Extensive publication bias for Phase I drug trials

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A study published in this week's issue of the open-access journal *PLoS Medicine* suggests that, in comparison to other types of trials, the results of Phase I drug trials are far less likely to be published.

In the study, Evelyne Decullier and colleagues from the University of Lyon, France, and Mayo Clinic in Rochester, Minnesota studied the outcomes and fate of a series of pharmaceutical trials approved by 25 research ethics committees in France. Development of new drugs typically follows a set pattern, with a new drug tested in humans for the first time in Phase I trials.

These studies are generally carried out amongst small numbers of healthy people (but occasionally patients) in order to get an initial idea of the drug's toxicity and safety, and to understand how it is metabolized in the body. Later trials (termed Phase II, and then Phase III studies) aim to evaluate whether the drug is effective at treating a particular disease in small, and then larger, numbers of patients. Before a clinical trial in patients can be conducted, the investigators obtain approval from their local research ethics committee, which evaluates a detailed plan for the study (termed the protocol).

Existing evidence suggests that the results of many trials are not made public, a phenomenon termed publication bias. However many of these studies have focussed on the characteristics of Phase II and III trials, and it is not clear whether publication bias is also a problem for Phase I trials.

In their study, Decullier and coworkers collected data from the research ethics committee files, and specifically the study protocols, for a series of 444 trials (140 Phase I trials, and 204 Phase II-IV trials). Trial investigators were contacted to find out if study results had been published. By the time the data were collected, 17% of the Phase I studies had been published in scientific journals, whilst 43% of the Phase II-IV studies were published. For around half of the Phase I trials, the results had not been made publicly available in any form, with confidentiality given as the main reason for not disseminating results.

The authors argue there is a strong ethical imperative for addressing publication bias for Phase I studies, saying that "The testing of new pharmaceuticals on humans is approved by ethics committees based on the assumption that the inherent risks of trial participation are balanced by the benefit of new scientific knowledge for society… If this knowledge from Phase I remains hidden, then any potential risk incurred by trial participation is excessive and could endanger human lives". A strength of the work is that the findings are generally representative of trials initiated across phases in France. Limitations include the age of the cohort of trials studied, and the low response rate from investigators (which meant that for many of the trials, the investigators could not find out whether they had been completed, and published).

There is now general agreement by journal editors and public bodies such as the World Health Organization that all trials in humans must be registered before participants are enrolled, so that the existence of the study is made public. In addition, legislation is now in place in the US (the FDA Amendments Act of 2007) which mandates registration, and public release of trial results within a year of completion, via the ClinicalTrials.gov website. However, this legislation excludes Phase I studies. The findings from Decullier and colleagues' study suggest that additional mechanisms are needed to ensure complete availability of results findings from Phase I trials.