Chapter 18
Publishing – Getting the Word Out to Doctors

Abstract The lifeblood of scientific discovery is information. Unless research findings are published and reach the medical community, they are of little value. However, there are problems with the present method of publishing medical research results. Peer review, a process by which experimenters review each other's work in order to weed out poor research, may not catch important errors. The results from some clinical research trials with negative findings may not be published and that also represents a serous problem. Paxil, a drug that some believe leads to juvenile suicides is used to illustrate this issue. A major Paxil trial with a positive result was published and presented at medical meetings, but a similar trial with a negative result ended up with no publication. The case illustrates that a drug's safety and efficacy problems can be deliberately hidden from the medical profession and the public. There are therefore calls for a clinical trial registry, which would contain the results of all clinical research investigations whether or not published in a journal. In addition, an innovative plan by faculty members of the London School of Hygiene and Tropical Medicine is used to suggest a radically way to change the current publication system.

Keywords Clinical trial registry · medical journal · peer review · publication bias · unpublished studies

> *Most physicians are not formally taught how to critically evaluate published results of clinical trials*. (H. Rubins, *Controlled Clinical Trials*)

The lifeblood of scientific discovery is information. The findings from each research project serves as a base for new research in a continuous chain. Each clinical study contributes to an evolving body of evidence. To make the process work, research findings must be published and be easily available to the medical community. The sharing of ideas, successes and failures, helps researchers discover new knowledge that leads to better health for everyone. But, anyone familiar with medical research recognizes that there is a litany of challenges with the publication process.

R.R. Gauch, *It's Great! Oops, No It Isn't*,

After completing a clinical study, the researcher's attention turns to writing a report of the trial and getting it published in a medical journal. Not all medical journals are equal and the most important research findings usually end up in the top U.S. and U.K. journals. The best journals publish a wide variety of articles covering molecular research, clinical practice developments, political issues, and ethical behavior. There are also excellent journals for every kind of medical specialty, from allergy to urology. Thus, researchers have a choice of a broad array of journals where they can submit their research papers. Frequently a medical journal is produced by a medical society. For instance *JAMA*, a highly regarded journal, is the property of the American Medical Association, but journals may also be owned by for-profit originations. The well-respected journal *Nature*, for example, is owned by the publishing house Macmillan Ltd.

Peer Review

Medical journals serve as a key link in the information chain that runs from basic research on medical treatments to their broad use by millions of patients. Quite simply, they act as the gatekeepers for the veracity and usefulness of medical science news. Editors of journals naturally want to publish only well-executed studies that are accurate, relevant and presented with clarity. To achieve these goals, the editors rely heavily on what is called peer review to ensure the quality of the research they publish. Peer review can be defined simply as the process by which journal editors solicit evaluations of submitted articles from outside experts who remain anonymous to the authors. The role of journals as the filter for scientific work dates to the 17th century in Great Britain, though the modern process of "blind" peer review is much more recent. Until the mid -20th century, many papers were approved solely by a journal's editors rather than by independent reviewers, and for some journals this is still the case. The explosion of scientific productivity after World War II strained the review process, significantly extending the lag time between submission and publication. More personnel were needed and peer review was the answer.

In time, peer review not only speeded up the editing process, it also strengthened the ability to identify incorrect or inadequate work and improve the accuracy and clarity of medical reports. In theory, it provides a rational, fair and objective way to assess scientific reports. Peer review, then, should weed out serious methodological and content errors, but that assumes there is an ample supply of experts in multiple fields to review the article. It's true that the goals of peer review are appealing and the system has a long proud history, but the system has its critics and there has been little research to prove that peer reviews achieve the purposes for which they were established.

In general, medical journals enjoy a high degree of respect for their selection and vetting process. But as in any media enterprise, there are critics as well. One of those critics was J. Kassirer, an insider – the former editor of a top medical journal,

who wrote a critical review of his fellow journalists in the journal *Annals of Internal Medicine*. He cataloged the following flaws, which represent a broad array of issues that he found in too many published studies.

