



News

Encouraging results from the Oxford experiment

Oxford University Press is to extend its Open Access experiment after an overwhelmingly positive response from authors.

Oxford University Press (OUP) chose the popular annual Database issue of its flagship journal *Nucleic Acids Research (NAR)* to perform an experiment with Open Access publishing. The issue generated such enthusiastic feedback from authors that OUP has decided to extend the experiment further.

Last August OUP announced that it would ask authors to pay a £300 (around US\$540) fee in order to make their research articles freely available online (see *Open Access Now*, November 3 2003). OUP, the largest university press in the world, was interested in exploring the issues involved in switching a

well-established journal from a subscription-funded to 'author-pays' business model. The January issue of *NAR* included a record number of peer-reviewed articles (142), and 90% of authors agreed to pay the author charge. "We are delighted with the results of our experiment so far," said Martin Richardson, Director of the Journals Division at OUP that published over 180 scholarly journals. "We entered this experiment in a spirit of careful exploration, eager to collect and analyze as much data as possible before deciding how to progress with Open Access."

Richardson stressed that OUP, as a university press, is keen to respond to the changing needs of the research community and explore new publishing models. "Our first-hand experience is allowing us to better understand the challenges a publisher might face when

transforming a journal from one business model to another."

OUP plans to extend the experiment to include the annual Web Server issue of *NAR* that is published in July. Richardson pointed out that the current author charge does not cover the true cost of publishing and that in the future OUP would gradually need to increase the charges several fold. "By taking a staged approach we hope to work with authors, their institutions and funding bodies to explore how a transitional period would work."



Martin Richardson

www.oup.co.uk/nar

News

House of Commons begins oral evidence sessions

The Science and Technology Committee of the UK House of Commons has begun hearing evidence from publishers and researchers as part of its inquiry into scientific publication and access to scientific research information.

Last year the Committee called for written evidence from the scientific community, to address the issues of the pricing of scientific journals and the consequences of the increasing number of Open Access journals. In March, the second phase of the inquiry began with the first two oral evidence sessions. Ian Gibson MP, the Chairman of the Committee, had promised that "The Committee will have some very tough questions for publishers, libraries and government on these issues." The sessions are open to members of the public, and the Committee chairman expressed his surprise at the large turnout "We shall have to get an even bigger room next time," said Gibson. "We will have to get the Albert Hall, or we might take over the Chamber [of the House of Commons] as there are more of us than them."

In the first session, on March 1, the Committee heard evidence from representatives of four large commercial publishers: Reed Elsevier, Blackwell Publishing, Macmillan Ltd (which includes the Nature Publishing Group), and Wiley Europe Ltd. The publishers faced questions about the current high prices of scholarly journals and the challenge of Open Access models. They all defended their companies' current positions

and claimed that academic institutions and universities would suffer if the system were changed.

Gibson challenged Crispin Davis, Chief Executive of Reed Elsevier, about his 'dismissive' approach to the Committee's Inquiry. Davis responded that although Reed Elsevier has a lot of doubts about Open Access, it is keeping an open mind about it. He defended Reed Elsevier's gross profits of 34%, and its significant annual price increases. All four publishers felt that changes to the system would compromise the peer-review process and standards over all.

In the second session, on March 8, the Committee heard about very different aspects of the issue. The case for caution on the part of learned societies and small publishers was put by the Institute of Physics, the Association of Learned and Professional Society Publishers and Oxford University Press. And the case for Open Access was argued forcefully by Harold Varmus of the Public Library of Science (PLoS) and Vitek Tracz of BioMed Central (which publishes *Open Access Now*). All the participants agreed that rigorous peer review would ensure that high quality standards are maintained.

The Open Access advocates emphasized the importance of centralized electronic archives. They hope that the Committee will make a recommendation to government to support a British digitalized archive initiative, perhaps run by the British Library, similar

to the US National Institutes of Health's PubMed Central archive. Varmus urged the Committee to recommend that the Government should mandate Open Access publishing for publicly funded research and to explain to funding bodies and the public that "the cost of publishing is part of the cost of doing research."

Tracz emphasized the importance of central archives when he told the Committee: "this whole discussion ... is not really about business models or what is more profitable, but about a fundamental change in the way findings, especially in the biomedical field, are recorded and used."

www.parliament.uk

For more information see the special feature on the *Open Access Now* website.

www.biomedcentral.com/openaccess/inquiry

FEATURE: Clinical Trials
The public has a right to know

See inside...

