the world's pre-eminent AIDS drug testing network say the group reviewing their grants doesn't know what it's doing. But that group says some leading teams just wrote poor grants

Last January, a leading group of Harvard University AIDS researchers confidently applied to continue their membership in the world's largest AIDS drug testing network, the adult AIDS Clinical Trials Group (ACTG). They had every reason to be confident: The Harvard team had helped to start the network 8 years ago and served on its steering committees. But when a peer review panel ranked applications last summer, Harvard, it appeared, had missed the cut. Its proposal ranked 27th among the applicants for monminority trial sites, and it seemed at most 26 such sites would be funded.

Yet when ACTG's funder, the U.S. National Institute of Allergy and Infectious Diseases (NIAID), announced its final decisions on 30 November, Harvard was in. Instead of funding a maximum of 29 sites (including three minority sites) as originally planned—and despite budget pressure to fund as few as 22—NIAID decided to fund 30. The decision was made after the institute's advisory council—the "second layer" of peer review—reconsidered the rankings. "This was no different from any other peer-review process," says NIAID Director Anthony Fauci.

That's not the way some participants in the process view it, however. Some members of the review panel, called a study section, charge that NIAID subverted the review process to get Harvard into the group. "I felt like it was a slap in the face that they did an end run around the study section," says one reviewer. And several ACTG principal investigators (PIs) worry that enlarging the group means that its proposed $60 million budget will be stretched too thin. But other PIs say the study section—designed to prevent insider influence by excluding researchers with ties to applying scientists—was instead filled with nonexperts, and the rankings showed it. "The general consensus was that this was a lottery or a random list," says Fred Valentine, PI for the site at New York University (NYU), which was ranked 26th.

The rancor has opened a window onto the secretive grant review process at the National Institutes of Health (NIH). *Science* has learned many details through interviews with more than two dozen key players, including five study section members, who agreed to discuss their closed-door deliberations if they were not identified by name. At issue is the quality of the review process in the specialized world of large clinical trials: Is it possible to convene a study section whose members have diverse backgrounds and no potential conflicts of interest, yet enough expertise to make informed judgments?

This is a dilemma that researchers wrestle with repeatedly—and are wrestling with now as 22 sites of the pediatric ACTG come up for review. Researchers there are anxious to avoid a replay of the adult imbroglio, says Kenneth McIntosh, a pediatrician at Children's Hospital in Boston who heads the pediatric group's executive committee. "We have done a lot of talking about it," but solutions, he admits, are not easily forthcoming.

Knowing the score

Peer review for ACTG is greatly complicated by the broad scope of the group, which has launched more than 300 clinical trials. "Most of the high-powered AIDS researchers in the U.S. in some way or another interface with the ACTG," says Jack Killen, head of NIAID's Division of AIDS. The sites are designed to work together to enroll thousands of HIV-infected volunteers in a trial—a key factor for determining whether a new anti-HIV drug really works—as well as to fashion state-of-the-art laboratory techniques to evaluate results.

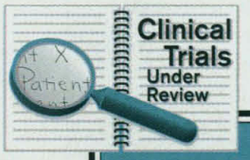
So it is little wonder that last year, NIAID staffers had trouble finding reviewers to evaluate the ACTG proposals. "There are so many sites and investigators involved with the ACTG that it was difficult to convene review groups that didn't have some level of conflict of interest," says the adult ACTG's vice chair, Constance Benson of Rush-Presbyterian Hospital in Chicago, part of Northwestern University's site. The 50 applications (35 of them from existing ACTG sites) sent in during the recompetition involved 3400 people. NIAID contacted 570 potential reviewers, and only 114 of those were willing and eligible to serve on the review panel.

But in the end, Killen says "we got some really good people." The 77 members, 80% of whom had M.D.s, Ph.D.s, or both, included AIDS researchers, nurses, pharmacists, statisticians, representatives from gay and minority communities, and even an anthropologist—a group familiar with most every aspect of conducting clinical trials. Ten of the 77 members were from Canada, where researchers have their own ACTG-like network.

