

marks. Such a procedure would not be particularly onerous and would allow students to learn from the experience of the OSCE, as well as the preparation beforehand.

OSCEs were first trialed in 1975 (11) and despite varied responses from both staff and students (12-16), they look set to stay with us. Although they are undoubtedly an improvement on the old 'long cases' in terms of fairness (1), the current use of OSCEs in the UK seems to present a number of missed opportunities in terms of both education and efficiency.

Jean Adams, BMedSci, MBBS  
School of Population and Health Sciences  
University of Newcastle upon Tyne

#### ACKNOWLEDGEMENTS

Many thanks to Prof. John Spencer and Dr. Martin White (both of Newcastle University) for engaging in discussions that help shape the arguments presented in this article.

#### REFERENCES

1. Wass V, Jones R, Van der Vleuten C. Standardised or real patients to test clinical competence? The long case revisited. *Medical Education* 2001;35:321-325.
2. Carraccio C, Englander R. The objective structured clinical examination: a step in the direction of competency-based evaluation. *Archives of Pediatrics and Adolescent Medicine* 2000;154(7):736-741.
3. Wass V. Getting through OSCEs. *Student BMJ* 2000;8(9):361-362.
4. Varma S. Should candidates be given their marked up papers back after examinations - the case for. *Student BMJ* 1999;7(11):456.
5. Duerson M, Romrell L, Stevens C. Impacting faculty teaching and student performance: nine years' experience with the objective structured clinical examination. *Teaching and Learning in Medicine* 2000;12(4):176-182.
6. Merrick H, Nowacek G, Boyer J, Robertson J. Comparison of the objective structured clinical examination with the performance of third-year medical students in surgery. *American Journal of Surgery* 2000;179:286-288.
7. Mavis B. Does studying for an objective structured clinical examination make a difference. *Medical Education* 2000;34:808-812.
8. Weetman A. Should candidates be given their marked up papers back after examinations - the case against. *Student BMJ* 1999;7(11):457.
9. Kaufman D. Assessing medical students: hit or miss. *Student BMJ* 2001;9(3):87-88.
10. Tomorrow's Doctors: Recommendations on Undergraduate Medical Education. July 2002. [http://www.gmc-uk.org/global\\_sections/sitemap\\_frameset.htm](http://www.gmc-uk.org/global_sections/sitemap_frameset.htm)
11. Harden R, Stevenson M, Wilson Downie W, Wilson G. Assessment of clinical competence using objective structured examination. *British Medical Journal* 1975;1:447-451.
12. Kearney P. OSCEs don't work. *Student BMJ* 2000;8(3):123.
13. Green T. OSCEs are useful to assess particular skills. *Student BMJ* 2000;8(4).
14. Morris C. Objective structured clinical examination. *Student BMJ* 2001;9(7):303.
15. Mottam V. Objective structured clinical examination. *Student BMJ* 2000;8(2):82.
16. Phillips S. OSCE oscars. *Student BMJ* 2000;8(4):168.

**Jean Adams** is in the second year of a three year PhD research fellowship at Newcastle University, UK. She graduated in medicine in 2001 and also has a BMedSci degree in health psychology and psychiatry. Her current research focus is socio-economic inequalities in health but she also has a wider interest in health behaviours and health promotion.

#### IRB REFORM IN NORTH AMERICA: CHALLENGES AND OPPORTUNITIES

Clinical research is necessary to advance medical knowledge and to test new drugs or devices. It is therefore vital to society, and ethically imperative, that clinical studies be performed if patients are to have access to safe and effective treatments. However, clinical research by its very nature involves risk. Subjects who volunteer in clinical studies may receive no benefit; in fact, they may be seriously harmed or even die as a result of their participation. Indeed, research-related injuries and deaths, though relatively few in number (1), have become the subject of much controversy in recent years (2). Thus, protection of human research subjects must be given the highest priority by researchers, their institutions, and the

government and regulatory bodies charged with overseeing the clinical research process. Central to this process is the institutional review board (IRB) in the United States (U.S.), or research ethics board as it is known in Canada. (For the purpose of this paper, the term "IRB" will be used to refer to both American and Canadian boards.) The IRB has frequently been referred to as the "first line of defense" in research subject protection (3), yet the specific roles and responsibilities of this board and its members are not clear (4). Defining these roles and responsibilities is more important now than ever before, for several reasons.

