ORI

Introduction to the Responsible Conduct of Research

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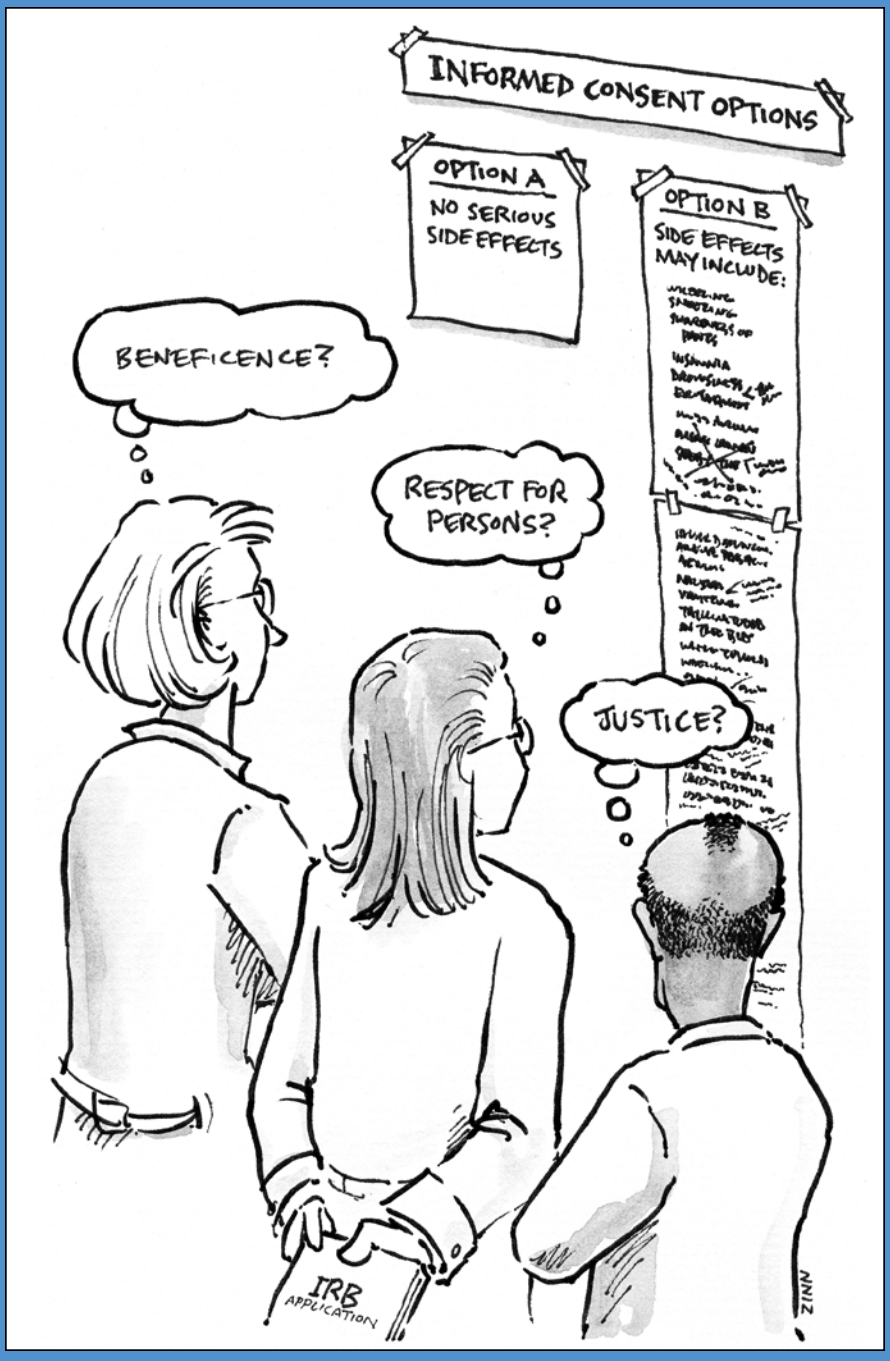
illustrations by David Zinn



Designing a responsible informed consent form

Chapter 3. The Protection of Human Subjects

The use of human subjects in research benefits society in many ways, from contributing to the development of new drugs and medical procedures to understanding how we think and act. It also can and has imposed unacceptable risks on research subjects. To help ensure that the risks do not outweigh the benefits, human subjects research is carefully regulated by society.

