Translated from ***Rev Prescrire*** **July/August 2006; 26 (274): 533-534**

Clinical trials in France: too many unpublished results

What becomes of clinical research projects once they have been approved by French ethics committees? Did the work actually start? Was it completed? Were the results published? And if not, why not? Did the nature of the results influence the decision to publish?

A French team based in Lyon conducted a retrospective study of a random sample of 25 of the 48 ethics committees in France (1).

A representative sample of official research in France. This was the first nationwide study of its type to be conducted in France (1). All of the committees agreed to participate. The authors studied 976 protocols approved in 1994, based on the committees' files and on the answers given by investigators responsible for protocols approved in 1994 (1).

In particular, the investigators were asked questions concerning the funding and duration of each study, the number of subjects enrolled, adverse effects, the status of the study (not started, abandoned, underway, completed), the reasons for abandoning the study, the nature of the results, and their publication.

Two-thirds of the investigators responded. Among 976 questionnaires that were sent out, 305 were not returned (non response rate 31%), and 22 were returned but uninterpretable (2%). The analysis therefore involved 649 protocols. Most were research projects assessing a drug (68% of cases); most received private funding (73% of cases); and most were conducted nationwide (82% of cases) (1).

Most studies completed… but not published. 581 of the 649 protocols (90%) were started (**a**). 501 of these 581 (86%) were completed (**b**) and of 190 of these 501 (38%) led to publication(s) in a scientific journal. Preliminary results of 7 of the 16 ongoing studies and of 8 of the 64 interrupted studies were also published (1).

In total, the investigators found that, 6 to 8 years after their approval by an ethics committee, 62% of completed clinical research protocols had not been published.

Too many "negative" results left unpublished. A publication bias exists when a sponsor, an author or a journal decides not to publish a study because the results are "negative", in other words do not support (or possibly disprove) the working hypothesis (2,3).

With a follow-up of 6 to 8 years, the authors calculated that a study had 4.6 times more chance of being published when the results confirmed the principal hypothesis. The main reason (26% of cases) for non publication of a completed study was that the results were "uninteresting" according to investigators; this occurs much more frequently than rejection of the manuscript by the target journal (only 5% of cases) (1).

Solution: an international research registry. Deliberate non publication of research findings conceals valuable information from the scientific community, patients and healthcare authorities. The publication bias introduces an underlying imbalance in published data that falsifies the conclusions of review articles and, as a result, undermines healthcare professionals' decisions. In general, it means that the efficacy of a new drug or diagnostic test is overestimated (3).

The authors of this study, and a growing number of institutions throughout the world, recommend that all human research protocols be systematically listed in a register so that their outcome can be monitored (**c**) (1,4).

Concrete action by ethics committees. Approval of research protocols by ethics committees should be conditional on obligatory and preliminary recording in a register of clinical trials, consistent with the norms recommended by the World Health Organization (5). In France, a decree dated 26 April 2006 dealing with biomedical research describes how the authorities should list research protocols in registries, unless the sponsor has valid reasons for opting out of this obligation (6,7). The decree provides for far less transparency than it should: only patient groups and healthcare consumers can request information, and their requests must not be judged excessive "*by their number, or systematic or repetitive nature*" (6).

a- *The reasons given for not starting trials included: a sponsor's veto (21 cases), problems of patient recruitment (15 cases), technical reasons or non feasibility (9 cases), and lack of funding (8 cases) (ref 1).*

b- *Reasons for non completion (64 cases) included: recruitment difficulties (28 cases), results of an interim analysis (13 cases), adverse effects (8 cases) and the sponsor's decision (8 cases) (ref 1).*

c- *There are currently at least two international registers meeting all the criteria set out by the World Health Organization: the International Standard Randomised Controlled Trial Number Register (http://www.controlled-trials.com/isrctn) and the register of the National Institutes of Health (http://www.clinicaltrials.gov) (refs 4,5). In Europe, and for drug trials only, sponsors are already required to register their protocols in the European trials database (EudraCT, http://eudract.emea.eu.int) of the European Medicines Agency, but this register is not accessible to the public. The main biomedical journals decided in 2005 to no longer publish the results of trials that are not recorded in a public trial register before the first enrolment takes place (ref 8).*

Selected references from Prescrire's literature search.

1- Decullier E et al. "Fate of biomedical research protocols and publication bias in France: retrospective cohort study" *BMJ* 2005; **331**: 19-22.
2- Prescrire Rédaction "Trop d'essais cliniques négatifs non publiés" *Rev Prescrire* 1999; **19** (196): 465-466.
3- Prescrire Rédaction "Les biais de publication" *Rev Prescrire* 1994; **14** (146): 718-720.
4- Krleza-Jeric K "Clinical trial registration: the differing views of industry, the WHO, and the Ottawa Group" *PLoS Med* 2005; **2** (11): 1093-1097.
5- World Health Organization "International Clinical Trials Registry Platform". Website http://www.who.int/ictrp accessed 20 April 2006.
6- "Décret n°2006-477 du 26 avril 2006 modifiant le chapitre Ier du titre II du livre Ier de la première partie du code de la santé publique relatif aux recherches biomédicales (dispositions réglementaires)" *Journal Officiel* 27 April 2006: 23 pages.
7- Prescrire Rédaction "Essais cliniques: de nouvelles règles pour la protection des personnes" *Rev Prescrire* 2005; **25** (267): 858-863.
8- De Angelis CD et al. "Cet essai clinique est-il entièrement inscrit? Déclaration du Comité international des rédacteurs de revues médicales" *CMAJ* 2005; **172** (13): online 1-3.