

within 15 years after surgery.^{1,2} Within 10 years after surgery, 53 percent of patients require one or more reoperations for postoperative complications, and 10 percent of patients require pouch excision by 10 years. Despite all these limitations to the ileoanal-pouch procedure, we believe the procedure remains a valuable treatment option for patients. However, now that an acceptably safe and effective medical treatment exists, we believe that all patients with medically refractory ulcerative colitis should be offered both colectomy and infliximab as treatment options.

Dr. Reinshagen inquires about the efficacy of infliximab therapy in patients whose disease is refractory to therapy with azathioprine or mercaptopurine. In the pooled databases of the Active Ulcerative Colitis Trials 1 and 2, the proportions of patients in the infliximab treatment groups who were receiving azathioprine or mercaptopurine and had a clinical response or remission at weeks 8 and 30 (response, 63.4 percent and 53.3 percent, respectively; remission, 26.9 percent and 35.2 percent, respectively) were similar to the proportions of patients who were not receiving azathioprine or mercaptopurine and had

a clinical response or remission at weeks 8 and 30 (response, 68.5 percent and 51.8 percent, respectively; remission, 38.5 percent and 31.1 percent, respectively). We conclude that, at both week 8 and week 30, a similar proportion of patients who were treated with infliximab had a clinical response or clinical remission whether or not they were receiving immunomodulators (azathioprine or mercaptopurine) at baseline.

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Clinical Trials Report Card

TO THE EDITOR: In the editorial, with Dr. Wood, on registration of clinical trials (Dec. 29 issue),¹ you unfairly criticize Pfizer and falsely claim that companies challenge the “spirit of the law.” Pfizer’s record is demonstrably excellent. Section 113 of the Food and Drug Administration Modernization Act (FDAMA 113) established ClinicalTrials.gov to help patients find clinical trials and new treatments for serious and life-threatening conditions. Pfizer has rigorously complied with the letter and the spirit of this law.

Your editorial concerned quite separate calls for greater transparency in registering new clinical studies. It failed to report the absence of agreed standards and ignored considerable efforts by Pfizer to develop solutions.

For example, we at Pfizer have registered all confirmatory studies at ClinicalTrials.gov. We have included 20 data fields, as developed as part of the April 2005 World Health Organization (WHO) consultation on clinical trial registration standards, but in rare cases, we have delayed disclosure of the Intervention Name and other fields

to protect commercial sensitivities. Any delay is a matter of timing only, and full disclosure is to be assumed once any proprietary issues are resolved. Also, remember that, in all trials, complete information is provided to regulatory agencies, institutional review boards, investigators, and each patient who is enrolled.

As of November 2005, we had registered 324 clinical trials. Zarin et al. acknowledge in the special article on registration of clinical trials in the same issue of the *Journal*² that Pfizer “rarely” chose to withhold the Intervention Name. It is therefore puzzling to read your complaint that our compliance was “astonishingly low.”

The antagonism shown by Drs. Drazen and Wood is unhelpful at a time when industry is cooperating fully and demonstrating enthusiasm for new processes.

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Editor's note: The current WHO International Clinical Trials Registry Platform is open for public comment at www.who.int/ictrp until March 31, 2006.

1. Drazen JM, Wood AJJ. Trial registration report card. *N Engl J Med* 2005;353:2809-11.
2. Zarin DA, Tse T, Ide NC. Trial registration at ClinicalTrials.gov between May and October 2005. *N Engl J Med* 2005;353:2779-87.

TO THE EDITOR: Clinical-trial registration increases transparency and accountability, but it is not enough. A protocol registry is also needed. Trial registration cannot prevent data-driven manipulation of the analysis — as, for example, in the matter of discretionary decisions and questions that arise concerning the outcome of an event. What is an event, who decides, what population is involved, what is the role of missing data, what statistical tests are applied, what are the covariates?