The public has a right to know

It is often argued that patients and their physicians have a right to access biomedical information and research. Information about clinical trials is of direct concern to patients and the public – and in particular to those who participate in trials as volunteers. Yet until recently there was no easy way to access comprehensive information about clinical trials currently underway, or the results of completed trials. We report here on recent initiatives to provide the public and the research community with online resources about clinical trials.

“Clinical trials have enormous potential for improving medical practice,” says Alexa McCray, Director of the Lister Hill National Center for Biomedical Communications at the US National Library of Medicine (NLM). “But reports of such trials are often difficult to find, and in some cases do not even exist.” She stresses that limited access to information is one of the greatest barriers to the practice of evidence-based medicine¹.

It is estimated that of the one million or so clinical trials conducted over the last fifty years only about half of them have been reported. Many trials are terminated early and never published. Over one third of randomized controlled trials (RCTs; see Glossary) are not indexed in MEDLINE and are effectively missed by researchers or physicians who rely on MEDLINE to search the literature. This creates what researchers refer to as the ‘publication bias’. “The fact that some trial results are never published would not be a problem, except that there is good evidence that the results from unpublished trials are systematically different from those of published trials,” claim Kay Dickersin and Drummond Rennie².

For many years, patient advocacy groups and physicians have demanded

that information about clinical trials should be readily available to the public. Initiatives such as the Cochrane Collaboration, founded in 1993 by Sir Iain Chalmers, have been trying to address this issue. The Cochrane Collaboration produces systematic reviews of healthcare interventions, in a bid to ensure that healthcare is based on the best available research evidence. In addition, the US Cochrane Center is assembling reports of published RCTs that compare two or more interventions. As part of this effort, over 2,000 journals are being hand-searched, page by page, by people around the globe. The Cochrane Central Register of Controlled Trials (CENTRAL) currently contains more than twice as many reports of trials as MEDLINE. But such mammoth efforts are time-consuming, inefficient and expensive. Many have argued that patients and researchers would benefit enormously from systematic registration of all clinical trials².

ClinicalTrials.gov

Pressure from patient groups and the American public led to the Food and Drug Administration (FDA) Modernization Act in 1997. Section 113 of the Act called for the creation of a public database of information on clinical trials: “A registry of clinical trials (whether federally or privately funded) of experimental treatments for serious or life-threatening diseases and conditions ... which provides a description of the purpose of each experimental drug, either with the consent of the protocol sponsor, or when a trial to test effectiveness begins. Information provided shall consist of eligibility criteria for participation in the clinical trials, a description of the location of trial sites, and a point of contact for those wanting to enrol in the trial, and shall be in a form that can be readily understood by members of the public.”

The ClinicalTrials.gov website is the result of this legislation. “The law originated from a large number of patient groups pushing very hard for greater access. So it’s definitely an Open Access issue,” says McCray, who coordinates the ClinicalTrials.gov project.

“Patient groups wanted access to trials information without depending only on their physicians, and they wanted a centralized location to find this information.” Within 18 months, McCray’s team launched ClinicalTrials.gov with a set of 4,400 NIH-sponsored trials. They also worked closely with colleagues at the FDA to produce a detailed Guidance Document describing the submission criteria.

The ClinicalTrials.gov registry was designed to include Phase II, III and IV trials (see Glossary) for serious or life-threatening diseases being conducted

stressing that data analysis is greatly aided by high-quality data. “Open Access isn’t just about throwing information out there. If it’s poorly designed or badly presented then it’s not so open.”

McCray sees the registry as a critical resource to allow patients to find out about ongoing US trials that they wish to participate in. Each entry lists eligibility criteria, location and contact details, and whether the trial is currently recruiting patients. The online record ends with reference to the NLM Identifier, an 8-digit ‘NCT number’

Open Access isn’t just about throwing information out there. If it’s poorly designed or badly presented then it’s not so open.

in the USA; the law did not mandate for Phase I trials. McCray points out that drug companies are particularly reluctant to disclose full information about early-phase trials, for proprietary reasons. She feels that those fears are misplaced, given that once patients enrol in a trial they are free to talk about their participation. The database currently contains information on 9,600 trials, including NIH-sponsored multi-center studies in the USA and studies from around 250 pharmaceutical companies; both RCTs and non-RCTs are included. “The public has a right to know about the results of the trials,” insists McCray.

