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TRIAL AND ERROR

The ethics committees that oversee research done in humans have been attacked from all sides. **Heidi Ledford** recounts the struggle to come up with alternatives.

Fourteen years of treating people with tuberculosis has taught physician William Burman what to expect when a patient walks through his door. Tuberculosis is not typically a disease of the well-heeled. Many patients in the United States are foreign born. English is their second language. Fewer than half have completed a high-school education, and many have spent time in jails or homeless shelters.

So when Burman, of the University of Colorado in Denver, joined in two studies run by the Tuberculosis Trials Consortium, he knew that the consent forms needed to cater to people with an eighth-grade reading level (comprehensible to an educated 13-year-old). The trials involved multiple institutions, and the forms were sent to 39 institutional review boards (IRBs) — committees designed to determine whether a proposed experiment is ethically sound. The final approvals came in 346 days later, but what the IRBs sent back, Burman found disturbing.

"The consent forms were longer. The language was more complex," Burman says. "And errors were inserted at a surprising frequency." In one case, a potential negative side effect of the treatment had been accidentally edited out. Burman responded to the problem as any researcher would: he studied it. He had an independent panel review the changes. The reviewers found that 85% of the changes did not affect the meaning of the consent forms, but that the average reading level had jumped from that of an eighth grader to that of a twelfth grader (around 17 years old)[1]. His results confirmed something he'd suspected for some time. "I started to think about what was happening and it just seemed like the system was flawed." It was time to change the system.

Burman is not alone. In the 40 years since their birth (see 'Time for ethics'), IRBs, also known as research ethics committees, have faced criticism from all sides. They're too slow, or too hasty, overprotective, or they flout basic safety. They're bureaucratic, wasteful and unavoidable. So, what are researchers to do? The will for change exists, says Sarah Greene, a researcher at the Group Health Center for Health Studies in Seattle, Washington. But recent attempts to fix the system have struggled to gain a foothold.

Obstacle course

In many countries, a complex network of local ethics committees handles the approval of research on humans. This focus on local resources allows committees to account for specific laws or cultural concerns in a particular region. But it leads to problems in multicentre trials, such as Burman's, which are becoming more frequent. When IRBs were first founded, multicentre trials were almost unheard of. A 1998 report[2] from the inspector-general of the US Department of Health and Human Services in Washington DC stated that a rise in the number of multicentre studies was throwing the system into crisis. And a recent analysis[3] showed that five of 20 trials seeking IRB approval reported significant delays as a result of IRB negotiations. Seventeen noted inconsistencies both in IRBs' review process and in their recommendations. In one case, negotiations between 65 IRBs delayed the study by a year.

> **"A national IRB could fail to recognize different needs of different communities."**
> — Lainie Ross

More frighteningly, the cumbersome system could even endanger the health of the studies' participants. The higher the hurdles — and the more unfair they seem — the less inclined researchers will be to jump them. "It's slow and frustrating to researchers," says Ezekiel Emanuel, chair of the US Department of Bioethics at the National Institutes of Health in Bethesda, Maryland. Researchers have reported that they are more likely to violate the regulations set by ethics committee if they feel that they or their application have been mishandled[4].