1. The use of intermediate endpoints rather than meaningful clinical outcomes
2. Results rendered meaningless because of small numbers of subjects
3. Strong conclusions based on findings that barely reached statistical significance
4. The use of placebo controls instead of insisting on active drug controls
5. Conducting unplanned analyses of variables based on the study results
6. The rejection of exploratory studies that provided useful information
7. Permitting authors to describe the value of their work rather than getting them to help readers to understand the weaknesses as well as the strengths of their studies

Indeed, it's not surprising that, in spite of good intentions, there are frequent errors in published research articles that have gone undetectable by peer reviewers. Obviously, such errors had to exist before the peer review process began. From the publisher's perspective, it often may not be possible to detect the errors based on what reviewers have to work with – a manuscript written by the researchers. The journal editor and the assigned peer review team, for instance, almost never have the individual case reports, the protocol, the record of decisions made before, during and after the trial was conducted. They receive a finished product. But that product may well lack the details on how it was assembled and produced in the first place.

An example of a flawed trial that made it into print is covered in a report published in *Circulation* by an NIH researcher G. May and his colleagues. The drug involved was Anturane, a medication approved by the FDA to treat gout, but early studies showed it also was an effective anti-clotting agent and that property could keep some patients from having a heart attack. It therefore made sense to conduct a study investigating the ability of Anturane to prevent cardiovascular deaths. The results, published in a leading journal, claimed that after using Anturane there was a 74 percent reduction in sudden death in patients who had suffered a heart attack.

However, unlike a medical journal, the FDA receives the raw data for a trial and when the FDA reviewed the data from the Anturane trial, it recognized that mistakes had been made on the way causes of death were classified. After correcting for this error and reanalyzing the data, the FDA determined that Anturane had no effect in reducing the rate of sudden death in recent heart attack victims. As this sorry example shows, articles on flawed studies can appear in distinguished peer reviewed journals because not enough information is available to either the editor or the peer reviewers.

Other problems such as authorship integrity, plague medical communications as well. A number of articles in medical journals, claiming to be written by the researcher who conducted the trial, are actually written by professional ghostwriters experienced in technical writing. These writers, whose names never appear in the report, are employed by the sponsor to make the report more appealing to readers. The opposite problem occurs as well, the name of highly respected co-author may be added, but the person may have played no role in the study and didn't know that

his or her name had been added. Journal papers have had to be retracted once this masquerade was discovered.

Journal articles can also leave out information without providing a rational explanation for the omission. For example, a 2005 critique of published studies found that not all outcomes in clinical trials are reported. In this telling review, published in the *British Medical Journal*, it was found that some outcomes measured in a trial were simply omitted in an article because of the authors' decision that it lacked clinical importance or it failed to be statistically significant. As a result, the medical literature can represent a selective and biased subset of study outcomes and readers need to be aware of this possibility. Here's an example that further illustrates the problem. An analysis of study protocols, and the corresponding published report by five noted research methodologists, came out in a 2004 paper in *JAMA*. It showed that the reporting of trial outcomes were seriously incomplete. About 50 percent of efficacy outcomes and 65 percent of harms were incompletely reported. Furthermore, over 60 percent of trial reports had at least one primary outcome that was added, changed, or removed from the protocol. Obviously, the consequence of these acts may well lead to a serious bias in the overall study result reported in a journal article.

To overcome this problem, it has been argued that protocols should accompany the submission of a research report to a journal. Requiring authors to submit the trial protocol along with their manuscript is in effect at some of the major medical journals today (e.g. *British Medical Journal* and *Annals of Internal Medicine*). With concurrent submission of the protocol, editors do not have to chase after authors when they run into a potential problem because the manuscript indicates that protocol deviations may have occurred.

Gratefully, editors of leading journals are not at all complacent about the content of study reports. An attempt to have high standards for what should be covered in a clinical trial article led to the creation of publication guidelines and represented a major accomplishment in elevating the reporting of medical research. A group of scientists and editors developed the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) guidelines to improve the quality of clinical trial reports and their publication. These standards include a checklist and flow diagram that authors can use when writing up their results. Many leading medical journals have adopted the CONSORT standards since they facilitate the preparation of a clear and informed description of a clinical research project. Nevertheless, as valuable as standards are, they cannot overcome all the many issues associated with the quality of medical publications.

