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Addressing Ethical Concerns Surrounding Clinical Trials in India

A. Sneha Vardhani

LL.M. Student at PGCL, Osmania University, Hyderabad

Abstract: ***This paper attempts to review the latest guidelines passed by the Indian Council of Medical Research (2017) in the light of persisting ethical concerns in India. The Guidelines drafted is an ameliorated attempt to strike a balance between the progress of clinical trials and associated ethical concerns. There are a great number of clinical trials that are greatly benefiting human-kind yet, there is disquiet about unethical clinical trials transpiring. Though the severity of the problem has been acknowledged on paper, the profundity of the guidelines is impaired for reasons discussed. However, these guidelines can be valued as a superior step taken towards a better law tomorrow.***

Keywords: Ethics, Clinical Trials, ICMR Guidelines (2017), Informed Consent and Ethics Committee

1. Introduction

Indian Council of Medical Research (ICMR) which is the nodal agency to *formulate*, *coordinate* and *promote* biomedical research has revised its guidelines in October 2017. "National Guidelines for Biomedical and Health Research Involving Human Participants" [1] and a separate "National Guidelines for Biomedical Research Involving Children" [2] by the ICMR have been put in action to oversee the modus operandi of clinical trials conducted in the country.

In India the following regulations on clinical trials are of paramount importance:

- ICMR Guidelines for Biomedical and Health Research Involving Human Participants, 2017 and ICMR Guidelines for Biomedical Research Involving Children, 2017. [3]
- The Schedule Y of the Drugs and Cosmetics Rules, 1945. [4]
- Good Clinical Practice Guidelines for Clinical Trials on Pharmaceutical Products, 2001. [5]

2. Guidelines and Regulations

- **Schedule Y of the Drugs and Cosmetics Rules, 1945** enumerates on not only the required permissions for approval to conduct clinical trial [6] and/or to import and/or to manufacture for sale [7] of new drugs for marketing in India but also lists the responsibilities of ECs, Investigators, Sponsors and formats of protocols, registration of ECs, EC approvals and cancellations, [8] reporting of Serious Adverse Events [9] and compensation [10] etc. [11]

- **India's Good Clinical Practice Guidelines** (2001) is an offshoot of ICH GCP. [12] GCP Guidelines specific to India have been in place from 2001 without any amendments so far. GCP aims to ensure that the studies are *scientifically and ethically sound* and that the clinical properties of the pharmaceutical substances under investigation are properly documented. These guidelines seek to promote two cardinal principles: 'protection of the rights of human subjects' and 'authenticity of biomedical data generated'. [13]

- **Indian Council of Medical Research (ICMR) Guidelines**: Scope of these guidelines extend to not alone the biomedical research but also the social and behavioral science research for health conducted in India involving human participants, their biological material and data. ICMR receives funding from the Ministry of Health and Family Welfare and the Department of Health Research, Government of India. The Council has been devising needful guidelines with respect to 'ethical considerations' involved in biomedical research on human subjects. First draft by ICMR was the 'Policy Statement on Ethical Considerations involved in Research on Human Subjects', 1980 which was revised in 2000 titled 'Ethical guidelines for Biomedical Research on Human Subjects' and later amended in 2006 into ICMR Code titled 'Ethical Guidelines for Biomedical Research on Human Participants'. This ICMR Code was being followed till the much awaited revision in October, 2017 i.e. 'National Ethical Guidelines for Biomedical and Health Research Involving Human Participants' along with 'Ethical Guidelines for Bio-Medical Research Involving Children' by the ICMR. [14] The ICMR has been making opportune revision of guidelines to keep a pace with the global developments in the area of Bioethics.

3. Ethical Concerns Associated with Clinical Trials

I. Informed Consent vs. Inducement

Informed consent requires *voluntarism* and *awareness* of pros and cons of a clinical trial by the subject before consenting. The rationale for volunteering in a clinical trial is - for the monetary gain or for medical benefits or to contribute to science and research. However, unless there appears a perceptible coercion on part of the perspective participant/subject, being told of clinical research proposal and signing the form means that a 'subject' is said to have agreed to take part in the trial. Depending on the nature of clinical research, trials are conducted not necessarily on the patients suffering from an illness but also require healthy volunteers. Most of the healthy volunteers are paid an amount by the institutions conducting research so as to compensate for their time spent, loss of wages and for incidental expenses if any. Should a volunteer be paid at all?

is yet another debatable ethical issue. To what extent are the said monetary benefits given to a volunteer qualify as an "incentive" that is sufficient to induce a healthy man/women to sign up for a clinical trial? A forthright answer to this would be to quote Section 2 of ICMR Guidelines (2017) "2.5.5. *ECs must review and approve the payments (in cash or kind or both) and free services and the processes involved, and also determine that this does not amount to undue inducement*." But this is not all to the question of 'payment for participation'.