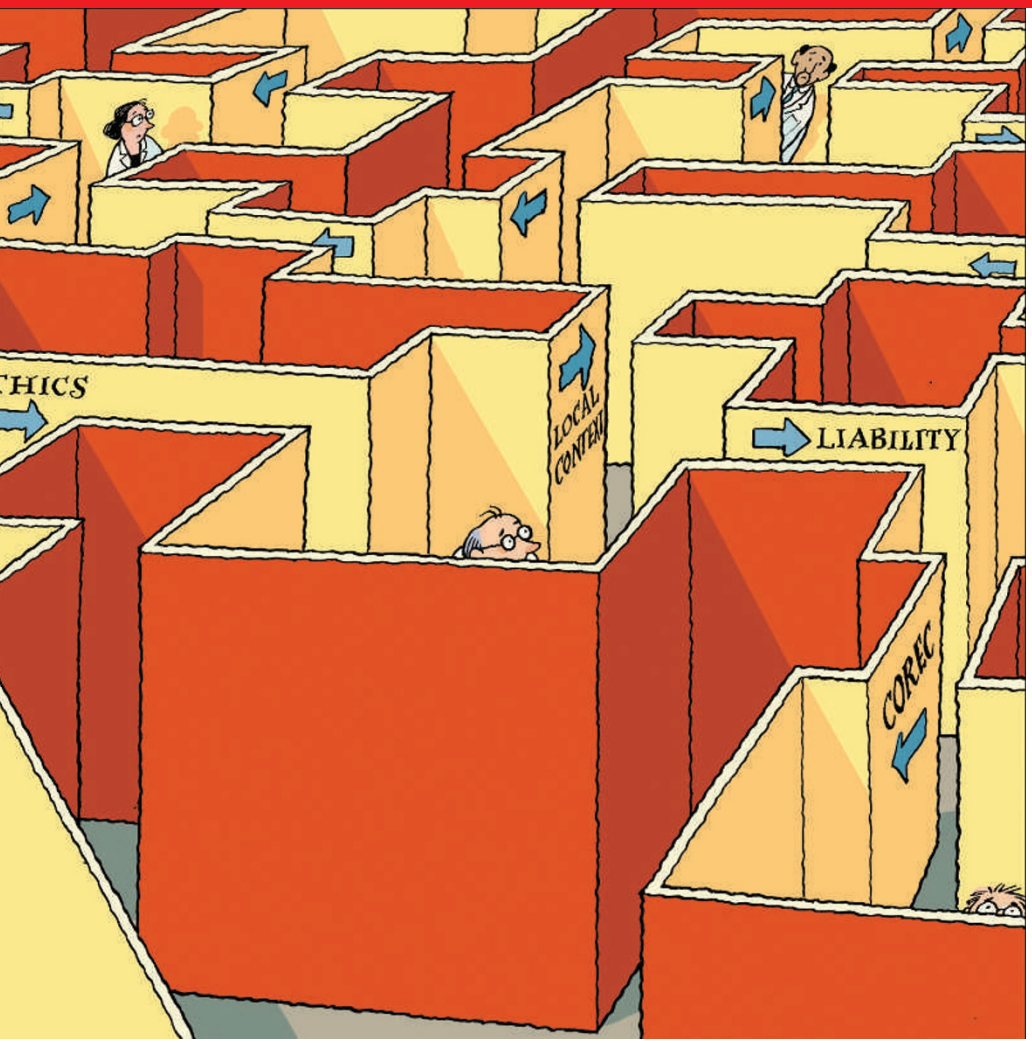
And even though IRBs are made up mostly of volunteers, they are expensive to run. In 2002, the median cost of running an IRB, taking into account the time spent by IRB members, was $742,000; the maximum was over $4 million[5]. So, for every protocol they assess, they charge a fee to cover support staff, facilities, and outside consulting. These fees are typically pulled from grants as part of the institutional overhead, or as direct charges to commercial sponsors, and they average just over US$1000 (ref. 5).

A proposed solution to the copious problems with IRBs is outsourcing, especially for multicentre studies, to some form of centralized review. That movement has met with resistance from those who say that local review provides valuable local context. But Burman counters that local context had little bearing on the changes in his consent forms. In his trials, only 1.5% of the tweaks to the consent forms were made to account for local context[1].

Risky process

But that's not enough to rule out the importance of local review argues David Wynes, vice-president for research administration at Emory University in Atlanta, Georgia. "I agree that the vast majority of changes are editorial, but I think there's a value in an institution having a process for identifying when local context is an issue," he says. "You might have to review a hundred protocols before you can see the value of local context. Is it OK if only 1% of the time you put subjects at risk?"

Burman argues that expertise with a specific patient group or disease should trump local context from detached review boards. "The local IRBs don't know the patients I take care of, because if they did, the last thing they



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would do is increase the length of the consent form and make the language more complex," he says. Instead, Burman and his colleagues have worked to create a designated panel at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, which keeps track of disease epidemiology in the United States, to review all tuberculosis studies.

Top trumps

But a centralized system will work only if the local boards are not allowed to overrule the decision of the central board, says Emanuel. It's a lesson, he adds, that the United Kingdom has had to learn the hard way.

In 1997, the United Kingdom created a system of regional review boards in which trials needed approval from just one board to proceed. In 2000, the system was brought under the auspices of the Central Office of Research Ethics Committees (COREC), based in London. The trouble was, local ethics committees refused to surrender control, and instead of expediting review, COREC had created a new layer of bureaucracy.

"Researchers were very upset with the way things were going," says Emma Cave, a lecturer at the Leeds School of Law, UK. "They thought the regulations were making the United Kingdom a bad place for research." In April, Britain dissolved COREC in favour of the new National Research Ethics Service, and changed the regulations to restrict the ability of local ethics committees to change the protocol approved by the national office.

In 2001, the US National Cancer Institute (NCI) in Bethesda, Maryland, launched a similar experiment — a central review board to review all NCI-funded research on humans. Local review boards retained the power to do a full review, but could opt instead for an expedited review in which they merely adjust for local context. (The NCI formed a similar review board for paediatric studies in 2004.)