Statistical Review

Previous chapters emphasized the vital role statistics plays in medical research. The report on a clinical trial benefits from the presence of statistical expertise in the preparation, execution and write-up of a study. Nonetheless, how often statisticians

participate in a clinical study is not known. An estimate of their rate of participation comes from a survey, by D. Altman and associates, who contacted the authors of clinical papers appearing in two of the leading medical research journals (the *Annals of Internal Medicine* in the U.S., the *British Medical Journal* in the U.K.). They asked the authors if they received assistance from a person with statistical expertise and the nature of any such contribution. They found that there was no statistical input in over one quarter of the papers. And in some of the papers that claimed there was statistical input, the assistance did not come from a professional statistician or epidemiologist.

The absence of sound statistical advice during a trial makes it more likely that there will be statistical errors in the manuscript submitted to a journal for publication. Unfortunately, the chance that statistical errors will be caught at the editorial review stage is problematic because, in spite of their importance, less than one in three medical journals does a statistical review. A related issue is to ask how many statistical errors get through the editorial and peer review system. The one study that looked for such errors appeared in *The Economist* in 2004. The examination was confined to two highly valued journals, both published in the U.K. They found that 38 percent of the papers in one journal and 25 percent in the other journal contained one or more statistical mistakes. Most of the errors were not likely to lead to grossly erroneous conclusions, but there were key mistakes that caused non-statistically significant conclusions to be incorrectly presented as significant ones. The editor of one of the journals subjected to the statistical critique noted that attempts to avoid numerical problems were handled by their routinely asking for the raw data, but the data were seldom received. On the other hand, a deputy editor of one of the journals also wondered whether it would be a good use of reviewers' time to scrutinize countless numbers and perform tedious calculations.

There have even been calls in the publication field for mandatory sharing of data to be a safeguard against fraud and the mishandling of patient information. In spite of a certain appeal for this approach, it has its negative aspects as well. As noted in previous chapters, there are so many subjective decisions in data analysis that sharing the study data from a trial could open up a Pandora's Box. Re-analyses of trials would become popular sport and few original conclusions would escape a "new" analysis that could easily reverse the initial findings.

The large number of statistical mistakes found in medical articles again suggests that statistical expertise may be missing or underutilized in too many medical experiments. It's entirely possible that research teams, that do not include a qualified statistician, allow the medical researchers (who may have only a shaky grasp of proper statistical techniques) too much leeway. No one knows how many medical findings claiming statistical significance have been wrong; the result of poor statistical technique. Since it is often felt that a key factor in the acceptance of an article for publication is a statistically significant result, there are clearly incentives to stretch the data and the analysis in order to declare there was a statistically significant finding.

The concern over an impartial statistical analysis has also motivated *JAMA* to add the condition to all industry-sponsored studies. *JAMA* will not accept a study

for publication, if the data analysis was conducted only by statisticians employed by the company sponsoring the research, unless there is an additional independent analysis performed at an academic institution such as a medical school.

Publish or Perish

Researchers obviously want their study results to appear in a medical journal – the more prestigious the journal the better off the researcher. Publications add to their stature among their peers and are a requirement to get additional funding to do more research. Higher stature and remuneration from their institution are additional motivations to publish a lot. These incentives can lead to their writing articles that gloss over problems and exaggerate what was found. Outright lying and faking results also takes place and the forged manuscript can sneak past journal editors as well as those doing a peer review.

How quickly one can publish also becomes an issue for clinical researchers. Being first brings much acclaim, being second is far less rewarding. However, the chances of getting a reasonably correct answer in a medical study can fall in the rush to publish. Quality control steps may be sacrificed, the search for alternative explanations minimized and ambiguous information ignored in order to beat the competition with a significant result. As a result, contradictory information from subsequent studies on the same topic is commonplace.

There are hundreds of medical journals looking for articles and an estimated two million new research articles are published worldwide each year. However, there are contrasting forces in play when it comes to publishing so many research articles. On the one hand, researchers are encouraged to undertake multiple projects and publish their findings thereby expanding the scientific knowledge base in their field. Yet, the net result can be information overload with few in the field of medicine able to keep up with the ever-increasing volume of information that never seems to end. It is therefore, disappointing to realize that some researchers are urged to milk a single study for as many papers as possible. The practice results in a more impressive curriculum vitae, but the redundancy can fool others into thinking there's been replication of a finding and, as noted earlier, it can have a negative impact on a crucial meta analysis.

