of repairing between 10% and 50% of defective beta-globins in cell culture.

From mouse to man

If this were transferred to human patients, the proportion of repaired RNA would be a clinically relevant, according to Sullenger. '50% would take you from being a sickle-cell person with two copies to basically being a carrier, which is normal,' he said. ' However, there is also good evidence that suggests that if you did it even at 10%, you would reduce the severity of the disease.'

Sullenger now plans to test the technology in a mouse model of sickle cell anaemia. 'Can we repair that level of RNA in those animals and observe a phenotypic effect on sickle cell disease?' he asked. 'Hopefully if that pans out, well then we'll consider clinical trials.'

The work is interesting, says Alfred Lewin, Professor of Molecular Genetics and Microbiology at the University of Florida (http://www.ufl.edu). But he is cautious about how easily the technique will transfer to an animal model, or to humans. 'This was done by transfection of non-relevant cells,' he said. 'So they have high level of expression of target and high level of expression of ribozyme, much higher than they could hope to achieve *in vivo*. [It] would be enough to encourage me to go ahead into the mouse or human cells. But just because this worked doesn't mean that that will work.'

The work was presented at the 53rd annual meeting of the *American Society of Human Genetics* 4–8 November 2003 (http://www.ashg.org).

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Ethics board review of biomedical research: improving the process

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Although researchers often find the process of research ethics board (REB) review of research frustrating, time-consuming and of limited value, REB review provides essential safeguards for research subjects and helps to ensure that research on human subjects conforms to stringent ethical and legal standards. Improvements in the process of REB review would benefit numerous stakeholders, including both research subjects and researchers.

Having participated in ethics review of biomedical research protocols at four institutions, I have some sense of the strengths and weaknesses of REBs (known in the United States as Institutional Review Boards, or IRBs) and the processes they use to assess the ethical adequacy of research protocols. Unfortunately, REBs are understudied social institutions. Although REBs play an important organizational and societal role in evaluating research projects, they are only sporadically subject to empirical study and analysis [1–3]. Raymond DeVries, a sociologist at the University of Minnesota, is one of a small cadre of researchers investigating the 'black box' of REB review of biomedical research [4]. Further qualitative and quantitative research will probably shed considerable light on the overall adequacy of REB activities. Do a handful of vocal interlocutors skew the deliberations of REB members toward particular outcomes? Are there reasonably consistent review processes across REBs? Are REBs sufficiently equipped and staffed to ensure that researchers properly address their recommendations and criticisms? Are REB members adequately trained in assessing research protocols? Do they have a clear sense of the standards that ought to be applied to the ethical assessment of research protocols? Careful study of the performance of REBs would help ascertain whether or not regulatory standards and institutions serve their function or are in need of revision in various settings.

Given the dearth of studies that assess the functioning of REBs, I propose to draw upon my practical experience as a member of four of these boards and offer several suggestions concerning how the process of ethics review of biomedical research might be improved. My experience is limited to hospital and university-based REBs in Canada and I have never served as a member of commercial, for-profit REBs. Consequently, I have no personal insight into how effectively 'commercial' boards function. Research by University of Toronto law professor Trudo Lemmens

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and the late McGill philosopher Benjamin Freedman suggested that commercial REBs have serious limitations [5]. Christine Arakelian, in a recent issue of *Drug Discovery Today*, addresses the importance of facing ethical issues within the corporate context [6].

Based upon my experience, I offer several criticisms and practical recommendations. My suggestions do not constitute a radical critique of the process of REB review. Instead, I offer recommendations that are intended to fine-tune the process of ethics review. If we are facing a 'crisis' in the review of research protocols, I suspect the most significant challenges are related to the sheer volume of research proposals requiring review rather than the integrity or intentions of members of REBs [7].

Use both scientific review committees and REBs

At my home institution, the head of the Office of Research Ethics at McGill University Health Centre is currently in the process of creating scientific review boards that will assess the scientific validity of research protocols before studies are forwarded to the REB. Given the time constraints facing most REBs, coupled with the growing number of studies currently submitted to most boards, I support this development.

Of course, scientific review can never be altogether distinguished from ethics review. There are integral connections between scientific research methods and the ethical adequacy of a study [8]. I am not attempting to make the case for a rigid demarcation between scientific review and ethical analysis. However, before reaching a REB, the research protocol should pass peer-review by a scientific review board capable of assessing the scientific merits of a study. If a research protocol does not display scientific validity, it should never reach the REB. Even if a research protocol meets the standards of a scientific review board, careful review by the ethics board might raise questions about the research methods and study design.