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The project immediately ran into trouble. The central board spent too much effort on scientifically reviewing proposals that had already been reviewed by the granting arm of NCI, says Richard Schilsky, chairman of Cancer and Leukemia Group B, an NCI-sponsored cancer clinical trials group. And at first, few local IRBs were willing to cede control to the central review board. "The concept is good," says Schilsky, "but the devil has been in the details of the implementation."

Since 2001, the number of participating institutions has climbed to 300. More than half of those have accepted the reviews of NCI's central board; the remainder are still developing ways to incorporate the central boards review into their own review process.. But Schilsky says that only about 20% of the institutions involved in his clinical-trials group — the largest in the United States — have signed on. The result was similar to what happened in Britain, adding to the bureaucracy. Schilsky estimates that the system has added two to three months to the time it takes to activate a new study.

Lainie Ross, a paediatrician and member of the IRB at the University of Chicago Medical School, says that she is opposed to surrendering local control. "A national IRB could fail to recognize different needs of different communities. I'm not just going to accept someone else's word for it."

Without fail, IRB members interviewed by *Nature* who were opposed to ceding control to a centralized board cited concerns about patient safety as their main reason. But Emanuel, who has also served on an IRB, says that there's another cause for concern. "There are no good data suggesting that there are local factors that are ethically relevant," says Emanuel. "It's really liability that's driving this."

Vulnerable populations

Liability is a thorny issue for local IRBs contemplating handing over control to NCI's central IRB, says Wynes. If a participant in a clinical trial felt that he or she were unjustly harmed during the course of the research, they could not hold the NCI legally responsible because it is a branch of the federal government. That leaves the local IRB legally vulnerable, says Clint Hermes, general council at St. Jude Children's Research Hospital in Memphis, Tennessee.

It is rare, but IRBs and even individual IRB members have been sued in the past. Bioethicist Arthur Caplan at the University of Pennsylvania in Philadelphia says that he has served on two IRBs that were sued but still thinks it's important to have a mechanism in place to hold negligent IRBs accountable.

Meanwhile, a profitable industry in private, commercial IRBs has sprung up. Although commercial IRBs can provide a sense of security by assuming legal liability, the institution doing the experiment will bear ultimate responsibility. But partial indemnity seems sufficient to comfort many researchers: commercial IRBs serve hundreds of companies, hospitals and research institutions. In 2005, the consulting firm Deloitte named Chesapeake Research Review of Columbia, Maryland

TIME FOR ETHICS

1947
The Nuremberg Code governing human research is released as a response to the Nazi experiments of large-scale sterilization and vaccine testing on prisoners intentionally infected with typhus fever.


BETTMANN/CORBIS

1963
Doctors at the Jewish Chronic Disease Hospital in New York City inject cancer cells into patients as part of a study of transplant rejection. Patients were not told what was in the injections.

1964
The World Medical Association issues ethical principles governing human research called the Declaration of Helsinki. These later become the basis for ethics committees around the world.

1966
Britain establishes its first ethics committee. The *New England Journal of Medicine* publishes a paper citing 22 violations of research ethics at major research institutions in the United States.


CORBIS SYGMA

1972
Authorities terminate a 40-year experiment in which treatment was withheld from men with syphilis in Tuskegee, Alabama. The men were told that they were receiving free treatment.

1974
In response to the Tuskegee scandal, America founds the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in Washington DC — its first office dedicated to protection of human subjects.

1997
Controversy erupts over US-funded trials in Thailand testing the effect of zidovudine (AZT) on HIV transmission from pregnant women to their children. Women in the placebo group received no treatment.

1999
18-year-old Jesse Gelsinger dies from complications of a gene-therapy experiment at the University of Pennsylvania in Philadelphia, launching a barrage of criticism about gene therapy and human research.

