Putting clinical trials into context

May 20, 2005, saw the first ever international clinical trials day,[1] celebrating the contribution of James Lind[2] to the concept of medical research and recognising that biomedical research can only be done as a partnership between the medical profession and the public. Biomedical research saves the lives of men, women, and children every day, in every nation around the world. However, biomedical research also poses risks.

Part of the danger associated with research is unavoidable: some new diagnostic techniques and treatments will be found to be less effective than the best alternative and some will be found to be harmful. This risk is underlined in consent procedures. It is the price paid for the altruism of participants in clinical research. More troubling are the dangers of research that are avoidable but incurred because of bad research practice. As societal awareness of problems associated with biomedical research grows, there is increasing recognition that bad research involves not only research conducted inappropriately, but also unnecessary research, research which is done but remains unpublished, and research which is published but not in a way that justifies its existence or its relevance. Unpublished research has recently been the focus of efforts to register certain types of clinical trial at, or as soon as possible after, inception.[3,4] But what of unnecessary and badly presented research?

Dean Fergusson and colleagues[5] recently illustrated the problems of unnecessary and badly presented research with the example of aprotinin to reduce perioperative blood loss. Using cumulative meta-analysis, they show that although 64 trials investigating the effectiveness of aprotinin were published between 1987 and 2002, its effectiveness, and effect size, were clearly established after the 12th trial in 1992 (figure). The following 52 trials were unnecessary and unethical, and wasted resources that could have been invested in more worthy work. In an associated comment,[6] Iain Chalmers explains how this is not only a failure in the integrity of the investigators doing those 52 trials, but also of the institutions that funded the research, the ethical bodies which permitted it, and the journals which continued to publish the results despite the fact that they contributed little or nothing to the scientific record. Moreover, this lack of contribution was not apparent from the published results because only a tiny percentage made any reference at all to the almost identical studies that had preceded them.

Continuing this theme, Ruth Gilbert and colleagues[7] examined the evidence about positioning sleeping babies on their back rather than their front to avoid sudden infant death syndrome. They found that although widespread advice to place babies on their backs was only disseminated from the early 1990s, the benefits of this strategy could have been apparent if systematic reviews of known risk factors had been done at any point after 1970. Such a review could have prevented around 10 000 deaths in the UK and possibly 50 000 in Europe, the USA, and Australasia.

In recognition that journal editors have a key part to play in ensuring that published research is presented in a way that clearly illustrates why it was necessary and what impact a particular trial has on the existing state of knowledge, *The Lancet* has decided to update its policies in this area. From August, 2005, we will require authors of clinical trials submitted to *The Lancet* to include a clear summary of previous research findings, and to explain how their trial's findings affect this summary. The relation between existing and new evidence should be illustrated by direct reference to an existing systematic review and meta-analysis. When a systematic review or meta-analysis does not exist, authors are encouraged to do their own. If this is not possible, authors should describe in a structured way the qualitative association between their research and previous findings.

Unnecessary and badly presented clinical research injures volunteers and patients as surely as any other form of bad medicine, as well as wasting resources and abusing the trust placed in investigators by their trial participants. Those who say that systematic reviews and meta-analyses are not "proper research" are wrong;[8] it is clinical trials done in the absence of such reviews and meta-analyses that are improper, scientifically and ethically. Investigators and organisations who undertake and coordinate reviews and meta-analyses now need the funding and recognition they deserve if public trust in biomedical research is to be maintained and resources used in an effective way.

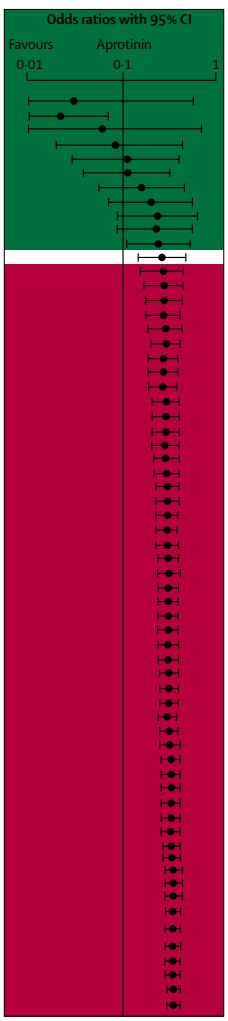

Figure: **Cumulative meta-analysis of aprotinin for perioperative bleeding**
Odds ratio of benefit in 64 randomised trials. After trial 12 (white), benefit was clear and subsequent 52 trials (red) were unnecessary. Adapted from reference 5 with permission.

