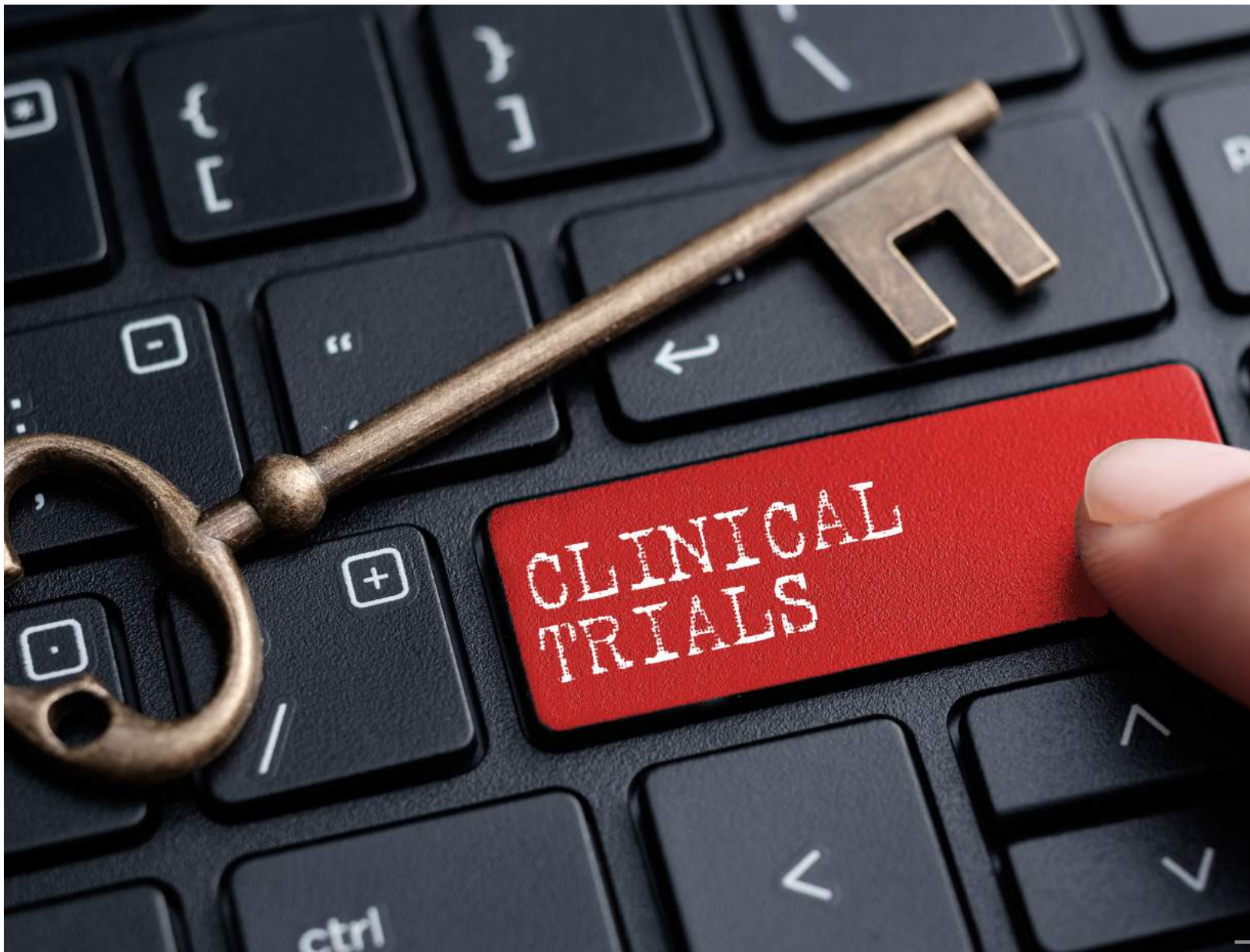




Challenges and prospects for clinical trials in India

A regulatory perspective

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Introduction

The ethical justification for undertaking health-related research involving humans is its scientific and social value: the prospect of generating the knowledge and the means necessary to protect and promote people's health.

-- Guideline 1, CIOMS, WHO, 2016.

At the behest of the Hon'ble Supreme Court of India,¹ the regulatory landscape for clinical research in India witnessed an overhaul in early 2013, resulting in a flurry of mainstream media articles wrongly referring to the aforementioned order as a ban on clinical research in India. While it is true that the number of ongoing and upcoming trials dipped from that point onwards, but this was more to do with the wait-and-watch policy of sponsors² of clinical trials, citing the supposedly stricter requirements while conducting them that were put forth. The foremost was that of providing for examination of serious adverse events and procedures for compensation in case of clinical trial-related injury or death. The second was the audio-visual recording of the informed consent process. The third was the arbitrary cap on the number of trials an investigator could simultaneously undertake. The fourth was the requirement of a minimum threshold of public medical institutions (with predefined standards) to be chosen as clinical trial sites³. The fifth was about inspection and monitoring of clinical trials, and finally about registration requirements for EC.

