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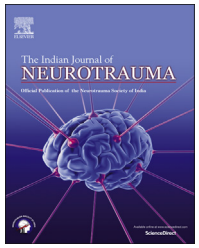

Editorial

The death knell for academic led clinical trials in India?

On the 10th December, 2013, the Times of India announced that 'India is head-injury capital of the world. Even with best available prevention programme, patients will continue to need treatments to save their lives and minimise disabilities from traumatic brain injury (TBI). The best way to make sure patients get effective treatments is through the conduct of well-designed randomised controlled clinical trials'.

However, recently in India, clinical trials have developed a bad reputation. In 2009, ethical concerns were raised by Sandhya Srinivasan and Sachin Nikarge from the Centre for Studies in Ethics and Rights, Mumbai, India. They concluded that some trials exploited the fact that most Indians do not have access to good quality and affordable care and therefore may accept offers that might provide better quality and free treatment (such as those available in clinical trials). They reported that trials were conducted on people who were vulnerable because they could not afford good quality treatment or the most effective drugs. These patients were also vulnerable because they were seriously ill.[1] Further, in March 2013, the Indian Health Minister testified in the Rajya Sabha, the upper house of the Parliament, that between 2005 and 2012 over 2868 deaths were recorded during government-approved clinical trials of new drugs. Of these, 89 have been officially accepted as clinical trial-related.

To assure the safety of trial participants and to streamline the conduct of clinical trials, three new amendments have been introduced in the Drugs and Cosmetics Rules; one in January and two in February with a new notification of intention change made in November 2013. By these Rules, it has been made mandatory that before starting any trial, compensation for any injury or death during the trial has to be prescribed, permission has to be taken from Drug Controller General of India (DCGI) to conduct the study, the Ethics Committee (EC) has to be registered with the DCGI before recruitment of any trial participants, all Serious Adverse Events (including death for whatever cause have to be forwarded to the DCGI Expert Committee for review) and in addition to written, audio–visual recording of consent is needed.

The following detail the changes made to the Drugs and Cosmetics Rules:

1) Insertion of Rule 122-DAB in the Drugs and Cosmetics Act, 1945. Drugs and Cosmetics (First Amendement) Rules 2013 [relating to Insurance, 30 January 2013].[2]

Rule 122-DAB states the requirement for providing free medical management as long as required, in the case of an injury occurring to a clinical trial subject. If the injury suffered by the trial subject is related to the clinical trial, they shall also be entitled to financial compensation as per the order of the Licensing Authority. In the case of a clinical trial related death of the participant, financial compensation, as per the order of the Licensing Authority, has to be compensated to the nominee(s) of the deceased subject.

2) Insertion of Rule 122 DAC in the Drugs and Cosmetics Rule, 1945. Drugs and Cosmetics (Second Amendment) Rules 2013 [relating to permission to conduct clinical trials and SAE reporting – 1 February 2013].[3]

Rule 122 DAC states that the Licensing Authority must be satisfied that the proposed clinical trial fulfils the conditions set out in the amendment and must grant permission for the study to be conducted. Additionally these rules allow the Licensing Authority to impose any additional conditions upon the clinical trial it considers necessary regarding the objective, design, subject population, subject eligibility, assessments, conduct and treatment. All SAEs [as defined by the rule] must be forwarded to the DCGI within 10 days for review by the expert committee.

3) Insertion of Rule 122 DD in the Drugs and Cosmetics Rule, 1945. The Drugs and Cosmetics (Third Amendment) Rules 2013 [relating to Ethics Committee registration, 8 February 2013].[4]

Rule 122 DD states that no Ethics Committee shall review and accord its approval to a clinical trial protocol without prior registration with the Licensing Authority.

4) Office Order dated 19 November 2013.[5]

Following the Supreme Court Order dated 21.10.2013, it is now a requirement that in addition to obtaining written informed consent, an audio–visual recording of the informed consent process is completed and the documentation preserved adhering to the principles of confidentiality. The audio–visual recording should include the procedure of providing information to the subject and their understanding of such information. This is applicable to the new subjects to be enrolled in all clinical trials including Global Clinical Trials.

What do these changes mean for patients and researchers?

