ETHICAL issues are assuming prominence in the conduct and interpretation of research studies. Recent controversies about the conduct of research, both in the developing and industrialized world, initiatives to update overarching codes of conduct for research, and discussions about what makes research ethical, all indicate the importance of considering ethical dimensions in the production and use of research knowledge in practice.

There have been few systematic efforts to help consumers of research analyze or critique its ethical dimensions. The contribution of the EBMWG has been paramount in the modern assessment of the medical literature, but ethics dimensions have been lacking in these guidelines and similarly have been inadequately or incompletely addressed in published articles on therapy.

Why is this an important issue? Considerable effort has been devoted to creating a uniform standard for the conduct and reporting of RCTs. The CONSORT (Consolidated Standards of Reporting Trials) guidelines are now the standard for reporting RCTs but explicitly abjure consideration of ethical issues. This position, unfortunately, separates the ethical and scientific dimensions of medical research. The assumption that all peer-reviewed published research meets minimal ethical standards is questionable.

For example, although attention to the ethical dimensions of RCTs has improved, it was recently reported that in 9% of clinical trials published in major medical journals there was a failure to mention both informed consent and IRB approval. In this paper, we propose a framework that will aid in the assessment of the bioethical integrity of a clinical trial.

The Framework

The bioethical dimensions that we consider for analysis of a published study are listed in the Appendix. The answers to these questions can easily be found in some published literature, but are not uniformly required. Some elements may require expert judgment, reflection, and deliberation to arrive at conclusions. For each question we provide a brief analysis, including mention of the relevant ethical principles and, where relevant, illustrative examples and citations of relevant papers. The questions in the framework are grouped broadly under the following four categories: 1) independent review and informed consent; 2) fair subject selection and adequate harm/benefit ratio; 3) outcome measures and sample size; and 4) conflict of interest and publication ethics.

Independent Review and Informed Consent

Was IRB Approval Obtained for the Study? The approval of an independent review body is an essential element for...
research integrity. Although there is demonstrated variability among IRBs, they serve an important role in appraisal. Unlike scientific review, which focuses on the legitimacy of the research question and the appropriateness of the scientific methods proposed to answer the question, ethics review is concerned primarily with the protection of the research subjects and the adequacy of consent procedures. The provision of an ethical review is a necessary but not sufficient condition for ethicality of research. Increasingly, IRBs are burdened by an expanding set of duties and roles, and because they are largely voluntary bodies, often lack the time and expertise to do justice to all elements of a study protocol.

Was Informed Consent Obtained From Each Patient? As quoted by Vreatch, the Nuremberg Code famously declared that “... voluntary consent of the human subject is absolutely essential.” Informed consent is arguably the most important ethical dimension of research on human volunteers. The unfortunate history of research performed without consent, and the subsequent harm to such participants, bears out the importance of this principle. Medical journals are increasingly insisting on explicit inclusion of informed consent in manuscript submissions. The provision of informed consent acknowledges the importance of the ethical principle of autonomy, which regards humans as capable of self-determination and possessed of inherent value. It is believed by many in the scientific community that fully informed consent can never be obtained even in the best of circumstances in any clinical or research setting. Some researchers believe that their patients receive too much information about clinical trials, but studies of patients’ perceptions do not bear out these concerns. Consent for surgical procedures or for participation in clinical studies is a complex and daunting task for patients and is probably most dependent on the patients’ trust in their physicians. Additionally, the existence of unforeseen risks in new therapies often cannot be fully anticipated and included in the consent process. An example of an unforeseen complication was the occurrence of two cases of devastating stroke from middle cerebral artery occlusion in a randomized study of brachytherapy for glioblastoma.

Fair Subject Selection and Adequate Harm/Benefit Ratio

Were the Eligibility Criteria for Entry Into the Study Fair and Appropriate? Inclusion and exclusion criteria for clinical trials are often made stringent to increase the internal validity of the study. This decision may affect its external validity or applicability in practice. For example, in trials of treatment modalities for malignant brain tumors, elderly patients are often excluded because they have been shown to benefit so little or even to be harmed by aggressive intervention, so that it is not fair to them or to the scientific process to include them. Tacit in such decisions are normative evaluations that are used to ensure the equitable entry, or potential eligibility of research volunteers. Critical questions concerning who is eligible for the trial and who is bearing its potential risks and benefits are important. This is particularly the case in international research and will increasingly be the case in genomic research, particularly stem cell studies for which vulnerable populations may be chosen. Alternately, many disadvantaged populations are often not included in research studies. Special care must be taken not to engage in research that can exploit vulnerabilities. This question illustrates the principles of fairness and nonmaleficence.