All records from ClinicalTrials.gov can be downloaded as tagged data in XML (eXtensible Markup Language) format for meta-analysis. “The ClinicalTrials.gov team had to think a lot about standardized data elements and controlled vocabulary, in order to generate a carefully designed data-entry structure,” recalls McCray,

that can be used to track the trial. McCray sees continual updating as an essential feature of the trials registry. “We have built a very rich information system with targeted links to additional information resources,” says McCray. “It’s a living, breathing, up-to-date registry. And, of course, that’s what everybody wants.”

Controlled-trials.com

Current Controlled Trials (CCT; a company within the same group as BioMed Central), an online publisher focusing on RCTs, has also created the *metaRegister* of Controlled Trials. “It’s unethical for patients to be asked to take part in trials and then not be able to know about what trials are currently going on,” says Anne Greenwood, Managing Director of CCT. “It’s also very important for clinicians and sponsors to make sure that they don’t duplicate research that is already taking place.” She emphasizes that researchers conducting meta-analyses

also find it very hard to find comprehensive information about trials that have been conducted. The CCT *metaRegister* focuses on international Phase III and IV trials in all areas of healthcare. Greenwood stresses that before the online registries, such as ClinicalTrials.gov and *metaRegister*, this information was often badly organized and scattered among many different sources.

In order to help patients, sponsors, researchers and clinicians to track

clinical trials CCT has developed a registration numbering scheme similar to the ISBN (international standard book number) system used to track all books that are published. The International Standard Randomised Controlled Trial Number (ISRCTN) scheme is open to anyone who wants to register – it is not restricted to any one geographic location or to any specific disease area. Applicants have to pay a fee of US\$128 (€116; £80) per trial. “Researchers feel that there is increasing pressure to declare that they are doing a particular trial and to make them more publicly accessible,” says Greenwood. Some countries also have laws enforcing trial registration. The UK’s Research Government Framework is a Department of Health guideline that encourages trial registration.

The idea behind the ISRCTN scheme is to make it easy to track trials that have been initiated in a given disease area. “It is in effect a sign-posting system to take people to the specialists involved in the trial,” says Greenwood. It differs from NIH’s ClinicalTrials.gov in that it only requires a one-off submission with basic information about the sponsor, the disease, the trial title, the participants and the interventions used. There are also contact details for the sponsor and the lead investigator. The ISRCTN Register is fully Open Access – there is no need to register to view all the information. “All people involved in meta-analysis say that this is a fantastic initiative. In the past, trials that were started but never published were simply lost from the face of the world, whereas here they will be maintained forever,” notes Greenwood.

CCT launched the ISRCTN scheme in May 2003, using UK data for the pilot

Tell us what you think.

What should governments do to actively encourage Open Access publishing/archiving of the research they fund?

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project. The numbering system was developed in close cooperation with the UK’s Medical Research Council (MRC). The National Health Service (NHS) has committed to register all the trials that it funds in England. “We have fairly good coverage of all government-funded trials in the UK,” says Greenwood. The World Health Organisation (WHO) has recently agreed to number all its trials, as have the Canadian Institutes for Health Research. The CCT website can also be searched using NIH’s NCT numbering system. CCT is keen to encourage authors to include ISRCTN numbers in abstracts of any publications reporting trial results. BioMed Central already requires all its authors to do so.

Greenwood regrets the lack of UK legislation requiring registration. “It’s really a good-will operation at the moment.” She hopes that registration will become the norm in the future, and is particularly disappointed by recent European Parliament legislation,

The Clinical Trials Directive, that comes into force this year. This directive mandates the creation of a confidential, rather than open, register of drug trials across member states. CCT did apply for European funding in the past but was unsuccessful. “This does not offer Europe anything like the trials register run by NIH. It is tragic for European citizens. Europe could have created something like the Open Access register that they have in the US.” Despite the setbacks, Greenwood is confident that registers of clinical trials will continue to grow as government, patients and the research community understand more about the benefits they bring to healthcare and the fight against disease.