Some might argue that a separate scientific review committee should not be established, or that scientific review and ethics review should occur concurrently by separate institutional bodies. These options are problematic for several reasons. For example, conducting ethics review and scientific review in the same session, or running concurrent reviews, would make sense if the vast majority of research protocols were based upon thorough literature reviews, used the most suitable research methods and displayed a sophisticated understanding of statistical methods. However, in my experience, many research projects submitted to REBs contain inadequate discussion of the relevant scientific literature, display a tenuous grasp of whether or not particular research methods are suited to the question under investigation, and reveal limited insight into the process of statistical analysis of research findings. Some studies provide no literature review and leave committee members unable to assess how the proposed study fits within a larger research program. Other studies note that data will be analyzed by a statistician, but do not state how the statistician will interpret the data.

Some individuals might insist that studies submitted to REBs display high levels of scientific competence. However, proponents of conjoined or concurrent ethical and scientific review need to recognize that REBs receive protocols from individuals with varying degrees of competency, training and experience in conducting research. Some protocols are submitted by highly competent researchers and the studies have already undergone extensive peer-review by demanding, critical funding agencies. Other studies are submitted by students, trainees, junior researchers and individuals who only sporadically participate in the design and implementation of scientific research. Consequently, the quality of scientific competency displayed in research protocols submitted to REBs is quite variable. To make the best use of REBs, research protocols should undergo scientific review before they are submitted for ethical review. Although particular research methods might raise ethical issues that need to be addressed at the REB meeting, REBs should not be expected to expend time and labor on explaining basic scientific concepts to inadequately trained or insufficiently prepared researchers.

Furthermore, the reliance upon REBs to conduct a thorough scientific and ethical analysis neglects the limitations of these boards. REBs are sometimes ill equipped to assess often highly specialized research methods even though they include scientists as board members and solicit commentary from scientific reviewers. They rarely have the resources or personnel to extensively review the scientific literature that serves as the backdrop to submitted protocols. Many REB members are not trained in the specific scientific disciplines required to have a solid understanding of the scientific validity of the study. Most bioethicists, community representatives and lawyers, for example, cannot be expected to calculate the appropriate sample size for a study or know when a study is underpowered [9]. A scientific review board staffed with the appropriate specialists would be much better equipped to critically assess scientific aspects of the research protocol. If a study suffers from the flaw of inadequate scientific design or ill-justified research methods, it should be rejected on those grounds. It should not even reach the stage of REB review. If a study passes scientific review and reaches ethical review, members of the REB might still have appropriate questions about the scientific design of the study. Such questions should remain part of the conversation when the REB meets. They might form the basis for a decision to return the protocol to the

scientific review committee. However, it is not a good use of the time of REB members to address basic questions concerning the scientific merits of the study. Members of the ethics board should generally be able to assume that a research protocol meets exacting scientific standards, enabling them to focus their attention on other matters.

In my experience, the quality of scientific analysis of research protocols is closely connected to the membership of the REB, the quality of internal and external scientific reviewers invited to assess the protocol, and the expertise of the board chair. Although the Office for Human Research Protections in the United States insists that IRBs must provide both scientific review and ethical analysis, the thorough investigation of both the scientific validity of the study and the ethical adequacy of research protocols can be a time consuming, laborious and specialized task. Because IRBs and REBs are burdened with increasing number of research protocols, it makes sense to insist that studies must undergo scientific peer review before being considered for ethics review.

Ensure consistency of review by REBs

REBs often take different approaches to the process of reviewing research protocols. At present, I am a member of an ethics board that meets every week and generally reviews two protocols over a two to two and a half-hour period. In the past, I have served as a member of REBs that have reviewed 12–15 research protocols over three hours. I am familiar with other boards that review even greater numbers of protocols within a two to three hour period [10]. Research protocols differ in their complexity, potential risks to research subjects and quality of preparation. There is little point in insisting that all studies need to be reviewed for a minimum period of time. Some research protocols deserve extended analysis. Other protocols can be reviewed with a minimum of deliberation. However, there seems to be little consistency in the amount of time REBs dedicate to protocol review, even when one takes into account the existence of credible reasons for variations in the review process. Some boards invite principal investigators and co-investigators as well as internal and external scientific reviewers to committee meetings and debate at length the study protocol, information sheets and consent forms. Other boards provide a more hurried examination; often overwhelmed with studies, they lack the resources to review most studies in a more than cursory fashion. Many REB chairs sensibly deal with the barrage of protocols through triage; they give extended consideration to the more complex or contentious protocols and reserve much less time for full ethical review of more straightforward protocols.