Some incidents unveiled in Andhra Pradesh-Telangana (South India) paint a sordid picture of rackets that lure people with easy money making, [15, 16] swindled informed consent process resulting in unethical clinical trials [17, 18] i.e. point-blank violation of rules and regulations. To list, Human Papilloma Virus Vaccine case (2009) where the HPV Vaccine was administered to 30,000 participants, who knew nothing about being on a trial. [19] With increasing incidents relating to illegal clinical trial rackets the irregularities by the Clinical Research Organizations (CROs) in the recruitment process of 'subjects', DGCI has put eight labs under scrutiny viz., Actimus Bio Sciences, GVK Bio, Nicholas Piramal, Vimta Labs among four others and suspended the licence of Axis Clinicals Ltd., (2011). [20] Further News Reports suggest subsequent occurrence of such incidents causing death in various parts of the country. [21] The latest case to make headlines is - unemployed youths from Telangana volunteering to undergo a clinical trial for a good amount of 8,000 to 20,000 rupees per sitting per head. One of the volunteers developed epileptic seizures [22] whereas, the other volunteer died [23] and another volunteer became a source of information, who informed police and media of the existing Whatsapp groups, middlemen who act as agents of clinical companies and their modus operandi. [24] In the light of such incidents, State Government of Telangana constituted a five-member committee headed by Justice Gopal Reddy in July, 2017 to probe into cases of 'illegal clinical trials' in the State and submit a report within thirty days but there has been no progress so far. [25]

II. Vulnerability vs. Volunteering

"*Voluntarism of vulnerable subjects is usually compromised; therefore, while inviting such patients for research participation and obtaining their consent, special precautions are required to be implemented and mode of consent must be approved by a competent EC*." [26] *Swasthiya Adhikar Manch And Anr.* v. *Union Of India* [27] points out that not only are the poor, illiterate, children, mentally ill and vulnerable sections of the society turn out to be subjects for 'illegal clinical trials' but their safety is also grossly compromised to an extent that any adverse events/serious adverse events that occur are unreported. The said petition was filed in 2012 when prevalent circumstances were such that the vulnerable persons as human subjects for clinical trials were unaware of themselves having volunteered for a clinical trial. And five years from then, circumstances today, are so that vulnerable populations who voluntarily sign up are taking clinical trials more often than they should medically be doing so. Some of the CROs have blatantly denied their liability in cases of SAEs/death for reasons that the 'subjects' have taken other clinical trials without a time gap of three months or have been unreachable in contact for a follow up by the pharmaceutical companies.

Voluntariness of professionals as researchers, EC members, institutions or sponsors can also be compromised due to financial or non-financial reasons and this is termed as 'Conflict of Interest' (COI). COI of any EC member has to be voluntarily declared at the initial stage itself and managed as per the research protocol but it has been reiterated time and again by activists that composition of EC defies this requirement.

III. Benefits vs. Risks

Benefits that follow the research must justify the risk the clinical research poses and establishing this rationality is a must of every clinical trial that is conducted on human subjects. However, there is an inherent risk factor involved in every clinical trial so, means in which the authorities seek to tackle the associated risks is of crucial consideration. Thus, 'benefit-risk assessment' is not said to be 'balanced' until the clinical research clearly signifies the mode of risk-handling mechanism/supplementary aid procedure in the research proposal itself.