#### THE ISSUES:

##### *IRBs in crisis*

First, biomedical science is advancing at an unprecedented rate, and the number of clinical studies is

increasing exponentially (5). This situation can only add to the strain on already over-burdened IRBs (6). Numerous articles in recent literature have made reference to the "crisis" in American IRBs (7,8), being unable to cope with the sheer volume of protocols they are asked to review, and the "pressure-cooker atmosphere" (9) IRB members must contend with as they struggle to balance the interests of subjects with those of the researchers. A report commissioned by the Law Commission of Canada indicates that Canadian IRBs are not faring any better (10). The U.S. Office of Human Research Protection (OHRP; the agency responsible for oversight of IRBs in the U.S.) concluded in a 1998 report that IRBs review "too much, too quickly, with too little expertise" (6), and that the entire system was "in jeopardy" (6). Though there is no equivalent to the OHRP in Canada, Canadian IRBs have not escaped criticism (11,12) or calls for reform (10,13). Clearly, IRBs in North America are overwhelmed under the current system. It is not reasonable to expect these same IRBs to handle double or triple their current workload without a significant reduction in the quality of their reviews. If IRBs are to continue to be relied upon as the primary safeguard of clinical trial volunteers, a clear mandate for their roles and responsibilities must be established. In defining these roles and responsibilities, it may be possible to lessen the current burden on IRBs by delegating certain responsibilities to other committees or regulatory bodies. Alternatively, recognition of the many obligations of the board and its members could result in provisions for increased support to give the members the resources they need to do their job properly.

#### *Liability and the IRB member*

The second reason for the impetus to define the IRB's specific roles and responsibilities is the alarming, albeit not new, threat of personal legal liability of IRB members. The U.S. National Commission for the Protection of Human Subjects Report and Recommendations: Institutional Review Boards, published in 1978, clearly states that IRB members may be held personally liable "for malpractice or negligence in discharging their IRB functions" (14). Angela Holder, a legal expert on human subject research, was quick to respond in her 1979 article "Liability and the IRB Member: The Legal Aspects", that such a thing would never actually happen (15). Times have changed. In 2001, a lawsuit filed on behalf of subjects who had participated in a study of a melanoma vaccine at the University of Oklahoma named twelve IRB members as defendants (16). The 130-page complaint contained many allegations, including inadequate procedures for the

manufacturing and safety testing of the vaccine, failure to adhere to the protocol inclusion/exclusion criteria, incomplete informed consent documents, and a failure by the IRB to meet its federal regulatory obligations (16). The individual IRB members were accused of negligence in their duties (16). This precedent-setting case sent shockwaves through IRBs across North America.

IRB members are, for the most part, volunteers who commit a tremendous amount of time and energy to the onerous task of reviewing the hundreds of protocols that pour into their institutions each year. Their work is often not respected by researchers, who tend to view the ethics review process as "a bureaucratic pain in the neck" (3). IRB members face a great deal of pressure from researchers, sponsors, institutions, and even the public to push through protocols at a rate that cannot possibly be consistent with a meticulous and thoughtful consideration of all the ethical issues at stake. Though the IRB has the power to require revisions to protocols, "exercise of this power does not enhance a committee's popularity within its institution" (17). In addition, IRB members must make difficult decisions about increasingly complex protocols that do not fall neatly under any guidelines currently in use (17). These decisions, which often come down to judgment calls, require "a fair exercise of intelligence and discretion on the part of IRB members" (18). As one article describes it, "the quality of an IRB's work depends to an inordinate degree on the conscience and commitment of its volunteer members" (19). The idea that individual IRB members could be held legally liable for these decisions is disturbing. This threat of legal action may result in IRBs rejecting more protocols than they approve, or reviews so painstakingly thorough that the review process effectively grinds to a halt (20). It will undoubtedly serve as a deterrent to future IRB members, at a time when it is already difficult to fill these positions (20,21). However, no one would suggest that IRB members be exempt from accountability. Certainly, even without a proper set of guidelines, one would expect IRB members to carry out their duties in a conscientious manner. But knowing precisely what they will be held accountable for, and what protections are in place for them, will be essential if these individuals are to be expected to continue this important work without fear of litigation.

