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Clinical Trials and Tribulations

In this issue David G. Nathan and Harold E. Varmus provide us with an overview of recent initiatives that the National Institutes of Health (NIH) has pursued to advance clinical research. New NIH funding programs have been implemented to promote clinical research at all levels, from the training of medical students and junior faculty to the support of established clinical investigators. Interest in these programs so far has been strong. The programs make up a small fraction of the NIH budget, however, and whether they will have a real impact on clinical research remains to be determined. That eminent scientists such as Drs. Nathan and Varmus have continued to focus their attention on clinical research is laudable, but as the authors point out it will take the collaborative efforts of the NIH along with private foundations, industry, academic institutions, and individual investigators to make a difference.

One large segment of clinical research that has been successful in building collaborations among researchers, institutions and industry is clinical trials research. Between 1997 and 1999, the proportion of US academic medical centers with a centralized clinical trial office rose from 9% to 45%. At the same time, industry-sponsored clinical grant revenue grew by 17%, compared to a 13% increase in the NIH clinical trials budget (the clinical trials budget makes up about one-third of the total NIH clinical research budget). The trials are expensive because of the great need for careful monitoring by managers and nurses. While human safety is paramount to these trials, researchers themselves sometimes face significant conflicts of interest between protecting patients and advancing their own research. Local Institutional Review Boards (IRBs) made up largely of voluntary faculty members within individual institutions are supposed to ensure that proper conduct is upheld. But there is tremendous work overload within IRBs, there are no detailed guidelines that all IRBs must follow and no system is in place to monitor their activities.

Recognizing a need to revamp the system, the NIH put together a committee to study the problems and make recommendations. The result was the creation in June of the Office for Human Research Protections (OHRP), under the Department of Health and Human Services (HHS). This office replaces the former Office for Protection from Research Risks within the NIH. The intention was to expand the role of the office and give it greater independence by placing it within HHS. A new director, Greg Koski, formerly an associate professor of anesthesiology at Harvard Medical School and director of human research affairs at Massachusetts General Hospital and then Partners Healthcare System, has just taken office. Dr. Koski has not yet publicly announced the specifics on how his office will assume its responsibilities, but he has said that it will focus more on prevention than on punishment. Although his investigative staff has been expanded recently to include a team of eight, it is difficult to imagine how such a small staff can monitor the thousands of ongoing clinical trials.

In a recent *New England Journal of Medicine* article, HHS Secretary Donna E. Shalala called upon leaders of academic medical centers to strengthen the conduct of research at their institutions. She called for taking a critical look at the mechanisms for the oversight of clinical trials, for allocating appropriate funding for protection of human subjects, and for providing IRBs with the authority and resources they need.

Under the current system, IRBs are supported by a portion of indirect cost reimbursement, a dangerous policy that leaves the funding up to the institution. This problem could be avoided if instead, government and industry fund IRBs directly. The contribution from the private sector seems justified when one considers that at least 75% of all clinical research is supported by industry. Through the OHRP, the government should monitor IRB staffing and activities to ensure that standards are being met among all institutions. But the office must be careful not to be too restrictive, thereby impeding researchers from undertaking clinical trials. Phone calls by *Nature Medicine* to several leaders of academic institutions whose research activities were halted as a result of allegations of misconduct went unanswered, suggesting a lingering reluctance to addressing the problems. Data collected by the Food and Drug Administration indicate that applications for gene therapy investigational new drugs (INDs) fell by almost 50% from FY1999 to 2000; in contrast the number of gene therapy IND amendments rose by over 70% during the same period. While gene therapy is only a small component of clinical trials research, these statistics seem to indicate that researchers are appropriately exercising more caution.

Regardless of the funding sources, clinical trials must be held to the highest ethical standards. Congress needs to allocate appropriate resources to the OHRP, and the OHRP should support direct financial assistance to local IRBs and formulate clear and uniform guidelines. At the same time, the OHRP must be accessible and attentive to the concerns of the research community and the public. Regulating clinical trials should focus on mending the shortcomings of the current system without impeding trials that are ethical and promising.

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