

EDITORIALS

## New Drugs and Clinical Trials Rules, 2019: The market trumps ethics and participant rights

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The enactment of the New Drugs and Clinical Trials Rules, 2019 (hereafter New Rules), on March 19 by the Ministry of Health and Family Welfare (MoHFW), Government of India (1), is the use of power delegated to the political executive by sub-section (1) of section 12 and sub-section (1) of section 33 of the Drugs and Cosmetics Act, 1940. Has this power been used wisely? Whose interests do these rules represent?

The dominant message conveyed to the media by the MoHFW spokesperson (2), and echoed in the reception of the New Rules by the clinical trial industry, was that they were designed to speed up clinical trials and approval of new drugs in India. The journal *Nature* noted: "India has announced new rules for clinical trials that will speed up drug approvals and remove the requirement for large studies to test the efficacy of drugs that have already been approved in other nations" (3).

### What are the regulations and the regulator for?

In 2005, India amended the rules on clinical trials of new drugs, and facilitated private business interests in the conduct of these trials. This was not accompanied by any increased investment in the regulatory process; increased investment would have included improving the competence of the regulator for trials of new drugs, the Central Drugs Standards Control Organisation (CDSCO). Thus, over the next seven years there were many reports of ethics violations and deaths in these trials. The public outcry against them brought the functioning of the CDSCO into sharp focus. The 59<sup>th</sup> report of the Parliamentary Standing Committee, which scrutinised the functioning of the CDSCO, says the following:

*The Committee is of the firm opinion that most of the ills besetting the system of drugs regulation in India are mainly due to the skewed priorities and perceptions of CDSCO. For decades together it has been according primacy to the propagation and facilitation of the drugs industry, due to which, unfortunately, the interest of the biggest stakeholder i.e. the consumer has never been ensured.* (4: p 2)

Chastised by Parliament, the MoHFW immediately formulated vision and mission statements giving primacy to public health and to the safety, efficacy and quality of drugs. These statements were initially carried prominently, scrolling across the home page of CDSCO's website. The spirit of those vision and mission statements has been forgotten in favour of speeding up business.

The Supreme Court had in its order of October 21, 2013 laid down three criteria for approval of CTs in India, namely (a) assessment of risks vs benefits; (b) innovation vis-à-vis existing therapeutic options and (c) unmet medical needs in the country (5). In other words, the Supreme Court stipulated that new drugs research should not expose the Indian people to undue risks; that the research ought to be only for genuinely innovative and scientific advances, and not for minor variations over the existing options in order to evergreen patents; and that the outcome of research must fulfil India's public health needs and not those of developed nations. These criteria have the potential to discourage some wasteful research, a major problem in the way that clinical trials are carried out at present worldwide (6). However, the New Rules do not make explicit efforts to operationalise these criteria.

### The New Rules' Ethics Committees: Transgression of authority, and more bureaucracy

Some heinous violations of research participants' human rights in history, such as the Tuskegee trials and the Nazi atrocities, did not involve any testing of drugs. Likewise, controversial studies on carcinoma cervix in India -- monitoring the natural history of the disease and the more recent trials of screening with no-screening controls -- did not test any drug. Yet, Indian laws had hitherto left out all non-drug research from regulatory standards and oversight.

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The New Rules seem to change that. But the effort is half-hearted and only makes the regulation more problematic.

What India needs is a comprehensive law, encompassing all drug as well non-drug research. Instead, the New Rules perpetuate the artificial separation between them. Chapters III and IV describe two separate ethics governance mechanisms by having two different types of ethics committees (ECs) with two authorities for their registration and monitoring; the New Rules also give primacy to different types of guidelines in assessing this research.

According to the New Rules, only clinical trials for new drugs and trials of bioavailability/ bioequivalence (BA/BE) will be reviewed, approved and monitored by ECs registered with the CDSCO. There will be separate ECs for “biomedical and health research” or BMHR – that is, research other than new drug trials and BA/BE trials. These studies will be registered with a new authority which is yet to be set up. Both registering authorities will be a part of the MoHFW, but there will be two separate bureaucracies, with their own inspectors to monitor the ECs registered under them. The silo mentality of bureaucracies is likely to entrench the hierarchy and perpetuate divided control of health research.

As if the double bureaucracies and control were not sufficient, the New Rules also give each set of ECs different guidelines for its work. ECs reviewing, approving and monitoring new drug and BA/BE trials will be governed by “(the New Rules), Good Clinical Practices Guidelines and other applicable regulations”. Strangely, in a significant departure from the past, there is no mention of the ICMR’s National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (7). Although the GCP guidelines mention that ECs would use the ICMR guidelines and the Declaration of Helsinki (8), the New Rules give the impression that the ECs are required to give primacy to the GCP and the New Rules *against* the ICMR guidelines in the event of conflict in provisions between the two.