These reviewers looked at proposals that detailed applicants' expertise and experience in conducting multisite AIDS trials, rather than plans to test specific drugs. Sites were judged on a range of criteria, including their ability to recruit patients, enroll minorities and women, publish studies in peer-reviewed journals, and provide leadership; the existing ACTG sites were also rated by their past performances in the network.

The sites received their numerical scores from the study section over the summer; NIAID, however, does not disclose relative rank. But as the institute had stated that it planned to fund between 22 and 29 sites, the PIs decided to compare scores to find out where each one stood. Charles van der Horst, the PI for the ACTG site at the University of North Carolina, Chapel Hill, compiled and distributed an unofficial ranking list (see table on next page).

The rankings weren't what the scientists had expected. "Many of the leading contributors, both with regard to the number of patients entered into clinical trials and the participation in leadership roles in the ACTG, were listed relatively low in the rankings," says virologist Martin Hirsch, Harvard's PI. And when it came to the written comments from the study section, even some PIs from high-ranking sites were



WHAT'S A PEER?

AIDSLine Citations	Study Section (n = 77)	PIs (n = 27)
0	33% (26)	0% (0)
1–5	22% (17)	0% (0)
6–25	24% (19)	7.4% (2)
26–50	10.3% (8)	37% (10)
51–100	6.4% (5)	40% (11)
101–200	2.5% (2)	14.8% (4)
Range	**0–179 cites**	**9–200 cites**
Average	**16.22 cites**	**66.63 cites**

SOURCE: AIDSLINE

Unequal representation. A comparison of citations in the AIDS literature shows a disparity between ACTG reviewers and the principal investigators (PIs) they reviewed.

shocked. "These reviews were so crazy and so capricious," says one such PI, who insisted on anonymity. "The kinds of comments we got in our critique emphasized a complete lack of understanding of what we're doing," charges another. NYU, for instance, was simultaneously praised and criticized for the number of women it has enrolled in its studies, Valentine says.

Studying the study section

For these irate PIs, the reason behind these rankings seemed clear: The study section did not know enough about AIDS research to evaluate the proposals. "The specific reviewers were neither experts nor peers," charges a PI from a high-ranking site.

There are few objective standards that can be used to judge the quality of a study section, just as there is no hard-and-fast way to judge the quality of a grant proposal. But one crude measure is whether study section members, as judged by their publications in the AIDS literature, have records comparable to the 27 PIs from nonminority ACTG sites that made the cut. " 'Peer' means people who are your equal," says immunologist Robert Schooley of the University of Colorado, chair of the adult ACTG's executive committee.

Science combed through the AIDSLine database run by the National Library of Medicine and found that, on average, the study section members had about one fourth the number of citations of the ACTG PIs, and 33% had no citations whatsoever (see table on previous page). In comparison, nearly 90% of the PIs had 25 or more citations. "If you look at a similar distribution in a traditional study section, you wouldn't see that much of a mismatch," says Schooley.

There are many caveats about such an analysis, stresses John McGowan, head of NIAID's division of extramural activities. "You have study section members with specific expertise to review components of the PI's applications," says McGowan, and some of those experts wouldn't show up in the AIDS literature. Statisticians who specialize in cancer are one example. Yet he also says the AIDSLine citation analysis "shows how the current situation with the current conflict-of-interest rules makes it very difficult to hold a peer review."

Even some study section members say the panel wasn't made up of peers. "In the majority of cases, the people doing the reviews were not of the standards of the people being reviewed," asserts one, a prominent AIDS researcher. "The process was flawed to the extent that one of the leading groups was going to fall out of the running. ... It would have been absurd."

