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DRAFT NEW DRUGS AND CLINICAL TRIALS RULES, 2018

SUBMISSIONS TO THE MINISTRY OF HEALTH AND FAMILY WELFARE

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EXECUTIVE SUMMARY

In a notification dated February 1, 2018, the Central Government invited comments on the draft New Drugs and Clinical Trials Rules, 2018 ("**Rules**"). These Rules regulate the conduct of clinical trials (including clinical trial related injury and compensation), bioavailability and bioequivalence studies, and the import and manufacture of new drugs. They also govern the functioning of several entities such as the Central Licensing Authority, Ethics Committees and Bioavailability and Bioequivalence Study Centres. These entities and processes are currently governed by scattered provisions contained in the current Drugs and Cosmetics Rules, 1945, several gazette notifications, circulars and office orders. These Rules are a welcome step, and will help to consolidate and streamline the provisions under these different instruments. They will also increase regulatory certainty. However, certain issues must be addressed before these Rules can be effectively implemented.

First, there is a need to draw a clearer conceptual distinction between biomedical and health research broadly, and 'clinical trials' and 'academic clinical trials' as its components. Currently, there is a potential for overlap in the way clinical trials and academic clinical trials are defined. As opposed to clinical trials, the data generated from academic clinical trials are not intended to be submitted for the purposes of regulatory approval. For example, a trial for a new indication, new route of administration, new dose or dosage form could constitute a clinical trial or academic clinical trial depending on the drug being used. It may be difficult to classify a trial into one of these two categories in case of uncertainty about the status of the drug.

Further, the Rules also contain insufficient provisions to prevent the misuse of the data generated from these trials for commercial or regulatory purposes. Finally, there is a need to ensure that volunteers are protected against and compensated for risks arising out of any clinical research, whether it is academic in nature or not. For this, it is recommended that a 'risk-based' categorisation be adopted for the different types of clinical trials. Guidance may be sought from regulations in the European Union which make a similar categorisation. The safeguards and compensation provisions which apply to clinical trials must also be explicitly extended to academic clinical trials as well.

Second, there is a need to clarify and harmonise some of the definitions in these Rules with international standards. For instance, the definition of 'orphan drug' states that it is a drug meant for the treatment of a condition that affects less than 2 lakh people in the country. However, there is currently no official definition and prescribed prevalence rate for a 'rare disease'. The Rules must therefore not specify any such threshold while defining orphan drugs until an official definition is arrived at by the government, since the inclusion of an imprecise threshold may exclude several crucial diseases from the scope of this provision. Similarly, the definition of 'sponsor' must be harmonised with the Good Clinical Practices Guidelines ("**GCP Guidelines**") to include situations where the sponsor and investigator may be the same person, institution or organisation.

Third, there is a need for greater clarity on several provisions related to the composition and functioning of Ethics Committees. Most importantly, there are three different provisions prescribing the qualifications of members of these Ethics Committees, which are in conflict

with one another. Further, while the Rules state that members of these Ethics Committees must not have conflicts of interest, this term has not been defined. This allows for a great degree of ambiguity and provides insufficient guidance for Ethics Committee members.

Fourth, several Rules have been introduced which act as exceptions to the usual regulatory process. The provisions on accelerated approval and expedited review are welcome. However, there is a need to hold wider stakeholder consultation and take into account the international experience before several other provisions can be introduced. Most importantly, the provision for deemed approval for clinical trials in cases where the Central Licensing Authority does not reply to the applicant within a certain time period must be removed. The provisions enabling post-trial access to new drugs for clinical trial subjects and expanded patient access to any new drug on the opinion of a government medical officer or institution may also pose a risk to the safety of vulnerable patients. Stricter safeguards must therefore be introduced to prevent the exploitation of these patients.

Finally, there is a need to clarify several provisions in the chapter on compensation for participants in biomedical research to ensure that these are effectively enforced. More precise reporting requirements must be imposed on investigators and sponsors, and the non-payment of compensation in accordance with these Rules must attract stricter consequences. There is also a need to recognise the breach of sensitive health data as an 'injury' under these Rules. As a general comment, it must be noted that there are incomplete provisions and incorrect cross-referencing throughout the draft Rules. These must be corrected before the final Rules are notified. In these submissions, we have undertaken a clause-by-clause analysis of the Rules. Where possible, we have looked at the international experience and suggested alternative provisions.