#### *The IRB in the public eye*

Finally, for clinical trials to proceed and potentially life-saving treatments to reach patients who need them, researchers need the public's trust. Donors, funding agencies, government, and most importantly, clinical study volunteers and their families, all want assurance

that a solid system of checks and balances is in place to protect research subjects. Without the public's trust, the system cannot function. Unfortunately, this trust has been eroded in recent years by high-profile incidents involving the tragic deaths of research subjects, and the allegations of misconduct that followed. As Dennis De Rosia, chairman of the Association of Clinical Research Professionals, said in an interview, "Each time you have one of these incidents, there's a rash of publicity, and it gets harder to recruit volunteers" (22). Most notable among these are the cases of 18 year-old Jesse Gelsinger, who died while participating in a gene therapy trial at the University of Pennsylvania (23), and 24 year-old Ellen Roche, a healthy volunteer who died after inhaling hexamethonium as part of an asthma study at Johns Hopkins (24). Both of these cases drew international attention when failures of the research subject protection system were uncovered. Since 1998, the OHRP has suspended or restricted research at over a dozen institutions due to IRB inadequacies, including such prestigious institutions as Duke (25) and Johns Hopkins (26). In both Canada and the U.S., research-related deaths and injuries have landed IRBs or their sponsoring institutions in court (27,28). Subsequent investigations have often directed much of their criticism at the IRB involved (20). The reports themselves often reflect expectations of the IRB that are simply unwarranted. As an example, the report of the external review committee for the Johns Hopkins incident faults the IRB for not having a pharmacologist on their board (29). Yet none of the current guidelines for IRB membership contain any reference to a requirement for the presence of pharmacologist (30), nor is it obvious that "rigorous pharmacological review" (29) is the responsibility of the IRB (31). Discrepancies such as these serve as excellent examples to illustrate why the IRB and its members must be given a specific framework within which to act. The public's faith in the system is flagging (2,22); a clear set of responsibilities for the IRB would put an end to finger-pointing that further damages that faith.

#### COPING STRATEGIES AND SOLUTIONS:

##### *Commercial IRBs*

Several mechanisms have arisen over the past few years as means to cope with the over-burdening of local IRBs. As a result of the significant increase in industry-funded research, commercial or "for-hire" IRBs were established. Commercial IRBs now exist in both Canada and the U.S., though official information on the number of these boards operating in either country is lacking (18). These IRBs primarily review research to take place at research centers affiliated with pharmaceutical companies, at contract research

organizations, or in private clinics by medical professionals not associated with academic research institutions (32).

