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INVITED MEDICAL REVIEW

What makes a high quality clinical research paper?

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The quality of a research paper depends primarily on the quality of the research study it reports. However, there is also much that authors can do to maximise the clarity and usefulness of their papers. Journals' instructions for authors often focus on the format, style, and length of articles but do not always emphasise the need to clearly explain the work's science and ethics: so this review reminds researchers that transparency is important too. The research question should be stated clearly, along with an explanation of where it came from and why it is important. The study methods must be reported fully and, where appropriate, in line with an evidence based reporting guideline such as the CONSORT statement for randomised controlled trials. If the study was a trial the paper should state where and when the study was registered and state its registration identifier. Finally, any relevant conflicts of interest should be declared.

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A high quality research paper should start with high quality research. But that's easier said than done. In new or particularly difficult areas of research, particularly when there are ethical constraints, imperfectly conducted studies often have to suffice. And when clinicians conduct studies the high relevance of their research may have to be traded off against limited methodological expertise and lack of specific funding. Good enough research is sometimes the best that's available.

Moreover, good research does not necessarily need great expertise or resourcing. It does, however, require good scientific method and objectivity. American sociologist Robert K Merton argued that science is underpinned by four moral elements: communalism (where scientists give up intellectual property rights in exchange for recognition and esteem), universalism (where truth is evaluated in terms of universal criteria), disinterestedness (where scientists are rewarded for acting in ways that appear to be selfless), and organised skepticism (where all ideas must be tested and are subject to rigorous, structured, community scrutiny) (Merton, 1942). To put it more simply: scientific advances involve the sharing and peer review of research questions that have been objectively tested.

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The research question

All too often, clinical research comes unstuck because it lacks a clear research question that is testable, answerable and, ideally, both original and important – unless it's a large enough study to require the support and close scrutiny of external funders at the planning stage. Too many studies done by clinical investigators are based on research questions which nobody really cares about, not even those investigators. This is often because they are driven by the need to get something – anything – published rather than by genuine scientific inquiry and the desire to fill a gap in the evidence base. And far too many studies begin with someone looking at routine clinical data and trying to see some patterns, rather than conducting a literature search and talking with other clinicians and statisticians to choose and refine a proper research question.

Relying on patients' records to yield up a research question is risky. Case notes and routine clinical databases often lack consistent, reliable information and may be biased and confounded by factors the investigator has no control over. This approach can result in what editors and statisticians call a fishing expedition, leading to data dredging and analysis of multiple outcomes and, in turn, to false positive results (type I errors) and false negatives owing to lack of power (type II errors). A statistician is often called in at this point, but it can be very hard to rescue a study which has been conducted back-to-front with no prior hypothesis and no clear sampling method.

It's also hard to rescue a paper that has been written from scratch after the study has ended. Editors and peer reviewers look for signs of scientific method. They weigh up the importance, relevance, and originality of the research question and decide whether the right methods have been used to answer it. They can tell when the literature has been searched only to compile a paper's introduction and discussion sections, rather than to design a protocol's background and methods. For many papers, the journal's rejection letter should probably say simply, 'I wouldn't start from here'.

Clear reporting of methodology

Doug Altman, professor of medical statistics, pointed out these problems 15 years ago, asking 'What should we think about researchers who use the wrong techniques (either wilfully or in ignorance), use the right techniques wrongly, misinterpret their results, report their results selectively, cite the literature selectively, and draw unjustified conclusions? We should be appalled. Yet numerous studies of the medical literature, in both general and specialist journals, have shown that all of the above phenomena are common' (Altman, 1994). Have things improved since then?

They have, but only slowly. A decade after Altman's challenge to researchers he coauthored a review of more than 500 published clinical trials, showing that more than half failed to state a primary outcome and two-thirds did not report whether blinding or masking was used (Chan and Altman, 2005). Over many years Altman and other methodologists have come to the rescue through publications on study design and analysis and through developing standardised ways of reporting research clearly and fully. The best known of these reporting guidelines is the CONSORT (CONsolidated Standards Of Reporting Trials) statement, which has been shown to improve the clarity and completeness of published randomised controlled trials (Plint *et al*, 2006). There are now more than 80 similar guidelines for different kinds of biomedical study and, helpfully, these are now all available in a free and open online library called the EQUATOR network (Enhancing the Quality and Transparency Of health Research http://www.equator-network.org/). If I were planning a study I would start from here.

Reporting guidelines usually comprise a checklist for stating which items in a submitted paper appear on which page, a flowchart to show the flow of participants and data through the study, and explanatory notes on why the various items matter. They prompt researchers to say unambiguously what they actually did and did not do in their study, how they did it, what they found, what worked and what did not, and what it means, thus aiding understanding and replication of a study and the translation of its findings into practice or policy. And, although the guidelines were designed to help authors write their papers, they also provide excellent templates for designing studies. Indeed, in 2010, the first guideline produced specifically for planning studies will be published: the SPIRIT statement for clinical trial protocols (Standardized Protocol Items for Randomized Trials http://www.equator-network.org/resource-centre/library-of-health-research-reporting/reporting-guidelines-under-development/).