Although most of these reforms were deeply desired, the absence of adequate regulatory guidance on specific issues, lack of clarity on legal terminologies and dearth of a sound communication strategy on the part of the drug regulator rendered the reform process counterproductive, resulting in confusion and uncertainty, an 'over-correction'. To add to the woes, the lack of an open resource⁴ enumerating the nature of clinical trials conducted in India led to the public debate taking an undesirable turn. As a result, the global perception of India in the context of clinical research suffered a serious setback.

The purpose of this policy brief is to bring back focus to the debate on clinical research by providing hard data and clarity on issues based on extensive data mining from both secondary and primary sources as well as stakeholder interactions across 4 Indian states and 7 countries across 4 continents. The policy recommendations that follow takes cognizance of the regulatory constraints in low-resource settings, and hence categorized for immediate, medium and long-term implementation to render them actionable.

¹ The Hon'ble Supreme Court of India, vide its order dated 03.01.2013 in the matter of W.P. (C) No. 33/2012 of Swasthya Adhikar Manch, Indore & Anr Vs. Ministry of Health and Family Welfare & Ors. with WP(C) No. 779/2012 regarding clinical trials, had directed that until further orders by this Court, clinical trials of new chemical entities shall be conducted strictly in accordance with the procedures prescribed in Schedule Y of the Drugs and Cosmetics Act, 1940 under the direct supervision of the Secretary, Ministry of Health and Family Welfare, Government of India.

² Another reason cited behind the drop in clinical trials was the mandatory requirement of registration of ethics committees (ECs). As a matter of regulation, ECs across the globe have to be registered by a nodal agency. In India however, there was no such provision. Hence, registration of ECs was a welcome step. However, mere registration of an EC does not ensure compliance with Good Clinical Practices (GCP). The latter is ensured with periodic GCP inspections/audit of an EC, while accreditation by a recognized body helps this cause, but is a step yet to be implemented in India.

³ The third and the fourth requirement were taken off with the August 2016 CDSCO order, removing the restriction on the number of clinical trials an investigator can conduct at any time. See, <http://www.cdsc.nic.in/writereaddata/restricion%20of%20conducting%20three.pdf> (last accessed on 4th April 2017). Further, the CDSCO order changed the requirement that trials be conducted at sites with more than 50 hospital beds to simply requiring the ethics committee to decide whether the site is suitable. See, <http://www.cdsc.nic.in/writereaddata/requirement%20of%2050%20bedded%20.pdf> (last accessed on 4th April 2017).

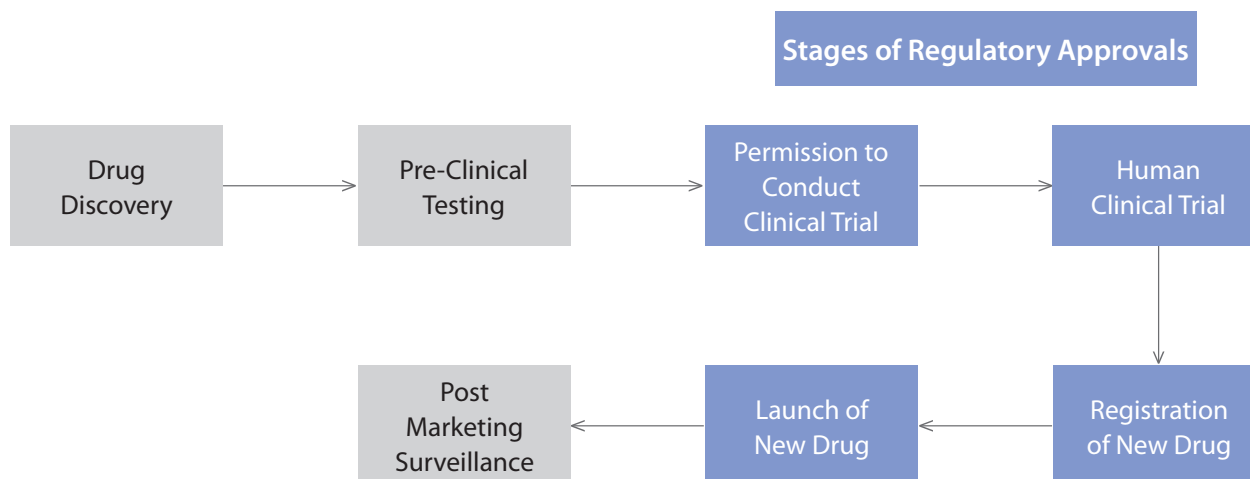
⁴ Before a volunteer is recruited in a clinical study in India, it has to be registered with the Clinical Trial Registry of India (CTRI) which is an open repository for public use. However, the current structure of the database poses difficulties in undertaking a meta-analysis.