Were Patients Who Were Ineligible for the Study Disadvantaged Either Physically or Psychologically? This question speaks to the issue of equity in research on a large scale as well as in individual patients. It is important that those excluded from studies not be denied access to research evidence that may have important implications in the management of their illness. In research involving vulnerable populations or diseases with uniformly poor prognoses, there may be considerable desire on the part of prospective participants to be enrolled in experimental therapy; there is therefore the potential for psychological harm to those who fail to meet eligibility criteria. In this case it is the researcher’s moral responsibility to explain adequately and to educate such patients, in simple and understandable language, rather than to ignore their concerns, and to try to make them as comfortable with the situation as is humanly possible.

Were Patients Who Entered the Study Disadvantaged? Were complications acceptable in the experimental arm? Were patients deprived of a longer or better quality of survival by being randomized to either arm? These questions speak in part to the role of independent oversight and ongoing monitoring of the study. Preordained rules for stopping trials should be constructed, articulated, and followed so that patients are protected from harm. Those performing the trial should have an independent body assessing whether participants in the experimental arm or the control arm are bearing disproportionate harms or failing to realize meaningful benefits. This role is variably filled in modern research, and the existence of a safety and monitoring committee is often not reported unless the study is stopped prematurely. The provision of independent monitoring reflects concern for accountability and respect for persons. It is also important to note that there is some evidence that volunteers involved in prospective research actually regard participation as a benefit in itself.

How Were Patients Who Demanded the Experimental Therapy Off-Study Handled and How Were Patients Treated When They Expressed a Strong Desire to Be Randomized to the Experimental Arm but Were Randomized to the Standard Therapy Arm? How patients who request the experimental therapy should be treated is an important and difficult question. Because medical research is now a public enterprise and because patient advocacy groups have expanded their agenda to include influencing the conduct of research, medical research no longer exists in a void. We believe it is fundamentally unethical to provide the experimental therapy on demand in the context of a randomized study; unfair to the other patients who have entered the study and to the scientific process, which will have inherent bias introduced. In this situation, however, researchers have a moral obligation to counsel such patients how and where to obtain the therapy off-trial. For example, in a randomized brachytherapy study, patients who demanded the treatment off-study were referred to a center that was providing it outside a clinical protocol setting. One innovation that has been developed is the open-label trial, because it became apparent in many antiretroviral trials that participants had successfully
Framework for bioethical assessment of an article on therapy
determined the difference between interventional drug and
placebo and were sharing the active drug with friends who
were not eligible or not enrolled in the trial. Such contamina-
tion undermines the scientific integrity of the research.
Patients should be aware that they are free to leave the study
at any time without compromising their care. There is evidence
that many patients’ expectations of treatment are un-
malfially important clinical differences from patients’ perspec-

tives.34,57,70 There is also research evidence demonstrating

to statistical grounds. There is emerging literature on mini-

Traditionally, power calculations have been derived on
outcome is distinct from a statistically significant outcome.
Simply a Statistically Significant One?

Was a Clinically Meaningful Effect Sought as Opposed to

WAS THE STUDY PLACEBO CONTROLLED? Is the Placebo Ethically
Acceptable? The issue of placebo controls is a controversi-
one. When an effective therapy exists for the condition be-
ing studied, however, an argument must be made justifying
the use of a placebo as opposed to an active control. Sample
size, estimates of absolute treatment effectiveness, and cost
considerations should not be considered sufficient justi-

Was QOL Measured, and if so, was it Worse for Patients
Receiving the Experimental Therapy? Health-related QOL is
an important dimension of any new or innovative therapy,
perhaps even more important than survival.5,64 It is a small
consolation to our patients if a therapy is reported to have
benefits, but all relevant dimensions of a person’s experi-
ence related to that therapy are not accounted for, or worse,
are diminished. If the QOL is significantly better for pa-
tients receiving the intervention, even without an improve-

Outcome Measures and Sample Size

Was a Clinically Meaningful Effect Sought as Opposed to
Simply a Statistically Significant One? A clinically relevant
outcome is distinct from a statistically significant outcome.
Traditionally, power calculations have been derived on
statistical grounds. There is emerging literature on mini-

Specifically, Was There any Conflict of Interest for the
Study Investigators? We do not believe that it is ethically unacceptable for
principal investigators also to act as the primary caregiv-
sers for patients enrolled in clinical studies. In fact it is desir-
able, because without the intellectual interest and invest-
ment of clinician–researchers working on a certain disease,
such studies would not be generated and executed. The added
cost, cumbersomeness, and impracticality of having one
team identify and recruit patients and another team perform
the clinical interventions is an unrealistic and unworkable
process. If this standard were enforced, it would result in a
marked decline in RCTs, a development that would be un-
derstandable in its own right because new medical evidence to
help health care providers give the best care to their patients
would be blocked by practically insurmountable barriers.
The presence of a multidisciplinary team, the rigor of
modern IRBs, the presence of checks along the way, and the
basic virtue and trustworthiness of dedicated professionals,
all mitigate the concerns that the principles of respect for
persons, beneficence, and fairness will not be upheld when
clinicians and researchers are one and the same. We believe
that it is a cynical view to assume that doctors dedicated
enough to study innovative treatments in a scientific way
are any less dedicated to the goal of providing their indi-