Trial registration

Thorough and transparent reporting of clinical trials is particularly important. Their results underpin many clinical policies and funding decisions about treatments, and it is vital that their findings are robust and reliable. Until recently many trials were suppressed if their results disappointed or were reported selectively (Dickersin and Rennie, 2003). To ensure that all planned trials see the light of day, increase researchers' accountability, avoid unnecessary duplication, and encourage recruitment of patients many sponsors, funders, and publishers of biomedical science now mandate the prior registration of clinical trial protocols. To ensure that all trial registries include the same kind of information the World Health Organisation has developed a minimum dataset and a web portal that provides links to the major national and international trial registries (http://www.who.int/ictrp/).

Legislators have weighed in too. The US Food and Drug Administration (FDA) Amendments Act 2007 requires the registration at clinicaltrials.gov of the designs and results for all trials of products needing FDA approval (US Food and Drug Administration, 2007). The only exceptions are phase I drug trials and small feasibility studies of medical devices. Since September 2008 the main results of all such trials also have to be posted at clinicaltrials.gov, within a year of seeing the last patient in the trial. In 2009 reporting of harms was added to the requirements, and the next step may be a lay summary of the results. Noncompliance leads to heavy fines and public naming and shaming. The European Commission is following suit: it now requires the registration of paediatric trials and their results in the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database, and plans to extend this to adult trials shortly (European Commission, 2009).

Editors have also helped to give the campaign teeth. The journals on the International Committee of Medical Journal Editors (ICMJE http://www.icmje.org) now refuse to consider papers reporting unregistered trials and the committee encourages all biomedical journals to do the same. The ICMJE defines a clinical trial as 'any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioural treatments, process-of-care changes, and the like'. The policy was introduced with a wash-in period. Trials randomising human participants to investigate the cause and effect relationship between a medical intervention and a health outcome that commenced before 1 July 2005 can be registered retrospectively, but this must be done before submission to an ICMJE member journal. Trials that commenced after 1 July 2005 must have been registered prospectively, before enrolment of any participants. However, for trials where the intervention is not a medical product (for example is a health services or behavioural intervention) mandatory prospective registration only applies to those that commenced after 1 July 2008. Although all of these policies currently apply specifically to clinical trials there is increasing interest in registering all health research, including observational studies.

Publication ethics

Another important issue to sort out at the planning stage – as well as ensuring that the study will be conducted in an

ethical manner – is to agree on a publication plan among all the investigators. The path to successful research and a high quality paper should be relatively smooth if each investigator agrees at the start to keep an open mind, minimise bias, aim to publish even negative results, and agrees on everybody's roles. It is far better to decide before the study starts on who will be principal investigator, coauthors, and acknowledged contributors rather than leaving these things till the writing stage. Among the cases seen each year by the Committee on Publication Ethics (COPE) the worst are about fraud, plagiarism, redundant publication, and undeclared conflicts of interest, but by far the most numerous are about disputes between authors (Committee on Publication Ethics http://publicationethics.org/).

Writing the paper

There is no shortage of general advice on the web on how to write all kinds of scholarly medical articles. The most influential resource is the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (ICMJE http://www.icmje.org/urm_main.html), and this is the best place to start when sitting down to write a paper. These guidelines were initiated 30 years ago to save authors the bother of completely reformatting a manuscript when submitting it sequentially to several general medical journals. But now these uniform requirements have now been adopted by more than 800 journals, including Oral Diseases (http://www.wiley.com/bw/submit.asp?ref=1354-523X&site=1), and they encompass a wide range of editorial policies and advice on publication practice and ethics. Guidance from WAME (the World Association of Medical Editors), CSE (the Council of Science Editors), and COPE echoes and complements the uniform requirements.

Competing interests

International Committee of Medical Journal Editors latest contribution is a uniform declaration of competing interests (http://www.icmje.org/coi_disclosure.pdf), which the committee will pilot till April 2010 and then amend in the light of any important criticisms (Drazen *et al*, 2009). This asks authors to disclose four types of information 'Firstly, their associations with commercial entities that provided support for the work reported in the submitted manuscript (the time frame for disclosure in this section of the form is the lifespan of the work being reported). Secondly, their associations with commercial entities that could be viewed as having an interest in the general area of the submitted manuscript (the time frame for disclosure in this section is the 36 months before submission of the manuscript). Thirdly, any similar financial associations involving their spouse or their children under 18 years of age. Fourthly, non-financial associations that may be relevant to the submitted manuscript.'

Finding the right way to encourage authors to declare any relevant interests is a thorny issue, but it's one worth tackling. As one former editor-in-chief of *The New England Journal of Medicine* said 'Financial conflicts of interest threaten patient care, taint medical information and raise costs. They create deception, impair physicians' judgement and reduce their willingness to be their patients' advocates' (Kassirer, 2004). Editors cannot make people tell the truth, but they should certainly try, not least because there's plenty of evidence that undeclared interests can bias the evidence base (Bekelman *et al*, 2003; Jorgensen *et al*, 2006).

And finally

If researchers follow all of the advice highlighted here so far, they should have a good paper. The last two jobs are to find the right journal, ideally basing that choice mainly on the appropriate audience for the work and not just on journal prestige or impact factor, and then to follow the journal's instructions to authors very carefully. If you do not make the paper fit the journal format, you risk making it a tough read for the busy editors and reviewers, and you might blow your chances at the last minute.

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