Review through these IRBs is faster and arguably better and more consistent than that obtained through traditional IRBs, given the stipulations these boards may hold regarding the education and expertise of their members and the fact that there is less turnover in their membership. Using a commercial IRB for a multi-center trial may also save time and money by allowing researchers to forgo multiple, redundant reviews of the same protocol at each individual site (32). However, serious concerns have arisen regarding the inherent conflicts of interest that exist within commercial IRBs (18,32). Whether the commercial IRB is one set up by a pharmaceutical company to review research on its own products, or an independent review board on contract to review research taking place elsewhere, in both cases the IRB is a for-profit enterprise. Academic IRBs have also been criticized for conflicts of interest, as IRB members may be motivated by their desire for career advancement, future opportunities for collaboration, or even maintaining friendships with colleagues when reviewing protocols (33). However, because academic IRBs are non-profit institutions, these concerns - at least in terms of financial conflicts of interest - are less obvious. Further problems with commercial IRBs arise when a researcher who has a protocol rejected by one IRB simply takes it to another. The researcher has no obligation to inform an IRB of previous submissions of the same protocol, nor does an IRB have access to any other IRB's review. The problem of "IRB shopping" is a serious one, and one that did not exist when the traditional IRB was the only channel through which a researcher could have their protocols reviewed. Similarly, independent IRBs are not required to monitor the research they have approved, as is the case for traditional IRBs. Independent IRBs may also lack the familiarity with local research conditions and culture that traditional IRBs have. Thus, while the commercial IRB fills an important niche in the context of the current ethics review system, it is not without problems, nor is it a replacement for the traditional IRB. In fact, because there are no clear rules and regulations for IRB review, oversight and accountability, commercial IRBs are no better equipped than traditional IRBs to meet the challenges posed by the present system.

##### *Central IRBs*

A second development in recent years is the creation of the central IRB (CIRB) for multi-center trials. This CIRB could perform a detailed review of the science and experimental design of a protocol for multi-center trials, eliminating the need for the IRB at each

individual site to repeat this process (34). The local IRBs could then expedite their review of a protocol approved by the CIRB, focusing their attention on local issues the protocol may present (such as institutional policies, or language differences that may require changes to the consent form), rather than needlessly duplicating the review of the scientific aspects of the protocol (35). An added advantage of the CIRB would be in managing the ongoing monitoring of these trials. Safety reports and annual study reports from multi-center trials comprise a significant proportion of the workload of local IRBs (7). A centralized approach to monitoring these trials would not only free up more of the local IRBs time and resources to put toward other responsibilities (such as review of local studies), but may in fact result in more effective review of adverse events. The CIRB would be reviewing reports of adverse events from all individual sites in the context of the trial as a whole, a comprehensive view that most local IRBs do not have. Furthermore, the CIRB would have access to reports by data and safety monitoring boards (DSMBs) and information from the sponsor that is not available to local IRBs, but which could be crucial in making decisions with respect to monitoring. The CIRB approach is currently in the pilot phase at the National Cancer Institute in the U.S. (34). This pilot model was established in order to increase patient access to National Cancer Institute-supported trials. With sixteen members, all cancer experts, from both academic and community organizations across the U.S., the CIRB initially served 22 local institutions (34). Results so far have been promising, and plans are presently underway to expand to serve 100 (34). However, challenges still remain in terms of the division of responsibilities, both between the local and CIRB and between the CIRB and other bodies (such as the DSMB). Another potential complication is that local IRBs may also want to continue to conduct complete reviews of protocols even after CIRB approval if they are concerned about being held accountable for the decision to approve. This is another instance where defining responsibilities for IRBs would facilitate quicker reviews and more effective collaboration between partners in the review process.

#### *Delegating responsibilities*

A third way in which the research ethics review system is attempting to deal with its ever-increasing workload is by rethinking how the IRB manages its many obligations. By most accounts, monitoring is the function that IRBs perform most poorly. Canadian (11) and American (36) reports indicate that few IRBs conduct any monitoring beyond reviewing annual study reports, the bare minimum requirement in both