IV. Compensation

Swasthiya Adhikar Manch (SAM), a non-profit organization has been instrumental in filing a Public Interest Litigation petition that resulted in a remarkable judgment by the Supreme Court that entailed a thorough appraisal of existing regulatory framework on Phase II & III trials of New Chemical Entities (NCEs) discovered abroad and subsequent procedural changes to the 'Schedule Y of Drugs and Cosmetics Rules, 1945'. The said petition had also dealt with unpaid compensation claims of hundreds of families of subjects who have suffered serious side effects or suffered death. "Despite the powerful judgment Swasthiya Adhikar Manch (SAM) is still fighting for compensation in multiple cases across Madhya Pradesh and other States. Besides, there is still a need for formal regulation that sanctions ethical-transparent clinical trial juxtaposing the current framework" said Mr. Amulya Nidhi, spokesman of SAM. Cases pursued by SAM indicate that obtaining compensation is not an easy process and not every case gets lucky. However, few cases point gross violation of Rule 122 DAB (compensation in case of injury or death during clinical trial) of 'Schedule Y' as amended in 2013 by institutions. [28]

The purpose of this research is to review the latest guidelines in the background of the above mentioned persisting ethical concerns and to scrutiny the purview of the said guidelines in addressing the bane of concerns.

4. Review of Revised Guidelines (2017)

The researcher through this researcher paper has reviewed first part of "**National Ethical Guidelines for Biomedical and Health Research Involving Human Participants**" (Hereafter referred to as 'Guidelines (2017)') dealing with ethical concerns surrounding clinical trials on human subjects and following is the analysis:

1) The document consists of twelve sections to extensively deal with general ethical concerns, public health issues, general issues, bio-banking and health research, out of

which informed consent process, vulnerability and ethical review process of clinical research proposals are dealt vastly under separate chapters.

2) The document begins with reasoning out "socio-cultural ethos and varying healthcare standards" as a hindrance to application of 'universal ethical principles' to biomedical and health research in India.
3) **Informed Consent**: As per the revised guidelines one mandatory prerequisite to go ahead with a clinical trial is the 'voluntary consent of the human participant' to be obtained by the researcher before enrolling the human participant for a clinical trial. "Informed consent *is a continuous process involving three main components – providing relevant information to potential participants, ensuring the information is comprehended by them and assuring voluntariness of participation*." [29] Informed Consent Form in English is required to be backed with the consent form translated into the local language of the perspective participant and be duly assented. Informed Consent Document consists of a Participant Information Sheet (PIS) to disclose the relevant details of the research and an Informed Consent Form (ICF) to acknowledge that the participant has understood the proposed research and is voluntarily consenting to participate in research. It is the duty of the researcher to obtain the written, informed consent from the prospective participant and if a said participant is illiterate, consent must be taken in the presence of a literate impartial witness or from a Legally Acceptable Representative/LAR.
4) If a prospective participant cannot sign then a thumb impression can be obtained (5.4.4). This provision is equivocal for not mandating Audio/AV recording while invoking such clause or mandating attachment of a consent form translated into the local language of the perspective participant with the thumb impression. However, Audio/Audio-Visual recording of the Informed consent process is not mandatory unless it is for a clinical trial notified by the CDSCO.
5) Once the consent is obtained, the participant 'should' be given a copy of PIS and signed ICF unless the participant is 'unwilling to take these documents'. Such reluctance should be 'recorded' (5.9.1). Mode of recording, procedure to file such recording or authority for upkeep such recording is not discussed in the said guidelines. Lack of documents has deprived families of victims from obtaining compensation and no secondary evidence of the PIS/ICF is a leeway for the Institutions to erase the data regarding the participant if they want to.
6) Verbal/oral consent can be obtained when the participant is willing to participate but is unwilling to sign or give a thumb impression on approval by the EC, in the presence of an impartial witness who shall sign. Such process 'can' be documented through audio/AV recording (5.3.8).
7) Re-consent or fresh consent is taken only under circumstances prescribed under Section 5 (5.8) of the guidelines. However it acknowledges the need for re-consenting when *new information pertaining to the study becomes available which has implications for participant or which changes the benefit and risk ratio etc.;* but not when any unanticipated circumstances that aggravates the risk involved to the participant and requires re-consent.
8) EC reserves the right to 'waiving the consent' requirement in certain circumstances such as- *when research cannot be carried out without the waiver and waiver is 'scientifically justified' or where the participants are de-identified or cannot be contacted or research during humanitarian emergencies and disasters, when the participant 'may not' be in a position to give consent etc*., (5.2)
9) **Inducement**: EC shall determine the payments, reimbursements or/and services in such a manner to ensure that it does not amount to 'undue inducement' to the participants (2.5.5). "As potential participants are dependent on others, there should be no coercion, force, duress, undue influence, threat or misrepresentation or incentives for participation during the entire research period" (6.2.6). Participants are reimbursed for the following:
   a) Travel related expenses
   b) Inconvenience incurred
   c) Time spent
   d) Loss of wages
   e) Other incidental expenses either 'in cash' or kind or both (2.5.1).