CLAUSE-BY-CLAUSE COMMENTS

Clause No.	Clause text	Comments	Suggestions for Alternative Provision
1(3)	It applies to all new drugs, investigational new drugs for human use, clinical trial, bioequivalence study, bioavailability study and Ethics Committee.	These Rules are also applicable to sponsors, investigators, manufacturers, government hospitals, government medical institutions and expert committees for the determination of compensation for clinical trial subjects.	The clause should be amended to indicate all the parties these Rules are applicable to. In the alternative, the provision should be deleted.
2(1)(a)	"academic clinical trial" means a clinical trial of a drug already approved for a certain claim and initiated by any investigator, academic or research institution for a new indication or new route of administration or new dose or new dosage form, where the results of such a trial are used only for academic or research purposes and not for seeking approval of the Central Licensing Authority or regulatory authority of any country for marketing or commercial purpose;	(i) Academic clinical trials, as defined in this clause, may be conducted by any entity, including a pharmaceutical company through a clinical research organisation. While the clause says that the data generated from these trials is not to be used to seek approval from the Central Licensing Authority or the regulatory authority of any other country, it is not clear how the latter will be monitored. There is thus a possibility of the misuse of this provision where the sponsor or investigator may submit it for regulatory approval in another country. Especially due to data exclusivity and data protection laws in several countries, this may not be detected. Further, there must be some consequences attached to the submission of this data for regulatory approval to ensure compliance. Therefore, a provision may be introduced to	This provision should be amended to account for the risk posed by the clinical study. A possible definition is as follows: *The approval of the Licensing Authority shall not be required for studies where the risk involved to the participants is no more than that involved in the course of normal treatment. These include the following studies:* *(i) Studies involving the retrospective analysis of data* *(ii) Prospective observational studies, on marketed drugs where patients are being treated according to the judgment of the attending medical practitioner, where no randomisation code is involved, and where the study involves observing the outcome of the*

		penalise applicants if they submit this data to a regulatory authority, or use it for sale/promotional purposes. This penalty must be in addition to refusing to consider that application for regulatory approval. (ii) Studies on a "new indication or new route of administration or new dose or new dosage form" of a drug may still pose risk to clinical trial volunteers and the possibility of serious adverse events still remains, whether the trial is conducted for academic or commercial purposes. Therefore, instead of the possibility of submission for regulatory approval, clinical trials should be categorised in terms of the risk posed to clinical trial volunteers. For this, guidance may be sought from the EU regulations. In the 2014 regulations (No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use), clinical trials are 'low-intervention clinical trials' if they satisfy the following conditions: *"(a) the investigational medicinal products, excluding placebos, are authorised;* *(b) according to the protocol of the clinical trial, (i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal*	*treatment and may include non-invasive or minimally invasive tests such as blood collection. Such studies include post marketing surveillance studies, off-label use of the drug.* *(iii) Studies involving new indications, new routes of administration, new formulations or new doses of drugs that have already received marketing authorisation in India, provided that:* *1. The proposed dose, its duration, and the systemic drug exposure is the same or lower than that permitted by the Licensing Authority and reflected in the existing package insert; and* *2. There is prior pre-clinical and clinical data on the safety and efficacy of the proposed use of the drug.* *3. Application is made in the format prescribed in form …* Further, while granting approval, the Ethics Committee must also require the applicants to submit and conduct, as the case may be, adequate post-marketing risk minimisation plans, studies in special populations, post-marketing surveillance drug utilization, outcome studies and periodic study update reports.