countries (14,37). Papers in recent literature have proposed that monitoring should be delegated to a separate body, particularly for multi-center trials (7,34). Both the Office of Human Research Protection and the Food and Drug Administration in the U.S. are encouraging greater use of DSMBs, and the National Institutes of Health now require an independent DSMB for all Phase III trials (1). Others suggest that certain aspects of monitoring, such as consent monitoring (determining whether research subjects understand the risks and benefits of the research they are being asked to participate in) be delegated to a subcommittee of the IRB, or an intermediary (38). While at present these proposals are just that - proposals - the idea of delegating some of the IRB's responsibilities is attractive. Many IRBs already assign some aspects of the review process, such as the review of contracts between clinical investigators and sponsors, or the assessment of statistical power of clinical trials, to individuals who are not members of the IRB. While the danger exists that adding several subcommittees or consulting bodies will increase the time and red tape involved in reviewing protocols, the reassurance that all the functions of the IRB are being fulfilled by persons with the expertise to perform them properly makes the additional layer of bureaucracy worthwhile. The IRB can then concentrate its time and efforts on thorough primary reviews and oversight of local studies.

#### THE FUTURE:

In considering any changes to the current system, it must be kept in mind that the IRB's primary purpose is the protection of research subjects. This mandate cannot be achieved without a formal regulatory framework within which the IRB can operate. Such a system would need to establish standards harmonizing national and international laws and policies. A single set of clear guidelines is required with respect to conflicts of interest, division of duties, and accountability. The IRBs need greater support from government and their institutions, both in terms of funding and staff, as well as training and ongoing education for IRB members and clinical investigators.

How close is this major overhaul to becoming a reality? It may be closer than it seems. Last fall, an Institute of Medicine committee delivered its recommendations for improving research subject protection in the U.S. (39). A central theme throughout the report is easing the strain on IRBs by reducing their workload and increasing their resources. Among the recommendations are calls for a national registry to track research participants, as well as the creation of a CIRB. The report also contains a plan to separate the IRB's functions into three committees: one to evaluate

the scientific merit of a protocol, one to assess potential conflicts of interest, and a third to integrate all the information, consider other issues and make a decision. The Institute of Medicine plan also proposes a no-fault compensation system for subjects who are harmed as a result of their participation in research, thereby avoiding litigation. It remains to be seen whether these changes will be implemented, and whether Canada will adopt similar strategies. If our governments, granting agencies and institutions recognize the value of clinical research and the independent ethics review process that must accompany it to our society, then they must also recognize that this important issue needs to be addressed, and deserves our immediate attention.

Marjorie Ellen Zettler, B.Sc.  
Division of Stroke and Vascular Disease,  
St. Boniface Research Centre and  
Department of Physiology, University of Manitoba

