Is clinical research still too haphazard?

Sir—Sarah Ramsay reports, in her July 21 news item, the death of a young volunteer in the Johns Hopkins study on hexamethonium, from pulmonary complications believed to be due to adverse effects of 1 g of the drug administered by inhalation. We believe that the case reflects features of physiological and clinical research that remain too haphazard, not as a consequence of the failure of individual researchers, but rather of a system that has not promoted the use of evidence-based methods in medical research.

Before embarking on new research, available evidence needs to be synthesised. The principle of building systematically on what is already known ensures that two important requirements are met: the ethical requirement of patients’ right to the best possible assessment of existing evidence about the benefits and risks of the treatments to which they are exposed, and the scientific requirement of explicit methods to design, conduct, and analyse research.

The world of research has not yet adopted principles that are widely accepted in clinical practice. The evidence-based medicine movement has highlighted the need for transparent and explicit methods in patients’ care and clinical research. Questions should be clearly formulated, and potentially eligible studies defined and sought by explicit search strategies.

We assessed how a systematic approach could have been used in a study such as the Johns Hopkins’ study. The investigators wanted to study the effect of hexamethonium on bronchodilatation in healthy volunteers challenged with a bronchoconstrictive agent. The systematic search for relevant existing evidence before the study needed to focus on adverse events of hexamethonium. Since the drug has not been used since 1972, to learn about the toxic profile, evidence should have been searched from the period of clinical use. An explicit search strategy must be provided and systematic reviews included in the reference list to allow members of the institutional review board to assess the comprehensiveness of the search methods.

We found additional data on adverse events of hexamethonium even in studies published after 1980, on three commonly used databases—MEDLINE, Old Medline, and Cochrane Controlled Trials Register. We found at least seven such reports, and an additional nine in the references of those reports. Five reports refer to pulmonary complications of hexamethonium in the title.

Proposals for new research should begin with a transparent and scientifically defensible systematic review of existing evidence. These features of research proposals are too commonly thought of as trivial and mundane by researchers and by institutional review boards, but they are crucially important.

Fortunately, these matters seem to be being taken more seriously. For example, the UK Medical Research Council and the Danish National Research Ethics Committee System now require investigators proposing new research to provide references to relevant systematic reviews and to discuss the need of the trial in the context of review. If researchers believe that their proposed study is the first to address a particular question, they must provide details of the search strategy they have used to try to locate other relevant research. We suggest that these principles be adopted more widely.

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