Absence of Reports

In December, 2003 clinical researchers held a meeting in Puerto Rico and FDA reviewers met in Washington DC to resolve a problem. The same question was probed by each group – does the use of antidepressants in children lead to an increased risk of suicide? The meeting in Puerto Rico included many of the researchers who had conducted studies on three extremely popular antidepressants.

However, this group faced a formidable problem – they did not have access to all the data they needed to cone to an informed conclusion. Because of confidentiality concerns, the drug companies that sponsored the trials refused to provide the requested data.

The suicide issue was first noted by British regulators who had earlier asked drug companies in their country for some of the unpublished data from the antidepressant trials they had conducted. In this case, the data the British authorities asked for was turned over to them. A review of that data suggested that a bizarre event could occur – antidepressants may prompt young people to attempt suicide. The possibility of suicide was not apparent from the published studies. It was only revealed in the unpublished studies. One drug, Paxil, seemed to be the most obvious offender. When the news media got hold of the story, the manufacturer of the drug, GlaxoSmithKline, was asked about the results from all their studies. They replied that all the results of their clinical trials had gone to the FDA, as required by law.

Paxil was originally approved for the treatment of depression in adults, but after securing approval, GlaxoSmithKline sponsored five trials of the drug in adolescents suffering from depression. By researching the drug in young people, the company hoped to extend the drug's use to this age group. In the process, they would also be entitled to a five-year patent extension for the drug because they had sponsored research in young subjects. Unfortunately, for the manufacturer only one of the five trials produced a good result for the drug. The investigators of the favorable trial published their results, but there was no publication of the any of the four failed trials.

As it turned out, not only did the unpublished trials fail to show any benefit for the drug in ameliorating depression in adolescents, they suggested that it might increase the risk of suicide. The FDA, which had all the Paxil data, now went to work establishing a regulatory position on Paxil. After completing their review, including the concern over teenage suicides, the agency recommended that Paxil not be used in children and adolescents for the treatment of serious depression. The FDA determined that each anti-depressant manufacturer should also include a warning statement that recommended close observation of adult and pediatric patients treated with these agents for "possible worsening of depression or suicidality". Then things got even worse for GlaxoSmithKline – in 2004, the Attorney General of New York filed a lawsuit against the drug maker.

The NY lawsuit claimed that the manufacturer engaged in fraud by failing to tell doctors that some studies of Paxil showed that it did not work in adolescents and might even lead to suicide. Instead of warning doctors, the lawsuit claimed that the company promoted the use of Paxil in youngsters. The Attorney General argued that the company was making selective disclosures of information and did not give doctors all the evidence available. Relying on FDA rules, that allow the results they receive about clinical trials for new drugs or indications to be treated as confidential on the ground that it is proprietary company information, the company disputed the charge. Therefore, GlaxoSmithKline took the position that they had acted responsibly in conducting and distributing the data from their pediatric studies.

The criticism of the company focused on two particular studies, which were used to show the inconsistency in the company's behavior. Both studies were

multicenter trials and were very similar except that one was conducted in the U.S. (study 329) and the other in countries outside the U.S. (study 377). Study 329, the positive trial that showed that Paxil was effective in adolescents with depression, was completed first. Its results were presented beginning in 1998 at several medical meetings. The study was published in 2001. In the case of Study 377, the one with negative findings, there was no publication – not even a press release. However, one of the investigators, a Canadian who conducted one of the segments that made up the multicenter trial, expressed a desire to report the findings from study 377. He felt that even though the results were negative, they could reveal trial design flaws and that revelation could help others design better antidepressant trials in adolescents. The Canadian researcher presented his study results at a scientific meeting, taking this action after the manufacturer told him that they did not intend to publish the results of the multicenter study.

Two and a half months after the lawsuit charging fraud was filed, GlaxoSmithKline settled. The terms of the settlement required the company to place negative data on the safety and effectiveness of its drugs in a registry that could be accessed at its web site. The company would also update the information as new data became available, and keep it available for at least 10 years. The Attorney General who brought the lawsuit noted that the settlement sent a signal to the other pharmaceutical manufacturers that there now was a new standard with regard to disclosure of clinical studies.