Challenges and prospects for clinical trials in India

Clinical trials (CTs) are indispensable to the drug development process (see Figure) to ensure efficacy and safety of any new drug—they are the mainstay for introducing newer and better therapeutics into the market. India has had favorable prerequisites for conducting clinical research and drug development – a large and diverse patient pool (trial participants), a highly skilled workforce of qualified scientists (investigators), medical colleges (sites), etc. Yet, an unfavorable ecosystem has undermined its potential – only 19 trials were approved in 2013, a drop of roughly 93 percent from 2012 (262 trials), and a fraction of its peak of 500 trials in 2010.⁵ Currently, India is home to 16 percent of the world’s population, 20 percent of the global disease burden, yet it has less than 2 percent of CTs registered worldwide.⁶

While the Indian pharmaceutical industry, has registered growth higher than several other sectors, the clinical research industry in the country has lagged behind. Today, public opinion in India is not quite in favor of CTs- as several Contract Research Organizations (CROs) have been blamed for conducting trials without due concern⁷ for procedural and ethical issues. Along with bad press and regulatory inadequacies, CTs almost came to a halt in India. This has had grave ramifications, from a counterfactual perspective, for public health due to delays in introduction of new and relevant therapeutics worsening of the problem of drug lag⁸ in the country.

Figure 1: Stages of Regulatory Approvals in the Process of Drug Development



⁵ See, [http://cdsco.nic.in/writereaddata/DCG\(l\)%20approved%20clinical%20trial%20registered%20in%20tri%20website%20\(Jan.2013\).pdf](http://cdsco.nic.in/writereaddata/DCG(l)%20approved%20clinical%20trial%20registered%20in%20tri%20website%20(Jan.2013).pdf) (last accessed on 4th April 2017).

⁶ See, <http://www.theweek.in/health/cover/clinical-trials-research-india.html> (last accessed on 4th April 2017).

⁷ See, for instance, the Parliamentary Committee 59th Report on the Functions of the Central Drug Standards Control Organisation (CDSCO).

⁸ A 'drug lag' refers to any delay in making a drug available in a particular market. However, it may also have positive externalities, if there is a danger of too-rapid introduction of medicines of unproven value. The term 'relevant therapeutics', hence, refers to a medicine that caters to the public health needs of a country.

Nature of clinical research in India

Globally, clinical research involves the conduct of clinical studies, and CTs represents a category of such clinical studies. However, the mass perception (built largely via media articles) in India equates all clinical studies as CTs of allopathic medicines sponsored by 'for-profit entities'.

However looking at the data on registered clinical studies at the CTRI,⁹ out of 7,232 clinical studies, 74 per cent or 5,336 studies are classified as interventional trials and are germane to the debate on CTs in India. Out of these interventional studies, only 2,522 or 48 per cent studies involve administration of allopathic entities-drugs/small molecules (2,065, 39%); biologics (256, 5%) and vaccines (201, 4%). The other 52 per cent studies¹⁰ involves interventions either based on alternate systems of medicine (AYUSH), probiotics or surgical procedures/use of medical devices (constituting non-drug), etc.

Out of the 2,522 studies, 902 studies or 37 per cent are sponsored by national and international non-profit agencies combined. Trials sponsored by foreign/global firms which stand at 864 and constitute 34 per cent of the total, while the Indian pharmaceutical firms have sponsored 728 studies, constituting 29 per cent of the total interventional trials under study.

Over 81 per cent of the trials sponsored by foreign firms are multi-country trials, while 97 per cent of the trials sponsored by both Indian firms as well as non-profit agencies (Indian and foreign combined) respectively are locally instituted trials.

Over 66 per cent of these are either phase 3 or 4 trials. Out of the studies labeled phase 3 (1092), over 53 per cent were sponsored by foreign firms, mostly representative of either trials of Investigational New Drugs (IND), New Chemical Entities (NCEs) or Global Clinical Trials (GCTs), while 35 per cent of these were sponsored by Indian firms, mostly representative of local bridging studies for new drugs. The remaining 12 per cent phase 3 trials were sponsored by non-profit agencies.