In addition to the reimbursement, by virtue of certain provisions participants shall be given medical care and facilities at no cost. However, 'duration' of such medical services if given is not prescribed.

1) Post research benefits *should be made accessible to individuals, communities and populations whenever relevant. And sometimes the benefits are indirect than direct i.e., improving their living conditions, establishing counseling centres, clinics or school, and providing education on good health practices* (2.11).
2) **Vulnerability**: Section 6 deals with vulnerable population as participants in a research. The chapter begins discussing the characteristics of vulnerable individuals *as incapable of making voluntary informed decisions for themselves* due to varied reasons; Example: *personal disability, environmental burdens or social injustice, lack of power, understanding or ability to communicate* among others (6.1). The document under clause (2.9.2) clearly states that "a vulnerable individual/population 'should be' included 'only' when the research is directly answering the health needs or requirements of the group." On the other hand under the same clause and clause (6.1.1) it states that "vulnerable populations have an equal right to be *included* in research so that benefits accruing from the research *apply to them as well.*" The phrase 'right to participate' should replace 'right to be included' in the clause above (2.9.2&6.1.1) to show an absence of leverage on part of the researcher.
3) Further, from a bird's eye view clinical trials are all conducted for the welfare of human beings and vulnerable individuals are also to be benefitted. Thus, there is a thin line that separates **what specifically benefits vulnerable populations that their participation is justified** and **what benefits everybody that inclusion of vulnerable populations can be avoided**. And there is a great onus on ECs and regulatory authorities in distinguishing them to control exploitation of vulnerable. There is a need to **establish a networking among the CROs** to share the profiles of

enrolled volunteers, so that a volunteer shall not sign up for another clinical trial immediately after completing one. Since a time gap of minimum of three months is mandatory.

4) **Voluntariness**: Conflict of Interest can be at the level of researchers, EC members, institutions or sponsors (2.8). Any COI disclosed even by the EC members shall be analyzed by the EC itself without any external interference, not even from the research institution and takes appropriate measure in accordance with Standard operating procedures (SOPs) of EC.
5) Clause (5.1.2) states that "the consent of the participant should be given voluntarily and not be obtained under duress or coercion of any sort or by offering any undue inducements".
6) **Benefit – Risk Assessment**: "The researcher, sponsor and EC should attempt to maximize benefits and minimize risks to participants so that risks are balanced to lead to potential benefits at individual, societal and/or community levels (Clause 2.1.1)." The type of EC review based on risk involved in the research, is categorized into - *Exemption from review* – Proposals with less than minimal risk involved; *Expedited review* – Proposal that pose no more than minimal risk; *Full Committee review* – All research proposals presenting more than minimal risk that and not covered under the types above (4.2). Moreover, any serious adverse event (SAEs) during the course of participation must be reported by the researcher to the EC within twenty-four hours from the time of occurrence (2.6.1). Researcher shall be accountable for ensuring free treatment and additional compensation (5.3.12).
7) Ancillary care i.e., free medical care for non-research-related conditions or incidental findings 'during the course of participation' in the research is granted to the participants (2.7). Further, the guidelines provide ancillary care such as setting up of a facility, school for unattended children of the participants or a hospital, or counseling centre (6.2.13). But the harsh reality stands at unattended compensation claims which still need to be disbursed.
8) **Compensation**: After 'due assessment' by the EC, participants who suffer '**direct**' *physical, psychological, social, legal or economic harm as a result of participation* shall be entitled to financial 'or' other assistance to compensate for any *temporary or permanent impairment or disability*. "In case of death, participant's dependents are entitled to financial compensation" (2.6) quantum of which is decided by the EC keeping in view of certain aspects. [30] The researcher in the proposal must include a budgetary provision for insurance coverage/compensation claims (2.6.4). EC is further responsible for establishing 'relatedness of SAEs' to the research and determine the required type of assistance accordingly (2.6.2). There is no provision to address long term **adverse events occurring post-research** probably as a consequence of participating in the research.
9) Guidelines permit 'withdrawal of participation' at any stage of the clinical trial after giving due notice. However, there is no provision providing after care to such participants. There is a need to address health concerns of such participants after due diagnosis and establishing the relatedness of ailment to the research. While determining the relatedness to the research, the stage of quitting by the participant must be considered.
10) There are instances where the perspective participants would not disclose his/her addictions/substance use/obsessive habits/whether on medication/other required information that might result in reaction or reversal of the administered substance causing SAEs or even death. Thus, **mandating prior consultations with a close family member** to know the health condition and habits of the participants would reduce the number of deaths caused not resulting out of the clinical trial. And the participants are not kept in the institution premises for the entire duration and sometimes cannot be contacted for a follow-up by the institutions. Mandatorily seeking a source of contact of family member/neighbor/friend from the same locality as the perspective participant would help break the chain - 'loss of contact' - 'no follow up' - 'no compensation'.
11) **Ethics Committee**: It is the autonomous decision making body on various clinical research proposals. Head of the institution is not part of the EC but acts as an *appellate authority handling disputes* and *appoints all members of EC independently*.