Case Study

Two weeks into the new semester, the professor in Mary's course on family health gives the class a special assignment that was not on the course syllabus. Over the next week, everyone in the class is to talk with three classmates who are not in the course about the way their families deal with medical emergencies and chronic illness. Next week they should come to class prepared to report on their interviews. The Professor warns them, however, that in talking about their conversations they should not mention any names to protect the privacy of their classmates.

The assignment makes Mary uneasy. In her basic psychology course last semester she learned about some of the rules pertaining to the use of human subjects in research. However, when she raises her concerns with her professor, he assures her that her informal conversations with classmates are not research and therefore not subject to regulation. Moreover, since she will not be mentioning any names, there are no privacy issues to worry about.

Should Mary be content with these assurances and conduct the interviews?

If she still has concerns, where should she turn for advice?

Did the professor act properly in giving this assignment to the class?

Investigators who conduct research involving humans that is subject to regulation must comply with all relevant Federal regulations as well as any applicable state and local laws, regulations, and policies related to the protection of human subjects. They are also expected to follow other relevant codes that have been formulated by professional groups. To meet these responsibilities requires, among other things:

- ✓ **knowing what research is subject to regulation,**
- ✓ **understanding and following the rules for project approval,**

- ✓ getting appropriate training, and
- ✓ accepting continuing responsibility for compliance through all stages of a project.

If you expect to use or study living humans in your research, no matter how harmless that use may seem, and receive Federal funding, familiarize yourself with your responsibilities and check with someone in a position of authority before making any contacts or undertaking any work.

3a. Federal regulations

Society protects the welfare of individuals in many ways, but it did not specifically address the issue of the welfare of research subjects until after World War II. Following the War, widespread concerns about atrocities committed during the War in the name of research led to the formulation of a code for human subjects research known as the Nuremberg Code (1947). Although not binding on researchers, the Nuremberg Code and the later Declaration of Helsinki (1964; latest revision and clarification, 2002) provided the first explicit international guidelines for the ethical treatment of human subjects in research.

The Nuremberg Code and Declaration of Helsinki did not put an end to unethical human subjects research. During the Cold War, U.S. researchers tested the effects of radiation on hospital patients, children, and soldiers without obtaining informed consent or permission to do so. Through the 1950's and 1960's, well after antibiotics effective for the treatment of syphilis were discovered, scores of African-American males in a long-term syphilis study (conducted by the U.S. Public Health Service in Tuskegee, Alabama) were not offered treatment with the new drugs so that researchers could continue to track the course of the disease. These and other questionable practices raised serious public concern and led eventually to government regulation.

Excerpts, Nuremberg Code (1947)

1. The voluntary consent of the human subject is absolutely essential.
2. The experiment should be such as to yield fruitful results for the good of society.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

http://www.hhs.gov/ohrp/references/nurcode.htm

To prevent these and similar abuses from continuing, in 1974 Congress required the Department of Health, Education and Welfare (HEW, currently Health and Human Services—HHS) to clarify its rules for the use of human subjects in research. With this mandate in hand, HEW codified its procedures under Title 45 of the Code of Federal Regulations, Part 46 (45 CFR 46). (At roughly the same time, the FDA codified its rules for human subjects research under 21 CFR 50 and 56.)

Congress also called in 1974 for the creation of a National Commission for the Protection of Human Subjects of

Biomedical and Behavioral Research. During the 4 years it met, the Commission issued a number of reports on the protection of research subjects and recommended principles for judging the ethics of human subjects research (discussed below).

In 1991 most Federal departments and agencies that conduct or support human subjects research adopted a common set of regulations for the protection of human subjects referred to as the "Common Rule" (45 CFR 46, Subpart A). Additional requirements on three sensitive research areas are also included in 45 CFR 46:

- ✓ **Subpart B – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research.**
- ✓ **Subpart C – Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects.**
- ✓ **Subpart D – Additional Protections for Children Involved as Subjects in Research.**

Together, 45 CFR 46, Subparts A-D, provide a comprehensive articulation of society's expectations for the responsible use of human subjects in research.