Clinical trials for NCEs and new drugs are often done as part of a concurrent global drug development program which translates to multi-country, multi-site GCTs¹¹ involving hundreds of participants in later stages of development (phase 3 and 4). However, for the introduction of new drugs by Indian firms in India, CTs often tend to be lagged phase 3 trials or local bridging studies, involving 100-200 patients.

With this data at hand, it is easy to appreciate the wide terrain of clinical research activity in India.¹² Clinical studies can be done for INDs, NCEs, new drugs; they can be lagged or concurrent; they can be sponsored by for-profit as well as not-for-profit agencies. However the overarching public perception of CTs is not informed of these finer details leading to an unfocussed discourse on the issue.

Select case studies are reproduced from our report to highlight major challenges for clinical research in India, with recommendations on how to address them. Wherever possible, an operationalization plan has also been included.

Implementation Horizon

- Immediate – term goal
- Medium – term goal
- Long – term goal

⁹ CTRI data analysed here is from the beginning of the year 2007 to 2nd Sept. 2016. The year of conduct of a trial and the year of its registration need not be the same, because until 15th June 2009, it was not mandatory to register a trial with CTRI. Hence, several studies have been registered retrospectively and likewise prospectively.

¹⁰ The analysis is restricted to only the former category of interventions involving small molecules, biologics and vaccines. The latter category of interventions although are relevant to clinical research, lie out of the scope of the discussion presented here.

¹¹ However, it should be duly noted that not all GCTs are for NCEs. A GCT may be done to explore or confirm new clinical indications/new dosage forms/new route of administration for an already approved drug.

¹² For a more indepth analysis kindly refer to our report on the 'Challenges and Prospects for Clinical Trials in India: A regulatory perspective'.

Actionable policy recommendations

Case Study 1: Capacity building in ethics committees

The Forum for Ethics Review Committees in India (FERCI) has established a network of ECs in India and has been contributing to training and awareness regarding research ethics through various initiatives. One of the noteworthy initiatives is the

CREaTe – FERCi initiative. Under the programme five IT enabled tools have been created to facilitate the day to day functions of ECs. The five tools are:

1. Simplifier

It is a database of key terms commonly seen in consent forms that are “simplified”. The jargon from the discipline of medicine is explained in simpler terms for a literate lay person to comprehend.

2. Interpreter

It is a database that has validated simple “interpretations” of terms commonly found in consent forms. At present this database has Marathi and Hindi interpretations. It is not a mere transliteration tool and derives its value because it is a compendium of words put together by brute force translation, which can go a long way to guide trial participants.

3. EthiX

It is a self-assessment tool to evaluate the ethical soundness of a clinical study protocol and an informed consent document. Scores are assigned on the basis of the responses of the scientific as well as ethical questions designed for different study designs. It is a user guided questionnaire based tool that scores a protocol based on its ethical soundness.

4. Regulert

It is a feed based free subscription service, which notifies the subscribers about relevant notifications and other information from various stakeholders including CDSCO, USFDA, EMA, MHRA, Health Canada, WHO etc.

5 eEC

This tool enables institutions to move their Ethics Committees review and approval practices on to the CREaTE Platform. Once on board, investigators can register with an institute and submit their studies/projects for Institutional Ethics Committee (IEC) approval. Once these are submitted to IEC, they will go through IEC staff verification and IEC members review and approval / rejection of project/submission.

Under the pilot, over 30 ECs have been trained which are now named “Smart ECs”, and the list is growing. The pilot is in its infancy, yet has been able to establish proof-of-concept, which is scalable for a pan-India implementation. All the tools combined together serve a much needed function, and can go a long way to rectify challenges affecting clinical research in India. Similar initiatives in other countries have only enhanced the capacity of ECs. For example: Council on Health Research for Development (COHRED) created an online platform ‘Research for Health and Innovation Organiser’ (RHInNO), which provides researchers with access to an easy to use automated system that enables them to keep track of the entire life-cycle of the research process. RHInNO enables users, researchers and research institutions to register research projects, issue calls for proposals and manage research data and publish research results. The ‘ethics’ version of RHInNO enables ECs to streamline the ethics review process, produce reports and track the progress of projects. One of the ECs interviewed confirmed the merits of deploying the online platform.