#### REFERENCES

- Office of Inspector General. Protecting Human Research Subjects: Status of Recommendations. Washington, D.C. Department of Health and Human Services, 2000.
- Drennan KB. Have the ultimate benefits of clinical trials been maligned beyond repair? *DDT* 6(12): 597-599; 2001
- Lemonick MD, Goldstein A. At your own risk. *Time* 159(16): 40-49; 2002
- Hirtle M, Lemmons T, Sprumont D. A comparative analysis of research ethics review mechanisms and the ICH Good Clinical Practice guideline. *Eur J Health Law* 7: 265-292; 2000.
- No author listed. Anticipating a clinical investigator shortfall. *Centerwatch* 8(April): 1,5-13; 2001
- Office of Inspector General. Institutional Review Boards: A Time for Reform. Washington, D.C. U.S. Department of Health and Human Services, 1998.
- Burman WJ, Reves RR, Cohn DL et al. Breaking the camel's back: multicenter clinical trials and local institutional review boards. *Ann Intern Med* 134: 152-157; 2001
- Levine RJ. The crisis in institutional review boards. *Ann Intern Med* 134: 161-163; 2001
- Phillips DF. Institutional review boards under stress: will they explode or will they change? *JAMA* 276: 1623-1625; 1996
- McDonald M. The governance of health research involving human subjects. Law Commission of Canada. Ottawa, Ontario, 2000.
- Weijer C, Shapiro S, Fuks A et al. Monitoring clinical research: an obligation unfulfilled. *CMAJ* 152(12): 1973-80; 1995
- Thorne, D. Researchers put patients at risk. *Edmonton Journal*. September 28: B3; 2002
- Bevan J. Toward the regulation of research ethics boards. *Can J Anesth*. 49(9): 900-906; 2002
- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Institutional Review Boards: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Federal Register* 43(30 November): 56186, 1978.
- Holder AR. Liability and the IRB member: the legal aspects. *IRB* 1(3): 7-8; 1979
- Robertson v. McGee, No. 01CV00G0H(M) (N.D. Okla. Filed January 29, 2001.)
- Freedman B and Glass KC. Weiss v. Solomon: a case study in institutional responsibility for clinical research. *Law Med Health Care*. 18(4): 395-403; 1990
- Lemmens T, Freedman B. Ethics review for sale? Conflicts of interest and commercial research review boards. *Milbank Q* 78(4): 547-84; 2000
- Edgar H and Rothman DJ. The institutional review board and beyond: future challenges to the ethics of human experimentation. *Milbank Q*. 73(4): 489-506; 1995
- Anderlik MR, Elster N. Lawsuits against IRBs: accountability or incongruity? *J Law Med Ethics* 29(2): 220-228; 2001
- Foubister V. Clinical trial patients sue IRB members. *Amednews.com*. February 26; 2001
- Abate T. Special report: experiments on humans. *San Francisco Chronicle*. August 5; 2002
- Stolberg SG. The biotech death of Jesse Gelsinger. *N Y Times Mag* Nov 28: 136-140, 149-150; 1999
- Smaglik P. Asthma study death spurs inquiry. *Nature* 138(5): 36; 2001
- Shamp J. Agency halts federally funded Duke research on new patients. *Herald-Sun* (Durham NC). May 12: A1; 1999
- Kolata G. U.S. suspends human research at Johns Hopkins after death. *New York Times*. July 20: A1, A18; 2001
- Weiss v. Solomon. (1989). *R.J.Q.* 731.
- Kus v. Sherman Hospital*. (1995). 268 Ill App 3d 771,644 NE2d1214,1216.
- Cassel C, Stock MC, Wood A, Zapol W, Hellman S. Report of Johns Hopkins University External Review Committee, Aug. 8. 2001.
- Protection of Human Subjects, 45 C.F.R. 56, IRB membership, § 107. (4-1-00 Edition).
- Protection of Human Subjects, 45 C.F.R. 56, IRB functions and operations, § 108. (4-1-00 Edition).
- Office of Inspector General. Institutional Review Boards: The Emergence of Independent Boards. Washington, D.C.: U.S. Department of Health and Human Services, 1998.
- Cho MK, Billings P. Conflict of interest and institutional review boards. *J Investig Med* 45(4): 154-9; 1997
- Christian MC, Goldberg JL. A central institutional review board for multi-institutional trials. *N Engl J Med* 346(18): 1405-1408; 2002
- Stair TO, Reed CR, Radeos MS et al. Variation in institutional review board responses to a standard protocol for a multicenter clinical trial. *Acad Emerg Med* 8:636-641; 2001
- Gordon B, Prentice E. Continuing Review of Research Involving Human Subjects: Approach to the Problem and Remaining Areas of Concern. *IRB* 19(2): 8-11; 1997
- Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada. Tri-council policy statement: ethical conduct for research involving humans. Ottawa: Minister of Supply and Services, 1998.
- Pilon S. When less is more - a new look at research monitoring. *BMC News and Views* 1:6; 2000
- Institute of Medicine. Responsible Research: A Systems Approach to Protecting Research Participants. The National Academies, Washington D.C., October 3, 2002.

**Marjorie Zettler** holds a B.Sc.(Hons.) in Genetics from the University of Manitoba, where she is currently in the final year of her Ph.D. in Physiology. She is a recipient of the Canadian Institutes for Health Research/Heart and Stroke Foundation of Canada Doctoral Research Award, and has been a member of the University of Manitoba's Biomedical Research Ethics Board for three years.