Authority for enforcing the HHS regulations for the protection of human subjects who participate in research conducted or supported by HHS now rests with the Office for Human Research Protections (OHRP) in the Office of Public Health and Science (OPHS). If you have specific questions about the Federal requirements for the protection of human subjects, contact your local institutional officials, OHRP (for research conducted or supported by HHS), or appropriate officials at the department or agency conducting or supporting the research.

3b. Definitions

Researchers are responsible for obtaining appropriate approval before conducting research involving human subjects. The need for approval rests on three seemingly obvious but not always easy-to-interpret considerations: 1) whether the work qualifies as research, 2) whether it involves human subjects, and 3) whether it is exempt. All three considerations are discussed in the Common Rule and guide decisionmaking about the use of human subjects in research. The authority to make decisions about the need for approval rests with the Institutional Review Board (IRB, discussed below) or other appropriate institutional officials.

Research. The Common Rule defines research as "systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" (§ 46.102(d), see box, next page, for full definition). This means that a project or study is research if it:

- ✓ **is conducted with the intention of drawing conclusions that have some general applicability and**
- ✓ **uses a commonly accepted scientific method.**

The random collection of information about individuals that has no general applicability is not research. Scientific investigation that leads to generalizable knowledge is.

Human subjects. Human subjects are "living individual(s) about whom an investigator conducting research obtains: (1) data through intervention or interaction with the individual; or (2) identifiable private information" (§ 46.102(f), see box, next page, for full definition). Humans are considered subjects and covered by Federal regulations if the researcher:

- ✓ **interacts or intervenes directly with them, or**
- ✓ **collects identifiable private information.**

45 CFR 46. 102
Protection of Human Subjects – Definitions

(d) **Research** means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

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(f) **Human subject** means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) data through intervention or interaction with the individual, or

(2) identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

If one of these two conditions applies and if the project or study qualifies as research, then institutional approval is needed before any work is undertaken.

Exempt research. Some studies that involve humans may be exempt from the requirements in the Federal regulations. Studies that fall into the following categories could qualify for exemptions, including:

- ✓ **research conducted in established or commonly accepted educational settings;**
- ✓ **research involving the use of educational tests;**

- ✓ **research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if unidentifiable or publicly available;**
- ✓ **research and demonstration projects which are conducted by or subject to the approval of department or agency heads; or**
- ✓ **taste and food quality evaluation and consumer acceptance studies.**

It is critically important to note, however, that decisions about whether studies are exempt from the requirements of the Common Rule must be made by an IRB or an appropriate institutional official and not by the investigator.

3c. IRB membership and deliberations

Federally funded research that uses human subjects must be reviewed and approved by an independent committee called an Institutional Review Board or IRB. The IRB provides an opportunity and place for individuals with different backgrounds to discuss and make judgments about the acceptability of projects, based on criteria set out in the Common Rule.

Under the Common Rule, IRBs must have at least five members and include at least one scientist, one non-scientist, and "one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution" (§ 46.107(d)). IRBs have authority to approve, require modification of (in order to secure approval), and disapprove all research activities covered by the Common Rule. They also are responsible for conducting continuing review of research at least once per year and for ensuring that proposed changes in approved research are not initiated

without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the subject.

IRBs weigh many factors before approving proposals. Their main concern is to determine whether (§ 46.111(a)):

- ✓ risks to subjects are minimized;
- ✓ risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result;
- ✓ selection of subjects is equitable;
- ✓ informed consent will be sought from each prospective subject or the subject's legally authorized representative;
- ✓ informed consent will be appropriately documented;
- ✓ when appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects; and
- ✓ when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

Researchers should consider each of these issues before completing their research plan and submitting it to an IRB for approval.