Additional Reading

1. A.T. McCray, “Better access to information about clinical trials.” *Ann Intern Med*, 133:609, 2000.
2. K. Dickersin, D. Rennie, “Registering Clinical Trials” *JAMA*, 290:51, 2003.

Glossary

Clinical trials are research studies that use human volunteers to answer specific health questions.

Interventional trials determine whether experimental treatments or new therapeutic strategies are safe and effective under controlled environments. Among interventional trials, **randomized controlled trials** (RCTs) are considered the ‘gold standard’: participants are allocated at random to receive one of several clinical interventions, and one intervention is a ‘control’. **Observational trials**, by contrast, address health issues in large groups of people or populations in natural settings.

Clinical trials are often classified into **phases**, each of which has a different purpose and answers different medical questions. In **Phase I**, a new drug or treatment is evaluated with a small group (20–80) of often healthy volunteers. Phase I trials provide a preliminary evaluation of safety and identify side effects. **Phase II** trials are therapeutic pilot studies performed on a larger number of people (100–300) and aiming to demonstrate activity and to assess drug safety further. Phase II trials are also used to establish new indications for treatment, or new improved combinations or schedules, for marketed drugs. **Phase III** comprises randomised trials in larger patient groups (1,000–3,000) to determine the short- and long-term safety/efficacy balance of the drug or treatment, as well as to assess comparative effectiveness, monitor side effects, assess drug interactions, and so on. **Phase IV** are post-marketing studies designed to define additional information including the drug’s risks, benefits and optimal use.

A meta-analysis is the statistical synthesis of data from separate but similar studies leading to a quantitative summary of the pooled results.

Resources

ClinicalTrials.gov: a clinical trials register run by the National Library of Medicine (NLM), part of the US National Institutes of Health (NIH). The registry includes both federally and privately funded trials.
<http://clinicaltrials.gov>

Cochrane Central Register of Controlled Trials (CENTRAL): a register that contains over 350,000 reports of published clinical trials results. The project is coordinated by the US Center of the Cochrane Collaboration, an international effort to pull together in one place the world’s best medical evidence for treatments, diagnostic techniques, and preventive interventions.
www.cochrane.us

Current Controlled Trials (CCT): the website of Current Controlled Trials Ltd, producer of the *metaRegister* and the ISRCTN Register. CCT is part of the Current Science Group (CSG) and is published by BioMed Central (publisher of *Open Access Now*). CCT provides free access to clinical trial information from all countries

of the world and in all areas of healthcare. It is funded by those contributing registers to the *metaRegister* and by ISRCTN applicants.
www.controlled-trials.com

ISRCTN: the International Standard Randomised Controlled Trial Number (ISRCTN) scheme assigns a unique randomised 8-digit number to each trial to ensure that a trial can be tracked unambiguously throughout its life.
www.controlled-trials.com/isrctn/

metaRegister: an international compilation of registers of completed and ongoing trials including randomised controlled trials sponsored by the UK Medical Research Council, the National Health Service (NHS), and the US Department of Veterans Affairs Co-operative Studies Program.
www.controlled-trials.com/mrct

TrialsCentral.org: a database of clinical trials bringing together over 200 US-based trial registers. It is run by Kay Dickersin, an epidemiologist at Brown Medical School who researches clinical trials, systematic reviews, and related methodological topics.
www.trialscentral.org

UK Inquiry Update

We have created a special feature on our website to keep readers informed about the written and oral evidence presented to the UK's House of Commons Science & Technology Committee.

"I think that the whole open access movement has made us realize that there is a real requirement, and a desire for people to have open access in certain circumstances."

John Jarvis, Managing Director of Wiley Europe Ltd

"We now have the means to create an online public library containing the collected published work of every scientist and physician, to scientists, teachers, students, physicians and the public around the world."

Harold Varmus, President of the Public Library of Science

"All of us are committed to increasing accessibility of scientific content."

Crispin Davis, Chief Executive of Reed Elsevier

"Let us be careful because this rather enticing statement that everybody should be able to see everything could lead to chaos."

John Jarvis, Managing Director of Wiley Europe Ltd

"The government is urged to seek to reverse the traditional publishing models and encourage a competitive Open Access model... which delivers the benefits of maximal dissemination and unrestricted use of scientific research literature."