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1 European Clinical Research Infrastructures Network. May 20th 2005, the first international clinical trials' day. May 20, 2005:http://www.ecrin.org/ecrin_files/news.php?level=1 (accessed July 4, 2005).

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3 De Angelis CD, Drazen JM, Frizelle FA, et al. Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors. *Lancet* 2005; **365:** 1827–29.

4 Gulmezoglu A, Pang T, Horton R, Dickersin K. WHO facilitates international collaboration in setting standards for clinical trial registration. *Lancet* 2005; **365**: 1829–31.

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6 Chalmers I. The scandalous failure of science to cumulate evidence scientifically. *Clin Trials* 2005; **2:** 229–31.

7 Gilbert R, Salanti G, Harden M, See S. Infant sleeping position and the sudden infant death syndrome: systematic review of observational studies and historical review of recommendations from 1940 to 2002. *Int J Epidemiol* April 20, 2005: DOI:10.1093/ije/dyi088 [Epub ahead of print].

8 Chalmers I. Academia's failure to support systematic reviews. *Lancet* 2005; **365:** 469.

What's maths got to do with it?


DISCORSI
E
DIMOSTRAZIONI
MATEMATICHE,
intorno à due nuove scienze
Attenenti alla
MECANICA & i MOVIMENTI LOCALI,
del Signor
GALILEO GALILEI LINCEO,
Filosofo e Matematico primario del Serenissimo
Grand Duca di Toscana.
Con una Appendice del centro di gravità d'alcuni Solidi.
IN LEIDA,
Appresso gli Elsevirii. M. D. C. XXXVIII.

Galileo's masterful *Discorsi e dimostrazioni matematiche* was first published in 1638 by Elzevir (the forerunner of Elsevier, *The Lancet*'s proprietors). He would not have had trouble multiplying 4 by −5, although negative numbers might not have been in general use then. Seemingly, all these centuries later, many do have such a difficulty. . . when they try to use a calculator. Researchers at the University of Swansea in the UK therefore developed a handheld calculator (from research called a "weapon of math construction") controlled by a stylus, to solve the input of complex expressions.[1] Apparently, people get such expressions wrong just over half the time with a traditional calculator. With the stylus control, only a fifth got wrong answers. It is unclear why anyone would need a calculator to solve 4×-5.

The other week, I surprised myself, when buying a cell phone, by doing longhand multiplication and division (on paper) to work out unit rates faster than the salesperson could find the answers with a calculator (ok, he got flustered as he side-eyed me). I stopped formal maths learning after O level, but all that drilling in of simple arithmetic has stayed with me. I do not mean to boast. I could not solve $x!=5040$ with or without the new Swansea calculator, but I know enough not to try—I do not know what it means. That is an important lesson: calculators are fine, but you need to mentally work out that the displayed result is in the correct range.

The Manchester Institute for Mathematical Sciences is sufficiently worried about maths training to have released a report, *Where will the next generation of UK mathematicians come from?*[2] The maths buffs describe a gloomy "spiral of decline" in the numbers of students taking maths at A level. They fear that the UK maths community will not be able to "reproduce itself".

The cloning analogy leads to the life sciences. Some, like me, thought we could escape maths by sticking to biology. How wrong could we be? Maths is the foundation stone of biological science and medicine. Without it, there would be no measuring, dosing, and risk assessing—let alone formal statistics and epidemiology. To my cost, I learnt that I should have studied maths for longer.

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1 Turner R. Calculator that could change exams forever. *Western Mail* July 2, 2005: http://icwales.icnetwork.co.uk/0100news/0200wales/tm_objectid=15691362&method=full&siteid=50082&headline=-weapons-of-maths-construction---the-calculator-that-could-change-exams-forever-name_page.html (accessed July 4, 2005).

2 Manchester Institute for Mathematical Sciences. Where will the next generation of UK mathematicians come from? June 27, 2005: http://www.ma.umist.ac.uk/avb/wherefrom.html (accessed July 1, 2005).