Making decisions about whether human subjects will be treated fairly and appropriately or given adequate information requires judgments about right and wrong (moral judgments). In the 1979 Belmont Report, the National Commission recommended three principles for making these judgments:

- ✓ **respect for persons** and their right to make decisions for and about themselves without undue influence or coercion from someone else (the researcher in most cases);
- ✓ **beneficence** or the obligation to maximize benefits and reduce risks to the subject; and

The Belmont Report (1979)
Ethical Principles and Guidelines for the Protection of Human Subjects of Research

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, thereby creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles.

http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm

✓ **justice** or the obligation to distribute benefits and risks equally without prejudice to particular individuals or groups, such as the mentally disadvantaged or members of a particular race or gender.

While this list does not exhaust the principles that can be used for judging the ethics of human subjects research, it has nonetheless been accepted as a common standard for most IRB deliberations. Knowing this, researchers should spend time considering whether their work does provide adequate respect for persons, appropriately balances risks and benefits, and is just.

3d. Training

To help assure that researchers understand their responsibilities to research subjects, the National Institutes of Health (NIH) currently requires

> …education on the protection of human research participants for all investigators submitting NIH applications for grants or proposals for contracts or receiving new or non-competing awards for research involving human subjects. (http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html)

Many institutions, including NIH, provide this training through special Web-based programs that summarize essential information and in some cases require some evidence of mastery. A description of the education program and who was trained must be included in applications for grants and contracts before they will be considered.

3e. Continuing responsibility

Once a project has been approved by an IRB, researchers must adhere to the approved protocol and follow any additional IRB instructions. This, unfortunately, is where a few researchers and institutions have occasionally run into problems and temporarily had their "assurance" (FWA - Federalwide Assurance) suspended. The continuing responsibilities that researchers have include:

✓ **enrolling only those subjects that meet IRB approved inclusion and exclusion criteria,**

Federalwide Assurance (FWA)

The Federal Policy (Common Rule) for the protection of human subjects at Section 103(a) requires that each institution "engaged" in Federally supported human subject research file an "Assurance" of protection for human subjects. The Assurance formalizes the institution's commitment to protect human subjects. The requirement to file an Assurance includes both "awardee" and collaborating "performance site" institutions.

Under the Federal Policy (Common Rule) at Section 102(f) awardees and their collaborating institutions become "engaged" in human subject research whenever their employees or agents (i) intervene or interact with living individuals for research purposes; or (ii) obtain, release, or access individually identifiable private information for research purposes.

In addition, awardee institutions are automatically considered to be "engaged" in human subject research whenever they receive a direct HHS award to support such research, even where all activities involving human subjects are carried out by a subcontractor or collaborator. In such cases, the awardee institution bears ultimate responsibility for protecting human subjects under the award. The awardee is also responsible for ensuring that all collaborating institutions engaged in the research hold an OHRP approved Assurance prior to their initiation of the research.

http://www.hhs.gov/ohrp/assurances/assurances_index.html

- ✓ **properly obtaining and documenting informed consent,**
- ✓ **obtaining prior approval for any deviation from the approved protocol,**
- ✓ **keeping accurate records, and**
- ✓ **promptly reporting to the IRB any unanticipated problems involving risks to subjects or others.**

While research institutions are increasingly monitoring the progress of human subjects research, the primary responsibility for conducting experiments as approved still lies with the individual researchers and staff who conduct the experiments.

3f. Ethical issues

Despite the many rules governing research with humans, tough choices continually arise that have no easy answers.

Informed consent. It is widely agreed that research subjects should be fully informed about experiments in which they may participate and give their consent before they enroll. However, some subjects, such as children, some adults with impaired decisionmaking capacity, and some critically ill patients, cannot give informed consent, either because they are not old enough to understand the information being conveyed or because they have lost their ability to understand.

These and other problems could be eliminated by forbidding researchers to do studies that raise difficult questions about respect for persons, beneficence, and justice, but this would make it difficult or even impossible to get some crucial information needed to make informed decisions about medicine and public health. Since children do not respond to medicines in the same way as adults, it is important to include children in some clinical trials. However, it is not easy to decide when they should be included and how consent can/should be obtained.