Challenge 1: Empowering ethics committees

RECOMMENDATION 1

NABH and FERCI should develop an IT enabled platform that enables ECs to manage a research project throughout its life cycle

Target Agency: NABH; FERCI; NIC

Rationale

IT enabled platforms for project management by ECs were found to be extremely useful in several countries

Operational Plan

- Rather than creating a platform from scratch, the tool 'eEC', should be further developed under the aegis of the National Informatics Centre (NIC) and adopted for pan-India implementation by National Accreditation Board for Hospitals & Healthcare Providers (NABH). End-to-end encryption for each project should be ensured for data protection
- The service should be monetized eventually and provided in a SaaS (Software as a Service) mode to make it self-sustaining

Potential challenges

- Lack of a push mechanism for adoption of the tool by the ECs
- Fear of sensitive data being leaked from project files may further hamper adoption
- Early monetization of the tool can hamper early adoption

Challenge 1: Empowering ethics committees

RECOMMENDATION 2

A web based interactive GCP learning module should be developed and online training using the module should be mandatory for every EC member

Target Agency: NABH; CDSCO; Indian Council for Medical Research (ICMR)

Rationale

GCP training delivered by online modules is a standard practice followed in USA, EU and several other countries, which helps members to stay updated

Operational Plan

- Experts from bodies like CDSA, FERCI, ICMR etc. should be roped in to create an interactive GCP learning audio-video module
- Such training should be made mandatory for all existing /newly inducted members of ECs and once successfully completed, a GCP course certificate (with a 3 year validity) should be issued based on the performance of the participant.
- After expiry of the GCP certificate, the certification should be renewed and module updates should be done, preferably every 3 years

Potential challenges

- Unless made interactive, the GCP module would be rendered largely ineffective
- Development of a performance matrix for every member in a EC can be difficult
- Early monetization of the certification process can hamper early adoption

Challenge 1: Empowering ethics committees

RECOMMENDATION 3

NABH should draft model Standard Operating Procedures (SOPs) for ECs

Target Agency: NABH, Clinical Development Services Agency (CDSA), ICMR, FERCI

Rationale

Model SOPs are reported to aid in uniform implementation of GCP

Operational Plan

- NABH, in collaboration with experts from CDSA, FERCI, ICMR etc., should draft model SOPs for adoption by ECs
- This would act as a benchmark for ECs to build and improve upon and prepare them for future accreditation

Potential challenges

- The technical jargons and terms used in SOPs should conform to the GCP guidance as laid down by CD-SCO to avoid conflicts
- Lack of explicit push mechanism for ECs to comply and adopt

Challenge 1: Empowering ethics committees

RECOMMENDATION 4

NABH should sign MOUs with other agencies of standing to aid faster accreditation of ECs in India

Target Agency: NABH; QCI

Rationale

Leveraging expertise in other accreditation bodies can help establish in-house expertise at NABH

Operational Plan

- The process of accreditation of ECs should be rolled out only once the above recommendations are implemented
- NABH and Quality Council of India (QCI) should institute a consultation with experts to identify other accreditation boards of standing in the region (Example: SIDCER, AAHRPP etc.)
- NABH should enter into Memorandum of Understanding (MOUs) with the accreditation bodies of standing in order to recognize accreditation by such agencies. Combined accreditation efforts can then follow
- As a push mechanism for ECs to take up research proposals from unaffiliated institutions, accreditation should be made mandatory (if allowed in the long term)
- In the long term only, accredited independent ECs should be allowed to review research proposals other than BA/BE studies

Major challenges in operationalization

- Lack of explicit push mechanism to undergo accreditation
- Lack of expertise and capacity to undergo accreditation
- Other accreditation bodies may not find merit in entering into MOUs with NABH
- In the absence of a periodic reevaluation mechanism for assessment of retaining accreditation, the entire exercise would be rendered ineffective

Challenge 2: Making consent more informed

Case Study 2: Speaking books – an audio visual aide

Idea: A range of easy-to-use audio books designed to get potentially life-saving health messages out to CT participants.

Method: The South African Depression & Anxiety Group (SADAG) created speaking books with simple audio buttons talking the user through each page. The first Speaking Book, voiced by South African actress and celebrity Lillian Dube, was called *Suicide Shouldn't Be a Secret* and focused on how depression is a real and treatable illness, encouraging people to get help when they need it. Several others were later created in different languages enumerating what does participating in CTs entail.

Verdict: Speaking Books have now produced 62 titles in 24 different languages and are now used in 20 African countries across the continent. The books now tackle a number of critical healthcare issues outside of suicide prevention such as HIV and Aids, malaria, maternal health and CT. Speaking Books have also expanded to other countries and are being increasingly used as an audio-visual aid for priming subjects entering CTs. They are usually deployed before a formal informed consent is taken.