Considerable variation in the quality of REB review has several unfortunate outcomes. Researchers can find themselves confronted with conflicting demands from various ethics boards [11,12]. Some boards insist on substantial revisions to the study. Other boards request minor revisions or are willing to grant immediate approval for the study to proceed. Variations in the quality of review can result in conflicting messages being sent to researchers. Greater consistency in the quality of review might lead to more uniform advice being given to study investigators.

Although the phenomenon is understudied, variations in the quality of review might also lead to the 'shopping' of protocols. Anecdotal evidence suggests the possibility that some boards have a reputation for stringent standards and lengthy periods of protocol revision whereas other boards are renowned for swiftly approving most studies. Inconsistency in the quality of protocol review might foster a climate in which some institutions become well known for a more casual approach to protocol review whereas other institutions become known as sites to avoid because of the stringent demands they impose on researchers.

Further research into the process of REB review might reveal how effectively different REBs assess research protocols. The discovery of significant variations in the quality of REB review would raise serious concerns about the adequacy of existing institutional safeguards in the conduct of scientific research. Better training of REB members, greater institutional support for REBs, increased standardization of REB review and the creation of more specialized REB committees in major research centers all might serve to ensure greater consistency in the ethical review of research projects.

Make better use of institutionally approved boilerplate text

Over time, most REBs develop particular standards that they want research protocols, information sheets and consent forms to incorporate. For example, many ethics boards insist that information sheets be written in the second person and urge that only the consent sheet contains the first person form of reference. REBs also insist that protocols should list a contact person in case research subjects wish to register concerns or complaints about a particular study. If a particular person is designated to respond to questions or complaints, this individual should be clearly identified to researchers before they submit their protocols to the REB. Boilerplate text – standard statements that need to be included in all documents provided to research subjects – and institutionalized standards should be conveyed to researchers before investigators submit their research protocols. A great deal of time that is spent discussing protocols at REB meetings could be saved if investigators revised their protocols to conform to existing standards and

used boilerplate text already approved by the REB.

Obviously, institutional boilerplate text needs to be used in a judicious manner. It is not possible to simply cut and paste text into documents. Amendments need to be made to reflect the particular features of specific studies. However, boilerplate text and a list of standard guidelines could improve the quality of research protocols and reduce the amount of time REB members spend endlessly correcting the same shortcomings in study after study. Furthermore, a clear, straightforward description of REB standards, coupled with the provision of sample text, would facilitate the task of preparing protocols for ethics board review.

The need for better training in research ethics

At most institutions, REB members, internal and external scientific reviewers and researchers are never examined on their knowledge of the ethical and legal standards governing research in their institution or country. To ensure that researchers and ethics board members have a firm grasp of ethical and legal standards governing research protocols, educational initiatives and formal assessment processes should be established for REB members and researchers [13]. REB members should have to demonstrate familiarity with guidelines governing research before they are permitted to review research protocols. Researchers should be expected to display familiarity with legal and ethical standards that govern the assessment of biomedical research before they are allowed to submit research protocols to REBs.

To ensure that researchers and REB members have adequate training in research ethics, appropriate educational initiatives should be introduced at hospitals, universities and other research centers. The Human Subject Assurance Training Module prepared by the Office for Human Research Protections in the US provides one model of an educational initiative that could be provided in conjunction with a formal assessment [14].

Many institutions provide ethics review of research protocols but offer few educational sessions that address the legal, ethical and regulatory standards that govern biomedical research. Researchers who are uninformed about the standards to which they will be held commonly spend a great deal of time revising research protocols and gradually become familiar with the standards their protocols must meet. There are more effective methods of learning how to meet existing ethical and legal standards. Regularly scheduled educational events might greatly assist them with the process of understanding how protocols, information sheets and consent forms need to be prepared to meet REB review. Similarly, ethics board members would benefit from regular exposure to educational events. They have an obligation to be fully informed of the regulatory standards that they are expected to apply to the critical review of research protocols. They need to ensure that they meet national or international standards of protocol review and do not gradually come to impose idiosyncratic expectations on researchers and their research projects.