Right to withdraw. It is widely agreed that research subjects should have the right to withdraw from experiments at any time, but in some cases they cannot. In the final stages of development, mechanical hearts are tested on patients whose own heart is about to fail. But if it has not failed, and once the mechanical heart replaces the weakened heart, there is no turning back. The patient can technically withdraw from the experiment and undergo no further testing, but he or she cannot withdraw from the conditions imposed by the experiment, no matter how distressing living with the mechanical heart might be. Knowing this, under what conditions should these experiments be allowed?

Risk without benefit. In one recent experiment, researchers wanted to test whether a common surgical procedure used to relieve arthritis pain had any benefits. To gather information about benefits they designed a clinical trial in which subjects in the control group received sham surgery. An operation was performed, but the common surgical procedure was not performed.

The researchers in this case complied with all regulations, which included thorough IRB review. None of the patients experienced any adverse effects, and the study concluded that the common surgical procedure did not provide significant benefits. However, since surgery always involves some risk, the subjects in the control group were placed at risk without any expectation that they would benefit. Should this be allowed, and if so, under what circumstances?

These and other questions must ultimately be answered by IRBs during the review process. Researchers who serve on IRBs need additional training to help them deal with the growing complexities of biomedical, social, and behavioral research. Researchers who use human subjects in research should seriously consider having some formal training in bioethics so that they can participate in the critical reasoning process needed to respond to the complex moral issues raised by the use of human subjects in research.

Questions for discussion

1. Why should some research on humans be exempted from regulation?
2. What other criteria could be used to identify necessary members for IRBs?
3. What should subjects know about proposed research and their protection before they enroll as subjects?
4. What other principles could be used for evaluating the ethics of human subjects research besides respect for persons, beneficence, and justice?
5. Should subjects be allowed to enroll in experiments that either promise no direct benefit to them or cannot provide them with the opportunity to withdraw completely?

Resources

Policies, Reports, and Policy Statements

Directives for Human Experimentation: Nuremberg Code. 1949. (available at: http://www.hhs.gov/ohrp/references/nurcode.htm)

Federal Policy for the Protection of Human Subjects, 45 CFR 46, Subpart A (2005). (available at: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm)

National Institutes of Health. *Guidelines for the Conduct of Research Involving Human Subjects at the National Institutes of Health,* 1995. (available at: http://www.nihtraining.com/ohsrsite/guidelines/graybook.html)

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World Medical Association. *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, Helsinki, Finland: World Medical Association, 1964, 2002. (available at: http://www.wma.net/e/policy/b3.htm)

General Information Web Sites

Food and Drug Administration. *Information Sheet: Guidance for Institutional Review Boards and Clinical Investigators*, 1998. http://www.fda.gov/oc/ohrt/irbs/default.htm

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Additional Reading

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Jensen, E. *Not Just Another GCP Handbook: A Practical Guide to FDA/DHHS Requirements*, New York, NY: PJB Publications Ltd., 2003. (available at: http://www.pjbpubs.com/cms.asp?pageid=287 &reportid=626)