Challenge 2: Making consent more informed

RECOMMENDATION 1

Development of IT enabled tools for more meaningful translation of Informed Consent Forms (ICF) into vernacular languages

Target Agency: NABH; FERCI; CDAC

Rationale

The current mechanism of translating and back translating ICF into vernacular languages are often motivated to ring-fence and protect those undertaking clinical research rather than those participating in such research

Operational Plan

- The IT enabled platforms of 'Simplifier', 'Interpreter' and 'EthiX' described in Case Study 1 should be adopted for scale up for pan-India implementation
- The tools may be further developed under the aegis of the Centre for Development of Advanced Computing (CDAC), because of its experience with domain specific machine aided translation tool called CDAC MANTRA
- The fully developed tool then may be hosted by CDAC and made available to all the stakeholders involved in clinical research under an open source license

Potential challenges

- The technical jargon used in the final tool should conform to the GCP as laid by CDSCO to avoid conflicts

Challenge 2: Making consent more informed

RECOMMENDATION 2

Development of audio-visual aids for deployment before consent for clinical research

Target Agencies: ISCR; OPPI, IPA, IDMA; Sponsors; ICMR

Rationale

It is difficult to simplify the contents of the ICF for legal reasons. Deployment of audio-visual aides have been found to facilitate the CT participants in making more informed choices in low-resource settings

Operational Plan

- Industry organizations and sponsors of clinical research should fund the development of audio-visual aides for clinical research participants
- Bodies like ICMR should vet the contents of such aides for any conflicts of interest
- Such aides can then be translated into vernacular languages to be used all across India

Potential challenges

- Requires meticulous translation of the contents into vernacular language in order to render the fidelity of the original message intact
- Absence of ethical clearance for contents of such aids may result in creating biases.

Challenge 2: Making consent more informed

RECOMMENDATION 3

Development of a final technical guidance on audio-visual recording of informed consent process in clinical trials

Target Agencies: CDSCO

Rationale

Audio-visual recording of informed consent process is not feasible for several disease conditions¹³

Operational Plan

- The existing draft guidance should be updated and the amendments brought till date should be incorporated in the document
- Option of not being recorded should be provided to the CT participant
- The trial participant should be given the freedom to have his/her consent not recorded without citing a reason
- The written consent form should also contain a statement to exercise this option
- The updated guidance should further enlist conditions/therapeutic categories for which exemptions for audio-visual recordings may be allowed

Potential challenges

- Absence of such a guidance document from other countries, hence lack of experience/lessons with audio-visual recordings

¹³ Several experts and clinical investigators with experience of conducting clinical studies on patients with existing psychological disorders expressed concerns about taking consents from such subjects in front of cameras.

Challenge 3: Compensating for injury or death related to a clinical trial

Case Study 3: From causality to relatedness - compensating SAEs in clinical research

One of the issues faced by the clinical research community globally is assessment of the causal association of adverse events to investigational products. While numerous methods for causality assessment of adverse events have been published in the past, few have focused on the issue exclusively from a CT perspective. The WHO-UMC system of causality assessment was designed primarily for pharmacovigilance as a tool to use in the assessment of case reports. While the WHO-UMC system provides a structure that can be applied to adverse events in CTs, it was not designed specifically for use with investigational agents before approval and labeling.

The ISCR (Indian Society for Clinical Research) and the MRCT (Multi-Regional Clinical Centre), Harvard, recognized a need to develop a more specific tool which can help standardize causality assessment in the context of CTs. The tool expands upon the existing WHO-UMC system and represents a comprehensive framework for CT causality assessment. The framework lists 22 data points and provides an assessment questionnaire (algorithm) with 29 binary-response questions. The responses to the individual questions in the questionnaire can be plotted against essential and supplementary criteria for classification of an event into one of the 4 WHO-UMC causality categories: 'certain', 'probable', 'possible' and 'unlikely'.

The framework is an algorithm-based non-proprietary tool that has the potential to enhance standardization of case causality assessment in CT and allow greater reliance on the use of the WHO-UMC system in clinical research. The causality assessment can then be used to arrive at a decision on whether an SAE was related or unrelated to a CT.