But other study section members deny that they were underqualified. About 20% of the members had more than 25 citations, and two members insist that these researchers tended to run the show. "The people who were primary or secondary reviewers, all of us were people with inside knowledge about AIDS research," says one, an accomplished AIDS investigator. "I don't believe it was the process in those closed rooms that failed."

ACTG SITES AND SCORES*

Institute	Score	Rank
Univ. of Alabama, Birmingham	115	1
Univ. of California, San Diego	123	2
Washington University	129	3
Seattle University	132	4
Univ. of Cincinnati	137	5
Johns Hopkins University	138	6
Univ. of North Carolina	146	7
Stanford University	147	8
Case Western Reserve University	148	9
Miami University	148	9
Univ. of California, San Francisco	153	12
Univ. of Minnesota	157	13
Univ. of California, Los Angeles	157	13
Memorial Sloan Kettering	160	15
Univ. of Colorado	162	16
Tulane University	162	16
Pennsylvania State University	163	18
Duke University	165	19
Mount Sinai		
Univ. of Texas, Galveston	166	20
Ohio State University	168	22
Northwestern University	169	23
Univ.of Rochester	177	24
Indiana University	179	25
New York University	181	26
Harvard University	185	27

* List does not include three minority institutions.

Rankings that rankle. These unofficial ACTG study section scores and relative rankings indicated that Harvard missed the cut.

Instead, these reviewers say that low-scoring proposals simply got what they deserved. "Harvard ranked so low because their application wasn't so strong," says one. "They were resting on their laurels and thinking, 'Hey, I've been in the ACTG since 1987; you're going to fund me again.' " Others noted that past performances were less compelling than proposals indicating that a group could perform innovative science in the future. They also complained that there were no data on how many patients completed a trial, which members felt was a crucial measure of a site's performance. "Very vague criteria made it difficult to conduct the reviews," complains one.

After learning their rankings, Hirsch, Valentine, and others who disagreed with their scores submitted strong rebuttal letters, complained privately to NIAID officials, and held their breath, awaiting NIAID's advisory council meeting in September, which would make the final cut.

The final outcome

The advisory council's recommendations were greeted with a sigh of relief by these PIs: NIAID should not fund 22 sites, but 30. That meant not only Harvard got in, but sites that rated slightly better as well. "It wasn't a question of 'let's get to Harvard,' " says Fauci. The issue was simply "what would make the strongest package?"

Privately, many study section members believe that getting to Harvard was precisely the objective; otherwise, they ask, why enlarge the group size over the stated limit of 29? Several ACTG PIs are wondering the same thing. The council's action, they say, means their budgets are going to take an unfair hit. "It's probably going to reduce my funding and may hurt my ability to do quality research," says one PI from a well-ranked site who asked not to be named.

NIAID's William Duncan, who helped organize the recompetition, says that "we will find the money" for all the ACTG sites. Although he does not rule out a cut, he says, "unless the budget is horribly different, there will not be drastic reductions."

Still, with dissatisfaction so widespread, several PIs have been mulling over how to improve the process. No one advocates abandoning the conflict-of-interest rules or barring, say, AIDS activists to get more sophisticated panels. But North Carolina's van der Horst argues that the NIH should give more guidance. "NIH officers should take a more active role in pointing out the strengths and weaknesses of applications," says van der Horst, who maintains that it would have "crippled the ACTG" if it lost Harvard. Study section members have suggestions of their own. "The whole process would have been much better if the NIH was really clear on what they wanted these applications judged on," says one.

That's advice that McIntosh of the pediatric AIDS group appears to be heeding. "We've done our best to keep the people involved [in putting] together the study section apprised of our views," he says. Pediatric sites will also provide the study section with more performance data. The adult recompetition "ran into problems," he says, because the study section emphasized scientific strengths over other contributions a site can make, such as an ability to accrue patients and conduct reliable lab work. By spelling these issues out in detail, he hopes, the study section can reach a decision that will be respected—even if the PIs are not their peers.

–Jon Cohen