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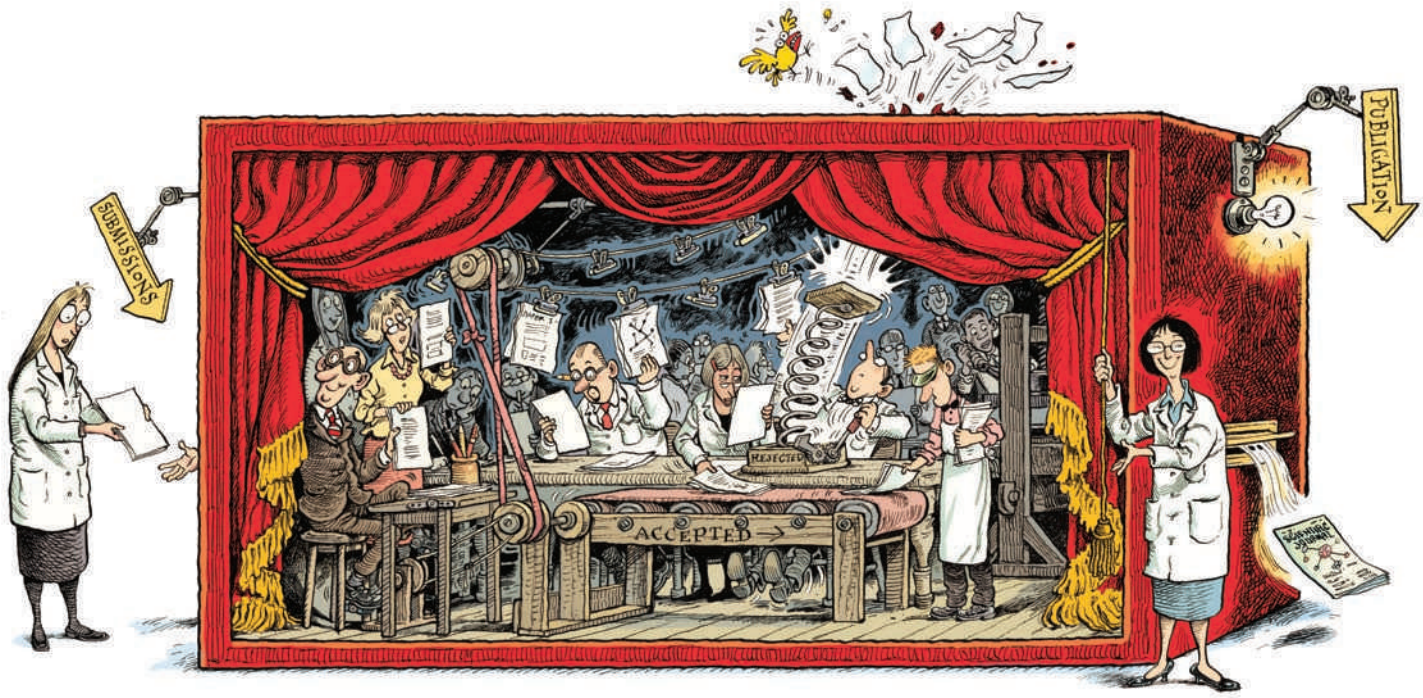
COMMENT



Transparency showcases strength of peer review

Bernd Pulverer reflects on his experience at *The EMBO Journal* of publishing referees' reports, authors' responses and editors' comments alongside papers, as other EMBO publications adopt the same policy.

Two years ago at *The EMBO Journal* we added transparency to peer review. We invited authors to allow inclusion of 'peer-review process files' alongside their published papers. Almost all have agreed. Now, more than 400 primary papers published in the journal showcase details of the editorial process: referee comments from every round of revision, editorial decision letters, the authors' response, as well as a detailed timeline of submission, decisions, revisions and publication[1,2] (see go.nature.com/nbus3f for an example of an *EMBO J.* process file).

In our view, these augmented papers are testament to the fact that carefully administered peer review works — works well, in fact. We were initially concerned that some authors and referees might be discouraged from contributing to the journal and so, until now, have made the files relatively hard to find. But, given the positive response from the community, we are this month extending the policy to all four European Molecular Biology Organization (EMBO) scientific publications — *The EMBO Journal*, *EMBO Reports*, *Molecular Systems Biology* and *EMBO Molecular Medicine* — and making the process files much more visible online.

The perennial concerns voiced about peer review and decisions made by professional editors — as opposed to part-time academic editors — stimulated us to think about how we might improve the process at EMBO. As a first step, we did a detailed annual analysis of where manuscripts rejected at our journal were eventually published, a summary of which we now publish annually (see go.nature.com/4y7fwp). This supported our sense that editorial decisions are generally informed and fair. For example, only 1% of manuscripts rejected in 2008 ended up in ▶

ILLUSTRATION BY DAVID PARKINS

journals with an impact factor two points or more above that of *The EMBO Journal*; and only 9% have a citation rate higher than the average paper in the journal.

Our second thought was that a huge amount of effort goes into peer review — effort that remains largely invisible. Many an editor and referee will attest to how much the process can improve a published paper — painful as it may be to go through. Referees can be the best writers of published analyses of single papers, such as *Science*'s Perspectives and *Nature*'s News & Views. So why hide all their incisive, constructive comments, which can remain pertinent even after revision and publication?