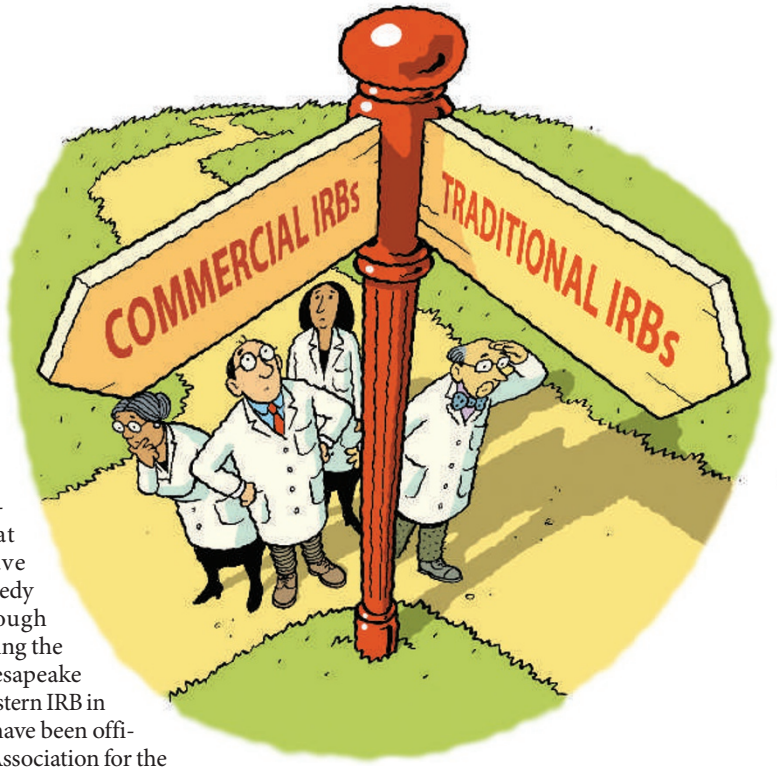

J. KEYSER//TIME LIFE PICTURES/GETTY IMAGES

2000
Britain establishes the Central Office of Research Ethics Committees in London to review multicentre trials. America refuses to sign a revision of the Declaration of Helsinki that limits the use of placebo-controlled trials.

KRT/NEWSCOM

2001
The US National Cancer Institute launches its central review board, to evaluate all human research funded by the institute. The board aims to standardize and expedite ethics review.

2007
In response to criticisms about COREC, the UK forms the National Research Ethics Service and restricts the ability of local review boards to demand changes in experimental protocols.



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— a commercial IRB and consulting service — as one of the fastest-growing technology companies in North America. The firm increased its revenues by 244% in five years, to reach nearly $5.5 million in 2004.

Proponents of commercial IRBs say that larger companies have good reputations for speedy turnaround and thorough reviews. Several, including the two largest players, Chesapeake Research Review and Western IRB in Olympia, Washington, have been officially accredited by the Association for the Accreditation of Human Research Protection Programs in Washington DC. Such societies provide a stamp of approval for IRBs, providing oversight and standardization to the field.

Financial gain

Still, others worry about the potential conflict of interest inherent to commercial IRBs, who could benefit financially from pleasing their customers and passing protocols with minimal fuss. "I'm a little cautious about this drive towards commercial IRBs," says Richard Bianco, associate vice-president for regulatory affairs at the University of Minnesota in Minneapolis, and a 15-year IRB veteran. Nevertheless, Bianco and other critics acknowledge that local IRBs also have a conflict of interest — clinical trials can bring in serious cash and prestige to the institutions they serve, and IRB members that are also scientists at the institution may feel pressured to approve a trial. "I'm somewhat surprised that no one has ever pushed to reform the private side of IRBs," says Caplan. "It's growing like crazy. Industry hires them because they're fast and efficient. It doesn't mean that they're right."

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Bianco also says that his colleagues have been under "intense pressure" by industry collaborators to relinquish control to commercial IRBs. Some trial sponsors, he says, even issue ultimatums: use the commercial IRB that we recommend or don't participate in the trial. "That was pressure," says Bianco. "But I've been around a long time. You come to know what to ignore." None of those threats ever came to fruition, he says.

For others, initial scepticism of commercial IRBs has given way to acceptance. "When I first came across independent IRBs, I questioned them, too," says Wynes. "But I've taken the time to get to know how they operate, and my comfort level has changed." In November 2005, while Wynes was still at the University of Iowa in Iowa City, he helped the university to switch to outsourcing industry-sponsored trials to Western IRB. Prices vary, but outsourcing to industry can cost twice as much as processing the application in-house, although commercial IRBs typically boast a quicker turnaround time. Whereas many commercial IRBs aim to review applications within a week of their receipt, non-commercial IRBs may meet only once a month.

Some see commercial IRBs as a stop-gap measure in lieu of real regulatory change. But despite the roadblocks, substantial change is inevitable, says Emanuel. The lingering problem, he adds, is that it will probably take a new scandal to push reform to the top of the agenda. "I think we're just one accident away, but it will still take the accident," he says. "In my opinion, that's the sad fact." ■

Heidi Ledford writes for *Nature* from Boston, Massachusetts.

1. Burman, W. *et al. Control. Clin. Trials* **24,** 245–255 (2003).
2. Office of the Inspector General, Department of Health and Human Services. Institutional review boards: a time for reform. (US Government Printing Office, Washington, DC, 1998).
3. Greene, S. M. & Geiger, A. M. *J. Clin. Epidemiol.* **59,** 784–790 (2006).
4. Keith-Spiegel, P. & Koocher, G. P. *Ethics Behav.* **15,** 339–349 (2005).
5. Sugarman, J. *et al. N. Engl. J. Med.* **352,** 1825–1827 (2005).

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