According to the scientific method, any decision making related to a clinical trial should be described in detail in the protocol and include the amendments and the statistical-analysis plan; proper scrutiny of most trial results requires having access to these documents and assurance that they have not been covertly altered in the process. Our proposal to archive protocols was published in 2002¹ and described sequestering the protocol, amendments, and data-analysis plan while the trial was ongoing; making this documentation available to reviewers when the trial results are submitted for publication; and making all this information generally available thereafter. Nothing approaching an overall plan such as this currently exists, but support for it may be surprisingly broad. Industry is as desirous as doctors and publishers are for a mechanism to assure validity of the process and yet preserve any proprietary aspects before publication. This proposal offers both.

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TO THE EDITOR: Registration of the results of clinical trials ensures that data from all trials of pharmaceutical interventions can be reviewed.

The GlaxoSmithKline (GSK) trial register reports results of more than 2000 trials.¹

Registration of protocol information is important; it encourages participation and publication. Our policy is aligned with that of the International Committee of Medical Journal Editors (ICMJE): not only do we register “all trials whose primary purpose is to affect clinical practice (phase 3 trials)”²; we register all trials in patients, regardless of phase, that began after November 1, 2004.

In their analysis, Zarin et al. find that 79 percent of GSK studies identified the Intervention Name, which underestimated the compliance of GSK with the ICMJE policy because it included trials other than phase 3 trials and completed studies. As of December 26, 2005, 95 percent of ongoing phase 3 studies included the Intervention Name. Some older GSK studies and those that were not phase 3 studies did not; we have been updating these. As of January 12, 2006, Intervention Names were provided in more than 95 percent of GSK-sponsored interventional trials that were considered to be actively recruiting, including 100 percent of phase 3 trials. We believe the report card for GSK — the registration of both protocols and results — should acknowledge this substantial progress.

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1. GlaxoSmithKline Clinical Trial Register. (Accessed March 10, 2006, at <http://ctr.gsk.co.uk/welcome.asp>.)
2. De Angelis CD, Drazen JM, Frizelle FA, et al. Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors. *Lancet* 2005;365:1827-9.

TO THE EDITOR: The description of trial-registration practices provided by Zarin et al. reflects a growing trend of universal access to information in an international attempt to ensure the integrity of scientific conduct and publication. Israel has long been considered a preferred site for conducting clinical research, as reflected by the relatively high number of trials, estimated at 2550 in 2005 alone. Furthermore, phase 3 trials account for more than a third of all trials evaluating drugs. The importance and implications of reporting data from these trials in a reliable, complete, and timely manner have been well emphasized and understood. Therefore, the Israeli Ministry of Health

issued guidelines in September 2005 that require the posting of clinical trials conducted in Israel on the U.S. National Institutes of Health Web-based registry, ClinicalTrials.gov. These guidelines are particularly important because they were developed after several instances of misconduct, some of which were debated in court. The impact of these guidelines has already been seen, both in the compliance of researchers and in the specific requirements issued by health maintenance organizations in Israel.

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TO THE EDITOR: The editorial by Haug et al.¹ (Dec. 29 issue) points out that trial registration does not mandate publication of the results. Patients are recruited into a trial thinking that they are contributing to medical knowledge by participating in the trial. If the results are not made public, the trial will not have contributed to medical knowledge. The patients will have been recruited by fraud. Thus, all institutional review boards should require as part of their approval process that the results of a trial be published within a reasonable period of time after the last bit of data is obtained.²

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1. Haug C, Göttsche PC, Schroeder TV. Registries and registration of clinical trials. *N Engl J Med* 2005;353:2811-2.
2. Reidenberg MM. Conflict of interest and medical publication. *Sci Eng Ethics* 2002;8:455-7.

DR. ZARIN AND COLLEAGUES REPLY: We agree with Drs. Johnson and Lassere that full clinical-trial protocols have information that cannot be found in a clinical-trials registry. However, completion of the existing fields in registering a trial at ClinicalTrials.gov with specific information provides a service both to potential subjects and to those who are trying to interpret results on completion of a trial.

Drs. Krall and Rockhold correctly note that some data providers, including GSK, added specific information to their entries after the end of our data-collection period. For example, since the publication of our paper on December 29, GSK has added specific information to the Intervention Name field in 9 records and has added Primary Outcome Measure information to 26 records.