An obvious solution was to publish our anonymous referee reports. It would showcase the quality and thoughtfulness of the majority of reports. And it would add interesting points about suggested further experiments, alternative interpretations and, sometimes, limitations.

Another appeal of this path was that peer review is rarely formally taught, yet so much depends on it. We hoped that the peer-review process files might serve as a teaching tool. Finally, a clear potential benefit was to fortify the peer-review process. Referees might feel compelled to take extra care when writing their report, as the report would be published, albeit anonymously.

It was immediately apparent that, for completeness, we'd have to post all referee reports on a paper, followed by the author response. In the spirit of transparency and accountability, and with the hope of addressing grumblings about professional editors, we decided to add editorial decision letters. We'd only correct simple typos in the reports, but we'd allow removal of data that were provided solely to address a referee's point, as they might be required for future publications.

IMPACT ASSESSMENT

The policy kicked off in January 2009 (ref. 1). We invite authors to opt out of the system at any stage, and referees are made aware at invitation that their comments will be posted in case of acceptance. In September this year we decided to discourage 'confidential comments for the editor' by referees, which are commonplace at many biological sciences journals[2]. Legitimate confidential comments are allowed — for example, notes about biosecurity or conflicts of interest. But we want to move away from anything that gives rejected authors the sense that something went on behind the scenes that led to their rejection.

NATURE.COM
See Nature's blog on peer review
go.nature.com/nqlawg

At the time, *Biology Direct* and a number of BioMed Central journals already included published reports and author responses. Nevertheless, as with any change to a long-established system, there were significant risks. Would we discourage trusted referees? Would they fear that their identities might be revealed, and would they write less incisive or less critical reports as a result? Would authors resent the airing of — in the words of one referee — the 'dirty washing' leading up to acceptance? What if reports were rude or even defamatory? Would divergent referee reports lend ammunition to those that believe the system is failing? More pragmatically, would producing the files increase our editorial costs significantly, and would this additional step slow down the publication process in a field in which every day can count?

The experience has been overwhelmingly positive. The number of submissions to the journal remains steady and just 5.3% of authors have opted out, few of them citing philosophical objections to the policy[2]. The objectors cite a reluctance to add to the already excessive literature or a perception that an otherwise excellent piece of work can be marred by prominent comments on small mistakes or limitations.

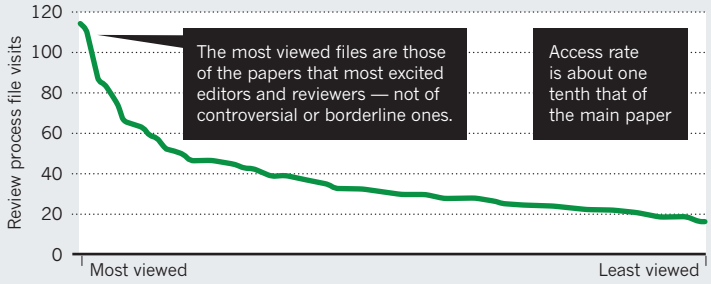
The rate of acceptance of invitations to review a paper has remained the same, and very few invited referees decline explicitly because of the policy. In one case, a referee who had failed to read to the end of his invitation letter in the first round did decline to re-review the revised manuscript, but agreed to post the first set of comments. Nor have we seen a significant change in the quality of referees' reports or authors' responses — for better or for worse. Several referees have acknowledged that they spend more time on phrasing their reports now and this is certainly true for my own two-finger-typed decision letters! And we estimate that each file takes around 1½ hours for our administrators and editors to produce.

Many of the process files include divergent referee opinions, but we feel that the reader is well aware that journals invite a referee panel with complementary expertise and thus different vantage points. It hasn't happened yet, but if we felt a referee's report was too aggressive, we'd go back to the reviewer to suggest a rethink, noting the possible publication of the comment.