Investing in institutional educational initiatives might greatly increase the quality of protocols submitted to REBs. Better-prepared protocols might reduce the amount of time and effort required to revise research protocols before their final approval or rejection by the REB. Furthermore, well-trained ethics board members might better understand the reasons behind the ethical concepts, legal standards and regulatory frameworks that guide their analysis of particular protocols. The development of formal assessment mechanisms in settings where such evaluations are not yet used would help to determine whether or not educational initiatives were fulfilling their intended purposes.

Improve the quality of multi-site review

Many contemporary research projects use multiple sites. Sometimes these sites are found within one city or region. In other cases, sites are located across an entire country or at multiple locations around the world. Multi-site REB review is a complex matter. Studies conducted in numerous countries must often meet different national standards. Although there are many research ethics norms and concepts found across national borders, there are also local variations in regulatory standards. Greater consistency in research ethics review across national boundaries will probably require the development of transnational institutions. Perhaps biomedical researchers require institutions that are roughly equivalent to the World Trade Organization. Although the Helsinki Declaration provides an example of a transnational standard for biomedical research, social institutions capable of better regulating transnational biomedical research still need to be developed. Although we are at the early stages of developing transnational institutions for the regulation of biomedical research, a great deal could immediately be done to improve the quality and consistency of ethics review within nations. At present, researchers are often faced with multiple and sometimes even conflicting demands when they submit their research protocols to multiple REBs [15–20]. Variations in ethical review will never be completely eliminated – members of REBs are expected to exercise discretion when providing research ethics review. The exercise of judgment will sometimes lead to variations in decision making. Therefore, It should come as no surprise that REBs sometimes reach different conclusions and offer different recommendations when reviewing protocols. However, steps need to be

taken to ensure that researchers are given reasonably consistent recommendations when asked to revise protocols, information sheets and consent forms. Researchers should not be subjected to a barrage of mutually inconsistent demands and then given no appeal mechanism to adjudicate these differing expectations.

How multi-site REB review might be improved is a difficult question to answer. One approach might include having a single REB act as the primary reviewer. This board would have the responsibility of reviewing the protocol before its distribution to other institutions, providing recommendations and making those recommendations and the reasons behind them available to other ethics boards. Other REBs would then review the protocol, recommendations and revised research project. This exercise would not eliminate further revision; different REBs might request additional changes even though one board had already approved the proposal. However, careful review by one board followed by the distribution of the findings of that board to all subsequent reviewers might improve the overall quality of review and reduce the amount of time required for shepherding a protocol through multiple institutions.

At present, REBs tend to be fiercely independent. Boards are reluctant to approve a protocol merely on the basis that some other board has approved it. This independent-minded attitude has its advantages – it helps to ensure that research protocols are subjected to careful review and meet both national and institutional standards. However, it can result in a process that imposes unmanageable and contradictory demands on researchers. I am not attempting to make the case for 'softer' research ethics review. I am suggesting that better communication among REBs might reduce the number of occasions contradictory advice is offered to researchers.

Conclusions

My recommendations concerning the improvement of the research ethics review process are provided on the basis of one person's experience as a member of several REBs in Canada. Scholars working in the area of research ethics tend to focus their work upon specific texts such as the Belmont Report and Helsinki Declaration, and particular concepts such as clinical equipoise, informed consent and risk/benefit analysis [21]. Although textual analysis and conceptual work is important, additional research needs to investigate the process of REB review. At present, regulatory standards and guidelines are open to critical scrutiny. However, REBs tend to be 'black boxes'; little is known about how they function, how effectively they deliberate and whether reforms might improve the quality of review. It is not my intention to argue that 'no one is watching the watchers', and we need to be profoundly troubled by the current gatekeeper function of REB review. I am more inclined to be agnostic about the current quality of REB review – we know little about how well these boards function. Further qualitative and quantitative research investigating REBs and the important social function they fulfill might provide valuable insights into how the ethical review of biomedical research protocols could be improved. Such findings would presumably be of value not just to research subjects, medical centers, universities and REBs, but also to researchers seeking fair, reasonable and effective mechanisms of ethics review.

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