On the other hand, ECs for BMHR would, as stated in the New Rules, “review and oversee the conduct of such research as detailed in National Ethical Guidelines for Biomedical and Health Research Involving Human Participants”. There is no mention of the applicability of any other rules of the Drugs and Cosmetics Act. Therefore, an obvious question is: by what law is a new authority for the registration of ECs and other procedures for BMHR in the New Rules, governed? Even the preliminary opening statements explaining the applicability of the New Rules (Chapter I) mention only new drugs, their CTs and BA/BE research; they do not mention BMHR. In any case, how, under a law meant for regulating drugs, could they promulgate regulations on non-drug trials without the approval of Parliament?

### **New drugs approval: Waivers for testing in India**

When the aim is to bring into the market as many drugs as quickly as possible, waivers are a must. The New Rules give powers to the regulator to waive a wide range of pre-clinical studies (toxicological, teratogenic, reproductive, etc.) before conducting CTs. They also confer powers to waive CTs in India if a drug has already been approved in certain developed countries.

This provision is one-sided, as no developed country has given this status to Indian drugs approved by the Indian regulator. Indian regulators do not get this status because standards of regulation in India are lax. The present obsession with speed will make them even more lax.

There may be one more reason for this provision: to bypass the question of the “ethnic factor”, namely, the need for clinical trials to ensure the drug’s safety and efficacy in different ethnic groups. The 59<sup>th</sup> Report of the PSC (4) had dealt with this issue, and passed stringent strictures against the CDSCO for approving drugs in India without local CTs and without paying attention to ethnic factors (pp 29-30).

The report of the Prof Ranjit Roy Chaudhury expert committee (9), which was appointed by the government at the instance of the Supreme Court “to formulate policy and guidelines for approval of new drugs, CTs and banning of drugs”, emphasised that “Ethnic differences affect the efficacy, safety and dose regimen of a medicine” (9: p 22). The report calls for the need to collect data from different parts of India because of the wide variations in ethnic factors, and enumerates many of them. The report also argues that if some centres in India are part of international multi-centric trials, then regulatory authorities should ensure the inclusion of adequate numbers of Indian participants with ethnic variations in them. They must do so to ensure that there is statistical power, that those data are amenable to separate analyses, and that we are not required to do a repeat trial of that drug in India, if it is found to be efficacious.

The New Rules, unfortunately, provide no details of the criteria for waivers as well as for consideration of ethnic factors. All of them are left to the discretion of the CDSCO.

### **Compensation for injuries and deaths**

S Srinivasan, in his article on the new Rules in *Scroll.in* (10), has explained in detail how the provision for “no-fault” compensation, proposed in the draft rules circulated earlier by the government, has been left out in the new Rules. The draft rules had proposed that 60% of the compensation as determined by the EC be paid upfront; this money would be non-refundable and could not

be refused even if the national committee of the CDSCO determined that the death or injury was not related to the CT. The government was under severe pressure to leave that provision out of the final Rules. Srinivasan states that such pressure was exerted not only by the pharmaceutical industry, but also by the World Health Organisation. The absence of this provision is a major setback to the struggle against exploitation in CTs.

### Participants devoid of rights, clinical trials devoid of transparency

The framers of the New Rules seem to regard research participants as mere providers of their bodies for experimentation, having no say in the proceedings (save for cursory consent). Even when they suffer permanent injuries, or die, they or their representatives are provided no presence at any level of decision making on compensation. They are not even given a minimum right to be heard by an EC, an expert committee or the CDSCO.

Another glaring omission is that of any mention of data transparency. The New Rules do not even make it obligatory for researchers and sponsors to bring into the public domain, within a stipulated time after the CT is completed, the primary and secondary outcomes of the CTs, let alone all anonymised data. This requirement is meant to prevent data manipulation and facilitate the meta-analysis of many such trials to generate scientific and clinical evidence.

### Where are we headed?

There is much more in the New Rules, bad as well as good. This comment is restricted only to certain particularly worrisome features. One only hopes that in their obsession with speeding up clinical trials and approval for new drugs in India for the expansion of the clinical research and pharmaceutical industries, the Rules do not re-inculcate the culture of the recent past when reckless ethics violations occurred in some trials. It was these violations that had necessitated the promulgation of the New Rules in the first place.

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