The fact that many patients in India do not have access to good and affordable treatments is a societal problem. One way in which this can be addressed is to find cost-effective interventions. Many patients and their families are made to pay for interventions for which there is no evidence of effectiveness. Most interventions used to treat traumatic brain injury (TBI) are yet to be shown to be effective. In 1998, a systematic review by Roberts et al showed that there was no evidence for the effectiveness of five interventions routinely used in the intensive care management of severe TBI.[6] Another review, ten years later by Ker et al (2008), showed that the majority of treatments for TBI still had no evidence to support their use.[7] The only Class A evidence for the treatment of TBI came from the MRC-CRASH trial which showed that a treatment (corticosteroid) which had been in routine use for many years increased the risk of death (MRC-CRASH trial Collaborators, 2004).[8] It was estimated that thousands of lives had been lost in Europe alone through the use of this unproven treatment. The MRC-CRASH trial conducted by academics and clinicians and funded by the UK Medical Research Council stopped the routine use of corticosteroid for TBI. This lead to lives being saved and prevented patients and families wasting their limited funds on an ineffective treatment. India, as the 'head-injury capital of the world' contributed patients to this trial and reaped the benefits of resolving this uncertainty.

With the changes currently being initiated to the conduct of clinical trials in India, the MRC-CRASH trial could not have taken place. Firstly, the Sponsor was an academic institution, which could not undertake to comply with Rule 122-DAB,[2] which lays down the requirement of providing free medical management as long as required, in the case of an injury occurring to a clinical trial subject. For example, if a patient had fallen due to paralysis suffered as a result of their TBI and suffered a fracture, the Sponsor, under the new Rule would be responsible for all costs associated with this event until resolution. This lays the weight of societal burden of adequate patient care and ongoing financial commitment on academic institutions for an unknown length of time.

Mortality from TBI is high (well over 20% in moderate to severe cases).[8] Families will need to be compensated in all cases of a fatal outcome of the TBI whether associated with the trial intervention or not. Why is compensating families for an expected outcome of TBI appropriate or ethical?

The fact that all deaths (classified as a Serious Adverse Event) must be forwarded to the DCGI within 10 days for review by the expert committee means that the primary outcome of the MRC-CRASH trial would have been compromised, as the only way the expert committee could have assessed attribution to a treatment would be for each patient to be unblinded. As the trial was powered on a sample size of 20,000, the number of patients recruited in India would have been insufficient for the DCGI expert committee to make any meaningful decisions. The trial had in place a global Independent Data Monitoring Committee charged with overseeing the safety of all participants, utilising all data gathered globally to make the best decision for all patients in the trial.

The MRC-CRASH trial included patients with moderate to severe head injuries, who were unable to give informed consent. The consent procedure followed the Declaration of Helsinki and the ICH-GCP Guidance on the need for consent in the emergency situation. The latest Supreme Court Order, for the addition of audio–visual recording to the informed consent process, will make trials in TBI impossible.

The review by the Government of India identified that there were 89 deaths related to the conduct of clinical trials in a seven-year period. However, the academic led CRASH-2 trial was a large, randomised trial involving over 20,000 adult patients in 274 hospitals across 40 countries.[9] The results of this trial showed that the drug tranexamic acid (TXA) a cheap, widely available treatment, manufactured by many generic companies in India, with a sound safety profile and easily administered, has the potential to prevent up to 100,000 deaths per year across the world. In India alone, the number of deaths which could be prevented is 12800 deaths per year. Yet there is no outcry to make sure patients benefit from the results of well conducted clinical trials.

Out of the CRASH-2 study the CRASH-3 trial was conceived. The CRASH-3 trial is to provide reliable evidence about the effect of tranexamic acid on mortality and disability in patients with TBI.[10] Worldwide, over 10 million people are killed or hospitalised because of traumatic brain injury (TBI) each year. Existing literature is promising and shows that TXA could significantly reduce intracerebral haemorrhage growth.[11,12] The CRASH-3 trial has been launched globally with well over 1000 patients recruited. Neurosurgeons in India contributed to the protocol development and the trial design, but in India, the review of the trial will not get beyond the DCGI. The Pre-screening application to the DCGI's office identified a total of 16 lacunae which only commercial Sponsors will be able to address, not an academic Sponsor working on a generic product where there is no commercial interest.

Well designed, ethically sound clinical trials of interventions for medical conditions which place a huge burden on the people of India must be allowed to continue. Many trials of generic products are done by non-commercial Sponsors. It is important to consider these trials in any changes to legislation. As a result, a new academic led trial which aims to assess the effect of tranexamic acid on mortality and disability in patients with moderate and severe TBI (CRASH-3) has been unable to progress.

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Yashbir Dewan*
Senior Consultant, Max Institute of Neurosciences, Dehradun, Uttarakhand, India

Haleema Shakur
Senior Lecturer, Clinical Trials Unit, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK

Taemi Kawahara
Trial Manager, Clinical Trials Unit, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK

Sanjeev Dua
Additional Director, Max Institute of Neurosciences, Dehradun, Uttarakhand, India

*Corresponding author. Tel.: +91 8171648648.
E-mail address: ydewan@yahoo.com

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