Composition of EC is Chairperson (optional), Secretary (optional) and Basic Medical Scientist, Clinicians, Legal Experts, Social Scientists can all be either Affiliated or Non-Affiliated, Lay Person (Non-Affiliated). Apart from 'lay person' all other members can be affiliated (belonging to the institution). Appreciable powers have been catered upon ethics committees (ECs) under the new guidelines. Composition of ECs is in itself disputable for not mandating inclusion of equal number of outsiders (non-affiliated to the institution conducting trial) as the members of EC [31] as the clause (4.3.3) states 'preferably' 50% of the members should be non-affiliated. And even the required quorum to make any decisions ultimately has minimal inclusion of outsiders. [32]

5. Conclusion

Revised guidelines are not mere embellishments rather have dealt with ethical concerns meticulously. There are two faces to current trend of clinical trials – there are ethically conducted clinical trials and on-going illegal trials. Combating the latter and regulating the former requires a precise all-inclusive stringent legislation. In a country where there is no specific legislation and where certain regulations/guidelines/rules are adhered to – obligations arising from such regulations should be incumbent. Guidelines (2017) is generally drafted i.e., not obligatory of certain needful requisites. Use of phrases such as 'can' in place of 'should' and 'preferably' in place of 'must' (highlighted in the section above) hint the reluctance to stringent the existing system. The said guidelines are of a paramount importance for having to deal with multidisciplinary aspects of our lives. In view of this, guidelines with escape clause and lack of infringement provisions can be trifling.

The document casts prodigious amounts of power on the ECs – being responsible for approving/rejecting proposals, monitoring the clinical trials, determining the relatedness of SAEs/death to the research, deciding the quantum of compensation/insurance claims, taking measuring to address conflicts, reporting SAEs/deaths etc. and even reserves right to approve certain types of research involving intentional deception of information to the participant (5.11).

Having prior consultation with 'scientific committee' constituted by retired Government Doctors that operate outside the ECs will reduce the scope for arbitrariness. Lastly, there is a need for 'Victim Redressal Committee' to be constituted to resolve and address the persisting concerns/claims. No external consultation would spur ECs obscurantism.

"**Power tends to corrupt, and absolute power corrupts absolutely**."

-Sir John Dalberg-Acton.

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[8] Schedule Y: Rule 122DB: Suspension or cancellation of approvals.
[9] As per the Schedule Y, Serious Adverse Event *is an untoward medical occurrence during clinical trials that is associated with death, in patient hospitalization, prolonged hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect or is otherwise life threatening*. Also available at: https://www.omicsonline.org/recent-regulatory-amendment-in-schedule-y-impact-on-bioequivalence-studies-conducted-in-india-jbb.1000154.pdf; last accessed on 11/3/2018.
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[29] Section 5, ICMR Guidelines (2017).
[30] Aspects to be considered are *type of research, extent of injury, loss of wages etc*.
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[32] Clause 4.3.6: (3) Minimum one non-affiliated member should be part of the quorum; (4) preferably the lay person should be part of the quorum. However, the 'non-affiliated member' under 4.3.6 (3) can in few cases be the lay person only because an EC can be constituted with 'lay person' being the only non-affiliated member.