So does anyone actually notice the process files? The numbers show that the access rate is about one-tenth that of the main paper and that almost all peer-review process files have been viewed. Access to the files correlates with access to the whole article. The most viewed files are those of the papers that most excited the editors and reviewers — not of controversial or borderline papers (see graph). We haven't been collecting data on how long readers spend looking at the files, but plan to. And now we've made the files much more visible and open access, we expect an uptick in access. Meanwhile, other journals, including the *European Journal of Cell Biology* have been taking note and are implementing similar enhancements.

PEER REVIEW PROCESS FILES ARE BEING NOTICED

Web access between April and July 2010 to the 100 most visited process files (referees' reports, editors' letters and authors' responses).



One crucial limitation of the policy is, of course, that we do not release reports on manuscripts that end up being rejected. It goes without saying that these are often the more interesting cases to consider. However, a workable way to redress this shortcoming has eluded us. A partial solution we're pursuing instead follows the example of the Neuroscience Peer Review Consortium. This cooperative of 37 journals has agreed to share referee reports if an author desires. 'Review recycling' is in our view an important way to address a key bottleneck in the publishing process.

WHERE NEXT?

To mix metaphors, we feel we have pried open the black box of peer review with this initiative — and shown that it is not Pandora's box. Now, like many others interested in optimizing the scientific publishing and grant-review processes, we are considering several other enhancements to traditional 'single-blinded' peer review. We remain convinced that a high level of quality assessment is essential to filter and validate the increasingly vast and diverse literature.

Many journals now allow post-publication commenting, often curated and usually signed. Despite the ubiquity of social media, commenting on scientific reports has not yet reached a level at which it could give peer review a run for its money. Inspired by the physical and computational sciences, where pre-publication commenting is commonplace, *Nature* ran an interesting trial a few

years ago in which authors were invited to open up their manuscripts to pre-publication scrutiny during a 'traditional' peer-review process. Around 70 authors participated and the editors carefully compared the input received in this and a peer-review-alone approach. In no instance did commenting add significant value[3,4] (see go.nature.com/n67mfk for the report).

Nevertheless, *Nature* opened all its published content for readers' online comments in March 2010. Comments, even on high-profile papers, remain sparse, however, even in journals such as *PLoS ONE* that specifically set out to supplement their assessment process with comments. Everyone is busy, and few may wish to risk outing themselves as critics without tangible benefit.

If peer review benefits from anonymity, why not also mask the author's identity ('double-blinded' review)? We remain interested in this possibility, but fail to see how to implement it without adding delays or requesting anonymized manuscripts for initial peer review (removal of author names does not suffice to anonymize a manuscript from one's peers). Conversely, why not add accountability by asking referees to sign their reports? The *British Medical Journal*, among others, has bravely pursued this path, and its editors claim that neither their referee pool nor their reports have changed[5]. In our view, the stakes often remain too high for this in the competitive world of biological research. Can a rookie investigator really be expected to write a critical report on a manuscript submitted by an eminent colleague who may well review their next grant? Can an author who has been asked to revise a paper significantly be relied on not to persuade the referee to back down?

"Online comments, even on high-profile papers, remain sparse"

Last month we started to encourage referees to comment on each other's reports, where they feel this would aid the editorial decision. Comments are only expected in cases in which a referee has taken a particularly extreme line or made a mistake, or if a referee wants to underline an essential point made by a colleague that they had missed. In line with some other journals, we have also implemented another change: we now explicitly prompt reviewers to declare the common practice of delegating peer review to others in the lab. We request that reports are vetted by the invited referee and that co-referees are named. We regard this as an essential component of good mentorship.

Most successful scientists spend a good fraction of their time reviewing papers. Yet, there is little tangible individual credit derived from the anonymous and voluntary contribution to this cornerstone of the research system. Thankfully, the remarkable culture of willingness to help colleagues and journals through peer review remains healthy, despite ever-increasing publication rates. Nevertheless, we are keenly pursing means to allow funding agencies and tenure committees to take this essential activity into account, and we welcome suggestions and collaborations on this and other possible enhancements. Peer review is the most remarkable manifestation of a collaborative spirit of science and needs to be nurtured and fortified where necessary. ■

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