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.
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,
Leading articles

Intra-ocular nematode worms: rare but important

Clinicians need help from a parasitologist for accurate identification

Migration of nematode larvae in the human body is a normal part of the life cycle of many parasites. Ocular disease caused by the abnormal migration of human or animal, juvenile or adult nematode worms in the eye is uncommon, but important as they induce visual impairment and pose diagnostic and management challenges. The detection of a worm, in or near the eye, is always a dramatic occurrence for both patient and clinician. Such patients frequently complain of the sensation of movement of an object in the eye, and the clinician can occasionally see the worm in the conjunctiva, on the eye itself, or in the anterior or posterior chambers.

The nematodes that have been isolated from the human eye are of human or animal origin and belong to different groups, including filariae, strongylids, metastrongylids and ascarids [1]. Parasites infect the eye either by extension from the infected adjacent tissues, or by haematogenous dissemination to the eye.

The adult worm of *Wuchereria bancrofti*, the causative agent of lymphatic filariasis, is found in the lymphatics, but has also been recovered and clearly identified from intra-ocular locations in humans. Fernando [2] described the first local case of adult *W. bancrofti* in the anterior chamber of the human eye. Although numerous reports of filarial infection of the human conjunctiva and the anterior chamber have been published [3–5], infections of the vitreous are rare. This issue of the journal (page 167) reports an instance of a *W. bancrofti* juvenile female worm extracted from the vitreous of eye—the first report of such a case in the world [6]. It is difficult to identify a female specimen of a filarioid with certainty, but the position of the vulval opening in relation to the oesophagus is an indication of the species [7].

*Loa loa* is a subcutaneous filarial parasite of humans, endemic in west and central Africa. It is reported sporadically from other parts of the world in travellers returning from endemic areas. This parasite has been reported in Sri Lanka in an expatriate girl who had been infected in Nigeria, hence classified as an imported infection [8]. Eye infections may occur when the adult

References


Colvin Goonaratna, Editor, Ceylon Medical Journal, 6 Wijerama Mawatha, Colombo; e-mail: <colvin_goonaratna@yahoo.com>.

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.

References


Colvin Goonaratna, Editor, Ceylon Medical Journal, 6 Wijerama Mawatha, Colombo; e-mail: <colvin_goonaratna@yahoo.com>.