Challenge 3: Compensating for injury or death related to a clinical trial

RECOMMENDATION 1

In addition to global introspection methodology, adoption of an algorithm for causality assessments to help in arriving at a decision on relatedness of an injury/death to an investigational product

Target Agencies: CDSCO; ISCR

Rationale

Objective algorithms are shown to bring uniformity in causality assessments and helps in building a broad consensus on final assessments

Operational Plan

- CDSCO should adopt the algorithm formulated by ISCR-MRCT for use in causality assessments by the designated expert committee
- A detailed guidance document may be drafted on how the algorithm may be applied to aid decisions made by experts

Potential challenges

- The use of the algorithm is only to aid the decision of an expert, who can still ignore the output from the algorithm

Challenge 3: Compensating for injury or death related to a clinical trial

RECOMMENDATION 2

CDSCO should adopt a more focused approach towards passing orders for compensation for injury or death related to a trial.¹⁴ For cases where an EC agrees to compensate a CT participant and the sponsor agrees to pay adequate compensation, submitting an authenticated proof of payment along with the SAE report to the DCG(I) should complete the SAE reporting cycle

Target Agencies: CDSCO

Rationale

An analysis for relatedness (in case of injury or death) by an EC, recommending to provide compensation to a CT participant is unlikely to be overturned by the regulatory authority or the SAE expert committee

Operational Plan

- Rules mandating submission of those SAEs reports where the sponsor agrees to pay fair compensation should be suitably amended to truncate further analysis of an SAE by the expert committee
- Only in cases where the trial participants or his/her nominee(s) as the case may be, do not agree with the decision of the EC, the report of SAE should be referred to the licensing authority i.e. DCG(I) for final examination and decision
- A detailed procedure should be provided, mentioning the modalities of providing adequate compensation based on promulgated formulas and generating authenticated proof of such payment made to the CT participant
- Detailed guidance should be issued laying out the entire procedure

Potential challenges

- Authentication of payment of compensation to the participant can pose several problems
- Generation of proof of payment would translate to compensating participants within 14 days and would pose a major challenge

¹⁴ For DTAB's recommendation on this issue see, Agenda S1 under minutes for 73rd DTAB meeting, available at: http://www.cdsc0.nic.in/writereaddata/73_DTAB_Minutes%20as%20approved%20_.pdf (last accessed on 4th April 2017).

Challenge 4: Addressing uncertainty

RECOMMENDATION 1

CDSCO should devise a comprehensive communication strategy for its policies, decisions and regulatory thinking on matters under their mandate

Target Agency: CDSCO

Rationale

The often cited problem with CDSCO was the lack of a formal communication strategy. Stakeholders communicated difficulties in navigating the drug regulator's website, lack of a notification system for updates on notices, orders etc. and the fact that things are often communicated verbally

Operational Plan

- Active use of social media platforms
- Information to be better labelled and segregated on the website
- Starting a feed based notification system. The IT tool of 'Regulert' from Case Study 1 may be adopted
- Time bound communication of SEC decisions to CT applicant
- Issuing technical guidance on all identified issues
- Posting minutes of meetings of every proceeding within CDSCO
- Meta data from SUGAM should be made available for trend analysis by stakeholders and media personnel
- Holding regular stakeholder consultations for feedbacks
- Every submission or comment from public or other stakeholders on draft rules, provisions, guidance etc. should receive an acknowledgement

Potential challenges

- Lack of a dedicated unit within CDSCO to execute a comprehensive communication plan

Challenge 4: Addressing uncertainty

RECOMMENDATION 2

CDSCO should delegate an independent body to undertake regulatory impact assessment of the regulatory changes brought to the D&C Rules that affected CTs

Target Agencies: CDSCO

Rationale

Revision of technical guidance documents are based on assessments of past changes in the regulation

RECOMMENDATION 3

The already proposed provision of Pre-Submission Meetings¹⁵ of CTs applicants with subject experts should be implemented

Target Agencies: CDSCO

Rationale

National Drug Regulatory Authorities across the world have pre-submission consultations as a regular feature with the aim to bring transparency, accountability, predictability and speedy regulatory approvals

RECOMMENDATION 4

In the long term, CDSCO should strive to build in-house capacity for scientific and ethic review of CT protocols

Target Agencies: CDSCO

Rationale

Across the globe, having in-house expertise within National Drug Regulatory Authorities aids speedy disposal of applications

¹⁵ See Agenda S1 under minutes for 73rd DTAB meeting, available at: http://www.cdsc.nic.in/writereaddata/73_DTAB_Minutes%20as%20approved%20_.pdf (last accessed on 3rd April 2017)

Challenge 5: Miscellaneous issues

RECOMMENDATION 1

The newly drafted D&C Rules for CT should include a provision for post-trial access to beneficial investigational products (NCEs) and a detailed technical guidance should be formulated

Target Agency: CDSCO

Rationale

An investigational drug is unlikely to be generally available to the community or population until sometime after the conclusion of the study/trial. Provisions for post-trial access is a key issue being currently addressed worldwide