Tamir and colleagues point out that the Israeli Ministry of Health has issued guidelines mandating the registration of certain trials at ClinicalTrials.gov. We are eager to work with Israel and other appropriate entities that wish to use ClinicalTrials.gov to meet their policy objectives.

Since the publication of our article, the registry has continued to grow at a rate of 252 new trials on average per week and now includes more than 27,000 trials. Overall, industry has improved the quality of its entries. For example, since our report, only one industry record has been added without an Intervention Name, whereas Intervention Name entries were improved by the addition of specific information in 113 records (including 81 improved records from Merck). However, the heterogeneity observed in the use of the Primary Outcome Measure field is still evident; those companies that frequently completed this field before October 11, 2005, have made many improvements to their entries, whereas those companies that rarely used this field during our study period have continued to omit this information in most of their records (Table 3 in our article). The one exception to this is Merck, which had used the field in only 20 percent of the records in our study but has subsequently added Primary Outcome Measures to more than 77 records.

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DRS. DRAZEN AND WOOD REPLY: Feczko's letter does not address the issue raised in our editorial and in the article by Zarin et al. The fact that of 2389 new records registered, 15 contained non-specific entries in the Intervention Name field and 14 of these 15 (93 percent) came from Pfizer suggests that the problem is not with the pharmaceutical industry in general, where overall com-

pliance is excellent, but with Pfizer specifically. Since, as Feczko himself acknowledges, this information is routinely provided to institutional review boards, investigators, and every patient who considers enrolling in a study, posting on ClinicalTrials.gov would not seem to be a burden. Zarin et al. have found that this information has been provided by Pfizer's competitors in their registrations at ClinicalTrials.gov; it is therefore difficult to accept Feczko's claim that "proprietary issues" are at stake when virtually every other company seems to have been able to resolve such issues. Thus, our editorial does not show antagonism to industry in general but, rather, simply points out the truth: Pfizer is unwilling to fully comply with the registration requirement with which most other companies have complied. We urge clinical investigators not to participate in trials that are not fully and meaningfully registered.

We are pleased to hear from Krall and Rockhold of GlaxoSmithKline's progress in updating the trial entries since the analysis of Zarin et al. was published. The progress made since the announcement of the ICMJE requirement that to be considered for publication, clinical trials must have been registered by September 13, 2005, is striking, and we are particularly encouraged by the evidence that industry is well on the road to full compliance with that requirement. We acknowledge the progress that the pharmaceutical industry has made in such a short time and look forward to full compliance in the future.

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DR. HAUG AND COLLEAGUES REPLY: We agree with Dr. Reidenberg that trial registration is only one step in the direction of increasing transparency and reliability in the reporting of clinical trials. Protocol registration and public access to results would be even better. As reiterated by Dr. Reiden-

berg, registration of trials does not hinder selective reporting or leaving unwanted results unpublished, thereby deceiving the altruistic persons who volunteer for research because they trust that their participation will contribute to improved health for others. At the very least, the participants assume that adverse events discovered in the course of the trial will minimize risks to others.¹ Though not all journals may see it as their obligation to publish all results from all trials, journal editors can participate in the effort to ensure that all data are made public. The questions are how to achieve these ends and what sanctions could be imposed on investigators or organizations that fail to bring the results of a completed trial into the public domain.

One suggestion is to set up a global database (or a network of databases of similar design) in which the results of all registered trials are deposited. After a specified period of time has elapsed (to allow the researchers to publish results in a peer-reviewed journal), an agreed-on synopsis of the data could be made public. Sanctions against researchers, institutions, and companies that fail to meet such a standard could include the following: denial of approval from ethics committees to conduct additional trials until the missing data have been added to the database²; a ban on publishing in journals that have adopted such rules; and economic sanctions.

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Community-Acquired Bacterial Meningitis

TO THE EDITOR: In their review article on community-acquired bacterial meningitis (Jan. 5 issue), van de Beek et al.¹ suggest that when bacterial meningitis is probable but neuroimaging is not avail-

able, lumbar puncture should be given preference in immunocompromised patients or in those with moderate-to-severe impairment of consciousness.

As emergency physicians, we frequently en-