Conflict of Interest and Publication Ethics

Is it Ethical for the Researcher(s) and the Care Provider(s) to be One and the Same Doctor(s) or Team? It can be argued
that when clinical researchers conduct a study and act as the
primary caregivers for patients entered in the study, there
exists a conflict of interest and an unethical situation. One
possible conflict of interest is the perceived potential for ca-

increasingly, concerns have been expressed about academic freedom and there have been notable recent exam-
ple cases in which industrial and academic partners have

J. Neurosurg. / Volume 98 / March, 2003
failed to negotiate appropriate security for the publication of data. Because the interests of industry may differ from the values of academic research and the needs of patients, such relationships should, at minimum, be made transparent. All authors should declare potential conflicts of interest and these should appear as part of the manuscript.

Do all Authors have a Justifiable Role as Coauthor? Contributionship and guarantor statements are required now by many journals. This is an additional sign of the integrity of the work. It is an important dimension because scientific fraud in the form of fabricated data, spurious or gift authorship, and duplicate publication continue to be problems in the biomedical sciences.

Discussion

The EBMWG criteria are very useful for providing a framework for the rigorous scientific assessment of an article on therapy. They provide guidelines to assess the issues of validity and accuracy of results and whether the results are meaningful to other clinicians treating patients who have the disease being studied. Lacking within this framework are broad or deep questions addressing ethical issues pertaining to the conduct of the published clinical research. The main ethical mandate of the EBMWG guidelines is to establish that the science is of high quality, because poor-quality research is unethical from the outset. If a study cannot answer the clinical question posed, it represents a waste of human and fiscal resources and an abuse of the trust patients have given to the clinician–researcher. Scientific quality, however, does not negate concerns about ethical appropriateness.

Emanuel, et al., have proposed a framework “to help guide in the ethical development and evaluation of clinical studies by investigators, IRB members, funders, and others.” They elucidate seven requirements that they believe are necessary and sufficient to make clinical research ethical: 1) potential value; 2) scientific validity; 3) fair volunteer selection; 4) favorable risk/benefit ratio; 5) independent review; 6) informed consent; and 7) respect for enrolled volunteers. Our proposed framework overlaps with this approach to a certain extent. The Emanuel framework may not be sufficient, however, because it fails to address important issues such as potential conflicts of interest, authorship and contributorship, and clinical relevance as distinct from statistical significance.

Providing information suitable to answer such questions as we have posed would not impose significant additional burdens on editors. Indeed, it is increasingly standard practice for journals to have conflict of interest and contributorship statements accompanying published studies. Also, as more and more scientific publications use the World Wide Web, it is possible to provide links to the study protocol, consent forms, and other documentation that is currently not easily accessible. Indeed, one online journal, BIOMED Central, provides a complete prepublication history, including peer review comments. Therefore, access to more documentation is feasible.

Conclusions

Clinical research is performed with the best interests of patients in mind. Many clinicians, however, are insufficiently educated about the scientific method and a significant number of the treatment studies published in major medical journals are poorly designed and/or have been reported suboptimally. Well-designed RCTs are invaluable to guide the best management of patients. Rigorous ethical as well as scientific integrity must be ensured in all studies, and if the standards of the major journals are elevated by compulsory fulfillment of scientific and ethical frameworks on the part of contributing authors, the clinical research performed will parallel these standards. We have presented an ethical framework that can be used to assess an article on therapy, but we do not presume to suggest that it is definitive or should be considered a standard. We do believe that it is a step in the right direction and a stimulus to other investigators to expand on and/or improve this framework so that ultimately the ethical components of clinical research on human volunteers will parallel the scientific scrutiny to which these studies are now being exposed.

Appendix

Framework for bioethical assessment of an article on therapy

Independent review and informed consent
1. Was IRB approval obtained for the study?
2. Was informed consent obtained from each patient?
Fair subject selection and adequate harm/benefit ratio
3. Were the eligibility criteria for entry into the study fair and appropriate?
4. Were patients who were ineligible for the study disadvantaged (either physically or psychologically)?
5. Were patients who entered the study disadvantaged?
   a. Were complications acceptable in the experimental arm?
   b. Were patients deprived of a longer or better quality of survival by being randomized to either arm?
6. How were patients who demanded the experimental therapy off-study handled and how were patients treated when they expressed a strong desire to be randomized to the experimental arm but were randomized to the standard therapy arm?
7. Was the study placebo controlled? Is the placebo ethically acceptable?
8. Was QOL measured, and if so, was it worse for patients receiving the experimental therapy?
Outcome measures and sample size
9. Was a clinically meaningful effect sought as opposed to simply a statistically significant one?
10. What are the ethical implications of the study being null?
Conflict of interest and publication ethics
11. Is it ethical for the researcher(s) and the care provider(s) to be one and the same doctor(s) or team?
12. Specifically, was there any conflict of interest for the study investigator(s)?
13. Do all the authors have a justifiable role as coauthor?

References

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