This case illustrates a major problem in medical research publication: results of negative clinical trials sponsored by drug manufacturers are not widely published. As a result, the medical profession can remain ignorant of safety and efficacy problems with a drug. Experts have long faulted the tendency in the industry to publish mainly positive clinical trials, arguing that this distorts the knowledge base of medicine. The term "publication bias" is used for this method of preferential selection. Research is more likely to be published if it has a positive finding supported by statistical significance. Reporting that (1) one drug is better than another, or (2) that one treatment produces fewer side effects than another, or (3) that one patient group has a better prognosis following treatment than another seems to be more interesting than research that finds no significant treatment differences.

In addition, it's worth repeating that the drive to reach a statically significant result is a quest industry and academic researchers can't resist. Thus, there is an incentive to tweak the data so that the all-important "statistically significant" label can be stamped on their findings. In fact, there are software packages for "data mining" that rumble through databases looking for every possible kind of relationship that has "statistical significance". That approach may be great for business organizations that collect masses of data and want to see what kind of relationships exist that may help their marketing approach. But for clinical research, data mining can be terribly misused. Clinical research studies are based on a single a priori hypothesis and data mining is an after-the-fact "discovery" which comes about after testing a vast number of possible relationships. Any remarkable result, positive or negative, is essentially accidental. In clinical trials to claim statistical significance for a relationship found through data mining is ridiculous. At best, data mining

results can suggest hypotheses that need further study, but they should never sneak into a report as an "extraordinary" finding.

From a commercial standpoint, it's useful to examine the rationale by pharmaceutical companies to withhold full disclosure of clinical research. Certainly, they are the ones with a lot to lose from a negative study about one of their products. Drug companies, however, have other explanations as well. They say that because they pay for a trial, they own the data and that their concern about data confidentiality is not intended to suppress possibly negative trial findings, but to make sure that data is properly analyzed before it is released. However, when this rationale is applied to a medical school that has researched one of their drugs, it is not particularly convincing, Medical schools run many clinical trials for pharmaceutical companies and the quality of their research is highly regarded as is their competency to properly analyze data. Yet the results of their studies may never appear in print because of the control exerted by drug makers. The reason for the omission lies in the data disclosure clauses contained in the pharmaceutical company contracts that medical school researchers sign. Those contracts generally forbid them to publish data without the company's permission. It is generally believed that unless medical schools take tough stands on issues like confidentiality and publication rights, their ability to publish will continue to be restricted. Leading academic research centers with a lot of clout and can get around this issue and eliminate such clauses, especially when they are the only ones conducting a study. But medical school researchers have less ability to set terms for a multicenter trial that is run at many academic and private testing centers. They may be able to publish the results from their center, but that's only one piece in a large puzzle and can be misleading.

A Clinical Trial Registry

In response to growing criticism about unpublished research, the American Medical Association urged the federal government to set up a public registry of all trial results. The editors of some of the world's most prestigious medical journals joined the crusade and want to require drug companies to register their trials publicly as a prerequisite to publication. The World Health Organization became involved in the effort in 2004, calling for the registration of all clinical trials to increase the public trust in medical research. Leading drug companies such as Eli Lilly and Schering-Plough also supported the proposal to create a public database that would include the results of all drug trials. The announcement of the creation of the clinical trial registry was made on International Clinical Trials Day, 2006 – a day devoted to raising awareness about the methods and challenges of medical research.

While the announcement was met with general approval, there still remained the issue of whether the registration of trial data would be mandatory or voluntary. Proponents said a mandatory program would eliminate the harm done by concealing negative data and provide researchers, physicians and the public, information they need.

The trade association for pharmaceutical companies, however, took a more conservative stand and supported a voluntary program. Supporters of voluntary registration pointed out that mandatory registration could reveal information that manufacturers consider proprietary, such as the results of small or exploratory studies and that could expose their research strategies and progress to competitors.

Perhaps the major roadblock to a mandatory program was that it would require Congressional action and whether that would happen depended on the unpredictability of political action. The answer came in 2007 when Congress passed and President George Bush signed the FDA Revitalization Act. A provision in the new law required the registration of all but early exploratory clinical trials to be placed in a public database.

