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Continued Overleaf

Mandatory registration of clinical trials

The ICMJE statement is salutary and timely but implementing its recommendations may pose some problems for less affluent nations

The International Council of Medical Journal Editors (ICMJE) released two joint editorial statements recently [1, 2] on registration of all clinical trials in a public registry with open access. These statements have consequences for biomedical researchers, funding agencies (including the pharmaceutical industry), clinicians, institutions devoted to safeguarding human rights, human volunteers in clinical trials and medical journal editors, that are more profound and far-reaching than the ICMJE's famous previous statements on uniform requirements for manuscripts submitted to biomedical journals. The *BMJ* has supported the concept of registration of clinical trials but differed on the type of registry [3, 4].

There is no gainsaying that the world of clinical trials is presently too opaque, inscrutable and secretive for the public weal. The public has a right to know what sort of research is being done, particularly the ones in which healthy volunteers or patients are participants, whether public funds are used for them or not. Adverse or negative results of clinical trials only rarely get published, and funding agencies, both public and private, may allocate money for trials that are already in progress or for ones that have been done but not published, unless all clinical trials are entered in an accessible registry before they are started.

Many researchers with foreign funding, and the pharmaceutical industry, are keenly aware that effective regulatory and surveillance mechanisms in regard to clinical trials are either non-existent, or at best less stringent and more easily amenable to unethical manipulation in the vast majority of developing countries, when compared with affluent ones. The temptation to abuse such lacunae is great. And the history of biomedical research is, unfortunately, littered with too many examples of damaged human bodies—nearly all of them black or brown, poor, illiterate or semi-literate, and politically weak—for humane doctors and their professional associations to remain complacent, or even to exult too much in the undoubtedly magnificent successes of good research.

Dr. Ruth Macklin, Professor in Bioethics at the Albert Einstein College of Medicine in New York, has published a comprehensive list of fundamental principles applicable to biomedical research in developing countries in her superlative book titled, "Double standards in medical research in developing countries"[5]. Two of the principles merit mention here: (a) There can be no justification for conducting research in a developing country when the same research could not ethically be conducted in the USA or Europe. (b) Since the burden of serving as research subjects falls upon the developing countries, the population in those countries… deserves the same type of benefits that flow to the wealthier or insured populations in countries that sponsor research.

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The ICMJE statements on registration of clinical trials are important initial steps towards making them fully transparent and accessible for examination by stakeholders. In 1999, the editors of the *BMJ* and *Lancet* wrote, "The case for registering all clinical trials – first advanced a decade ago [6]–is now unanswerable" [7]. But for five years thereafter, the pharmaceutical industry predictably mounted a formidable resistance to the idea of mandatory registration, powerful governments displayed inattention or feigned impotence, and major medical journals produced many words of wisdom but no decisive action. Now, at last, action has started in earnest. All ICMJE journals, and others that endorse their statement, will insist on registration for trials, starting enrollment of participants after 1 July 2005, before considering them for publication, with a grace period until 13 September 2005 for trials that had started enrolling before July. All trials must have obtained acceptable ethical committee approval too.

The registry should have at least the following information about the trial: a unique identifying number, a statement of the intervention (or interventions) and comparison (or comparisons) studied, a statement of the study hypothesis, definitions of the primary and secondary outcome measures, eligibility criteria, key trial dates (registration date, anticipated or actual start date, anticipated or actual date of last follow up, planned or actual date of closure to data entry, and date trial data considered complete), target number of subjects, funding source, and contact information for the principal investigator.

What sort of trials must be registered? The ICMJE thinking [2] on this point is as follows:

"Any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. By 'medical intervention' we mean any intervention used to modify a health outcome. This definition includes drugs, surgical procedures, devices, behavioural treatment, process-of-care changes, and the like. We update our 2004 editorial to state that a trial must have at least one prospectively assigned *concurrent* control or comparison group in order to trigger the requirement for registration".

This definition encompasses all "clinically directive trials", i.e. trials that test a clinical hypothesis about health outcomes. Excluded from mandatory registration are trials that seek to assess major unknown toxicity or determine pharmacokinetics (i.e. phase 1 trials). In doubtful cases, the advice given to researchers and authors is the same as for obtaining ethical review committee approval: if in doubt, register.

What are the criteria for a suitable trials registry? The *BMJ's* criteria [3] are shown in Box 1.

Box 1. **Criteria for a clinical trials registry**

- Free to access, searchable, and identifies trials with a unique number.
- Registration is free or has minimal cost.
- Registered information is validated.
- Registered entry includes details to identify the trial and investigator and includes the status of the trial.
- The research question, methodology, intervention, funding, and sponsorship must all be disclosed.

What should be the stance of the *Ceylon Medical Journal* regarding mandatory clinical trials registration? We ought to support the concept and work towards establishing a public registry. The *Sri Lanka Medical Association* is ideally positioned to take the pivotal role in that endeavour,

with funding contributions from the professional colleges, Ministry of Health, and the WHO (which has already taken some promotive and facilitatory initial actions in this regard [4,8]. Our *Journal* already has a policy decision in place not to consider for publication papers reporting clinical trials that have not received approval from an acceptable ethical review committee, before the trial started enrolling participants. When a suitable trials registry has been established, we will fall in line with the recent recommendation of the ICMJE [1–4].

Meanwhile, we urge all medical professional bodies and all editors of journals publishing biomedical research in Sri Lanka to support this ICMJE concept, and the Sri Lanka Medical Association to take all necessary steps, as a matter of priority, to establish a registry of clinical trials. To demur or delay now would place in peril the status of our biomedical journals, the international standing of our profession, and much more importantly, the altruism of our people who volunteer for clinical trials, as well as the trust and confidence patients have reposed in us.

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