Operational Plan

- DTAB's 2015 recommendation on "Post-Trial Access to Investigation Products,"¹⁶ should be implemented.
- A detailed guidance document should be drafted and provisions for what constitutes 'benefit' or 'beneficial'¹⁷ to the community with respect to the investigational product should be enumerated
- The guidance document should take cognizance of the ethical principles laid out in the International Ethical Guidelines for Health-related Research Involving Humans by CIOMS, WHO, 2016 and the Declaration of Helsinki, 2013

Potential challenges

- Defining what constitutes as 'benefit' and what doesn't, with reference to an investigational product can be a challenge

¹⁶ DTAB recommended that post-trial access of the investigational products may be provided to the CT participant, if during the course of the trial, an investigational product is found to be beneficial. This is to be based on the recommendations of the investigator and EC, especially in cases where no alternative therapy is available to the patient. However, such post-trial access of the investigational product should be permitted after obtaining the consent of the patient, however, there would not be any liability of the sponsor in use of the drug. The sponsor shall arrange to provide the drug in such cases free of cost as the drug might not yet have been permitted to be marketed. Drugs and Cosmetics Rules, 1945 may be amended appropriately. Available at: <http://www.cdsc.nic.in/writereaddata/newMinutes%20of%2068th%20DTAB%20meeting.pdf> (last accessed on 4th April 2017).

¹⁷ The term 'benefit' or 'beneficial' is a relative term in many of the CTs and it is often difficult to quantify the benefit of the investigational product compared to the standard of care. During the field interviews, the term was found to be of much controversy in South Africa where a guidance document had been drafted on "POST CLINICAL TRIAL DRUG ACCESS" by the Medicines Control Council, South Africa. The document is available at: http://www.mcca.com/documents/f27b533e2.42_Post_Clinical_Trial_Drug_Access_Apr16_v1.pdf (last accessed on 3rd April 2017).

Challenge 5: Miscellaneous issues

RECOMMENDATION 2

CDSCO should draft a detailed guidance on what constitutes a 'standard of care'¹⁸ for use in clinical studies

Target Agencies: CDSCO

Rationale:

In the absence of a regulatory definition of 'standard of care', a general advice on using a standard of care cannot be applied to all situations

RECOMMENDATION 3

Define conditions for a CT waiver and institute an accelerated approval pathway for drugs already approved in stricter regulatory jurisdictions

Target Agencies: CDSCO

Rationale

Clinical data from local bridging studies in India has not led to a single drug being denied marketing approval. DTAB recommendations in this regard should be implemented¹⁹

¹⁸ A standard of care may be universal or non-universal. The term 'universal standard of care' is usually defined as the best current treatment available anywhere in the world; the term 'non-universal standard of care' refers to regional and local standards that might entail a lower level of care. The costs of providing a particular standard of care may not be confined merely to the cost of providing medicines, but may also include the related costs of improvements to the healthcare system and infrastructure. A requirement for a universal standard can prevent research that has the potential to benefit people in developing countries from being undertaken. For example, research which aims to compare a new treatment with one currently available to the target population might not be possible. For a more detailed exposition see, report titled "The ethics of research related to healthcare in developing countries", Nuffield Council On Bioethics, 2002; available at: <http://nuffieldbioethics.org/wp-content/uploads/2014/07/Ethics-of-research-related-to-healthcare-in-developing-countries-I.pdf> (last accessed on 4th April 2017).

¹⁹ Rule 122A in DCR, 1945, states, "Provided that the requirement of submitting the results of local clinical trials may not be necessary if the drug is of such a nature that the Licensing Authority may, in public interest decide to grant such permission on the basis of data available from other countries", and hence provides for the waiver of the requirement of conducting a local CT in India. An idea was mooted during the term of an erstwhile DCG(I) that for applications with clinical data already evaluated by certain strict regulatory jurisdictions, the requirement of conducting a local clinical trial may be waived off. However, this was never brought into practice. A similar provision was brought via an office order in 2015 for biosimilars. See Appendix VI, entry 16a. This idea is again doing rounds in policy circles, see for instance, Agenda No. S-2, minutes of the 75th meeting of Drugs Technical Advisory Board (DTAB), held on 3rd January, 2017. Available at: http://www.cdsc.nic.in/writereaddata/Minutes%20of%2075th%20DTAB%20held%20on%2003_01_2017.pdf (last accessed on 4th April 2017).

Challenge 5: Miscellaneous issues

RECOMMENDATION 4

CTRI should restructure the database to improve public access to information

Target Agencies: NIMS, ICMR

Rationale

In-depth trend / meta-analysis of clinical trial entries from the CTRI dataset is currently problematic.

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