The importance of a drug registry played a leading role in one of biggest uproars over unsafe drugs that also occurred in 2007. In this brouhaha, the manufacturer was again GlaxoSmithKline and their drug, Avandia used to treat diabetics, came under attack in 2007 because of a meta analysis that reported an increased risk of heart attacks with the drug. The analysts from the highly regarded Cleveland Clinic published their findings in the *New England Journal of Medicine*. They used as their data source, trial results that were on the GlaxoSmithKline web site listing results from clinical trials with their drugs. The database used by the Cleveland Clinic analysts contained 42 studies and about 16,000 patients on Avandia plus an additional 12,000 patients who made up the control group. In their paper, the Cleveland Clinic author's noted that their approach had limitations because it had been necessary to rely on summary data rather than patient-specific information. They also acknowledged that there were weaknesses in a meta analysis, but in spite of these caveats, they still believed there was evidence of a potential serious risk of heart attacks with Avandia.

After the meta analysis by the Cleveland Clinic researchers appeared, there were Congressional hearings, accusations that the FDA had again failed to do its job, and charges that the manufacturer knew years ago of the heart attack risk, but did too little about it. GlaxoSmithKline reputed the charges and argued that it would be a big mistake if the FDA acted against Avandia prematurely. The company had a major trial going on that was looking into the heart related risks with Avandia and until those data were available, it would be unwise to remove the drug from the market. An interim analysis of the data from that study was performed, published in the *New England Journal of Medicine* and concluded that the findings were inconclusive. This was not unexpected since the trial was only about half completed. Nevertheless, critics of Avandia pointed out that the interim analysis showed the rate of heart attacks were higher on Avandia. However, they conceded that the rate was not as high as that found in the Cleveland Clinic analysis.

That was not the end of the story. In August, 2007 a paper in the *Annals of Internal Medicine* described a re-analysis of the data used in the Cleveland Clinic analysis and it should come as no surprise that the new analysis, which employed different meta analysis options, had come to a different conclusion. By choosing this alternative approach, the second group of analysts concluded that a greater

heart attack risk with Avandia was uncertain and that neither an increased nor a decreased risk could be established.

In the end GlaxoSmithKline again escaped the axe. An FDA advisory committee recommended that Avandia remain on the market, but with stricter label warnings. In addition the company also had to institute an extensive educational effort regarding the proper use of Avandia and the committee also requested further studies because none of the ongoing clinical trials was likely to provide a clear answer concerning the absolute heart risk for the drug.

Amending the System

For many, the system for the publication of clinical trial results is broken. Problems with peer review, the need to publish clinical trial findings fast and frequently on the one hand and not to publish them at all on the other, are symptoms of a ailing system. However, it would be terrible unfair to place the blame for the current situation primarily on the editors of journals. They pretty well inherited a flawed process and, in fact, have been in the vanguard promoting change. Nevertheless, editors and editorial boards are inclined to make modifications incrementally and that will take a lot of time and may not be enough in the end. Consequently, extraordinary changes may be the answer. For example, an innovative plan has been developed by faculty members of the London School of Hygiene and Tropical Medicine that would radically change the current system.

They propose that trial organizers post on the web, a review of the existing evidence about an experimental treatment they plan to study including its effectiveness and research needs in the future. A new trial would be registered and its protocol would appear on the web site, as well as the names of the research team members and their roles. The protocol would need to specify any planned subgroup analyses, stopping rules etc. Any interested party could add their comments about the information (e.g. completeness of the evidence, reliability of the research methods, etc.).

The proposed statistical analysis would be explained and when data collection was over, the full dataset would be added to the site. Description of the methods to avoid data fabrication and falsification would also be included. In addition, when data collection was over, the entire dataset would be uploaded and the statistical analyses presented. There would be no investigator commentary permitted. However, at a designated time the research team would be expected to prepare an updated review of the evidence concerning the treatment.

The London proposal offers some appealing features such as the emphasis on the totality of the evidence about a treatment rather than a focus on a single trial. There are, in addition, deterrents to unreported protocol changes and unwarranted statistical manipulations. Furthermore, in this plan there would be better control over the issues of multiple reports and no reports.

However, the advantage of having a great deal of input also means lots of opportunities for biased opinions, masquerading as honest critiques, to get equal attention in an arena without referees. In an entrepreneurship society, other avenues to present medical research studies could result in more chaotic and unfair systems. Nevertheless, what is needed, in addition to better-quality medical research, are new ideas and proposals to increase the timeliness, thoroughness and accuracy of medical findings so in the end researchers, public health officials, practicing physicians and their patients have the right information so they can make more informed medical decisions.