Jan Velterop, Publisher, BioMed Central

www.biomedcentral.com/openaccess/inquiry

register and the US Department of Veterans Affairs Co-operative Studies Program. Access to the ISRCTN Register and *metaRegister* is free online. CCT provides access to over 15,000 trial records in all areas of health care.

Who is behind Current Controlled Trials?

Current Controlled Trials Ltd is part of the Current Science Group of biomedical publishing companies, which includes BioMed Central (publisher of *Open Access Now*). The Managing Director of Current Controlled Trials Ltd is Anne Greenwood who has over twenty years of experience in academic publishing. The company benefits from guidance by an international Advisory Group, including academics, doctors and healthcare specialists. The Advisory Group is chaired by Gerd Antes of the German Cochrane Centre.

Why does Current Controlled Trials exist?

Current Controlled Trials Ltd launched the CCT website in late 1998 with the aim of increasing the availability and exchange of information about ongoing randomized controlled trials worldwide. CCT provides detailed and accurate information to researchers and clinicians about trials being conducted in all areas of healthcare; helps research funding agencies (public, commercial or charitable) to avoid duplicating research and to promote collaborations; and provides information that helps patients and clinicians to decide whether to actively participate in, and contribute to, ongoing clinical trials studies.

www.controlled-trials.com

Letters

Open Access authors express enthusiastic support and serious reservations

Dear Sir,

I have been a clinician for 30 years and just recently entered the field of scientific publishing. I have found the process of Open Access publishing to be of great value. I have now had three articles published in *Cardiovascular Diabetology*, an Open Access journal published by BioMed Central. As a newcomer to publishing and to use of the computer, I was impressed by the ease of the publishing process, the excellent staff support, and the quality of the peer-review process.

Publishing in *Cardiovascular Diabetology* has allowed me a rapid entry into the scientific community and has opened numerous doors, which would have remained closed to a late-blooming clinician-scientist like myself. Open Access online publishing has allowed me to make new friends in the scientific community all over the world. Seldom a day goes by without an email, a phone call, or a letter regarding our recent publications. This excites me and encourages me to do more in my field of study.

Thank you, BioMed Central, for your innovative courage and strength in providing a publication medium for sharing original ideas with the scientific and clinical community worldwide. Also, thank you my friends in the scientific and clinical community for reading, sharing ideas and comments, and encouraging me to continue my ongoing sabbatical in this exciting field of study.

Sincerely,

M.R. (Pete) Hayden, M.D.
Department of Family and
Community Medicine, University of
Missouri School of Medicine, USA.

Dear Sir,

The principles propounded for Open Access sounded quite promising initially and I was the first author to have a manuscript published in *BMC Nuclear Medicine*. But my support for Open Access has waned since then and now I strongly believe that Open Access should be discontinued. The reason is quite simple. Even from so called affluent countries, research costs billed to authors cannot be borne in many countries for which, unlike in the West, there is no organized system of

institutional support for research. Open Access will then be limited to either the 'rich' researchers, or those backed by an institutional system. For the majority of clinicians, who do high-quality research on their own, the added publication costs of Open Access will be a major stumbling block.

I would suggest a system like that of the *Journal of Clinical Endocrinology & Metabolism* as the way to go. All research becomes Open Access one year after publication. There are no author fees. This should be the face of Open Access, a way out for both authors and researchers.

Suhail A.R. Doi
Mubarak Al Kabeer Teaching
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Kuwait University, Jabriya, Kuwait.

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Read them
Cite them
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Who, What & Why?

As a short guide to the players and technical terms relevant to Open Access publishing, 'Who, What & Why?' keeps readers informed about the world of Open Access.

This week we feature Current Controlled Trials



What is Current Controlled Trials?

Current Controlled Trials (CCT) is an online publisher dedicated to providing services in the area of randomized controlled trials. These include trial registration and trial hosting. CCT has two main Open Access projects: the International Standard Randomised Controlled Trial Number (ISRCTN) scheme and the *metaRegister* of Controlled Trials.

The ISRCTN scheme assigns a unique randomized 8-digit number to each trial against a one-off administrative charge. This ensures that a trial can be tracked unambiguously throughout its life cycle. The *metaRegister* is an international compilation of registers of completed and ongoing trials. The *metaRegister* includes randomized controlled trials sponsored by the UK Medical Research Council (MRC), four National Health Service (NHS) registers, the National Library of Medicine's ClinicalTrials.gov