		products in any of the Member States concerned; and *(c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned;"*	These additional responsibilities will require stricter monitoring of Ethics Committees and their registration.
2(1)(k)	"clinical trial protocol" means a document containing the background, objective, rationale, design, methodology including matters concerning performance, management, conduct, analysis, adverse event, withdrawal, statistical consideration and record keeping pertaining to clinical trial;	The clinical trial protocol should also include the risk management plan. This is an important component of any clinical trial protocol.	The risk management plan should be included in this list.
2(1)(l)	"clinical trial site" means any hospital or institute or any other clinical establishment having the required facilities to conduct a clinical trial;	A reference must be made to the Clinical Establishments Act, 2010 to clearly define what qualifies as a 'clinical establishment'. A venue must not qualify as a 'clinical establishment' unless it meets the minimum requirements set out under the Clinical Establishments Act, provided that the Act has been notified or a state-specific legislation on clinical establishments has been enacted.	The following should be added: *For the purpose of these Rules, a clinical establishment shall be the same as defined under the Clinical Establishments Act, 2010.*
2(1)(s)	"investigator" means a person who is responsible for conducting clinical trial at the clinical trial site under these rules;	The definition in this clause is restrictive and must be harmonised with the GCP guidelines. There is also a need to clarify who the obligations under these Rules apply to in case of clinical trials involving more than one investigator. The GCP guidelines define these	The definition of 'investigator' must be harmonised with the definition in the GCP guidelines.

		different categories of investigators as follows: *"1.34 **Investigator** A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator."*	
2(1)(vv)	'orphan drugs' means a drug intended to treat a condition which affects fewer than two lac person in India.	The categorisation of orphan drugs as those meant for conditions which affect less than two lakh people in the country is not based on any sound scientific estimate, and could end up excluding people suffering from rare diseases who are in need of orphan drugs but where the prevalence exceeds this 2 lakh threshold. The National Policy for Treatment of Rare Diseases released by the Ministry of Health and Family Welfare in 2017 states that there is currently a lack of epidemiological data on the number of people who have rare diseases in the country. It has therefore recommended that a definition for rare diseases must be arrived at on a priority basis as soon as sufficient data is available. In the absence of this data and a standard definition, the Rules must not specify a number that qualifies a drug as an 'orphan drug'. Until an official definition is arrived at, it is recommended that the definition be kept	The definition of 'orphan drugs' must be re-drafted and kept broad till an official precise definition is arrived at. It must also include drugs that are used not just to treat, but also manage a medical condition. The following factors may also be accounted for in such a definition (National Policy for Treatment of Rare Diseases, 2017, p 11): Location- A disease which is uncommon in one country may be quite common in other parts of the world; Levels of rarity - Some diseases may be much rarer than other diseases which are also uncommon; and Study-ability- Whether the prevalence of a disease lends itself to clinical trials and studies.

		broader and be amended later. In this context, it is useful to refer to the definition of 'orphan drug' used by the USFDA. This definition states simply that an orphan drug is "a drug intended for use in a rare disease or condition".	
2(1)(zb)	"serious adverse event" means an untoward medical occurrence during clinical trial resulting in death or permanent disability or hospitalisation of the trial subject where the trial subject is an outdoor patient or a healthy person, prolongation of hospitalisation where the trial subject is an indoor-patient, persistent or significant disability or incapacity, congenital anomaly, birth defect or life threatening event	While this definition is in consonance with the GCP Guidelines, there is a need to ensure uniformity across different official documents such as the ADR reporting form under the Pharmacovigilance Program of India, where the definition of serious adverse event is as follows: *A reaction is serious when the patient outcome is:* • *Death* • *Life-threatening* • *Hospitalization (initial or prolonged)* • *Disability (significant, persistent or permanent)* • *Congenital anomaly* • *Required intervention to prevent permanent impairment or damage* In this context, there is also a need for greater clarity on what constitutes 'persistent or significant disability'. It is therefore recommended that the CDSCO issue guidance on this.	-
2(1)(zc)	"similar biologic" means a	Since there are multiple countries that are	The definition should be amended as

	biological product which is similar in terms of quality, safety and efficacy to reference biological product licensed or approved in India or any innovator product approved in International Council of Harmonisation (ICH)member countries;	now members of the International Council of Harmonisation, this definition must be restricted to the member countries notified under Rule 100 of the Rules.	follows: *"similar biologic" means a biological product which is similar in terms of quality, safety and efficacy to reference biological product licensed or approved in India or any innovator product approved in International Council of Harmonisation (ICH) member countries* ***specified in Rule 100 of these Rules***.
2(1)(zd)	"sponsor" includes a person, a company or an institution or an organisation responsible for initiation and management of a clinical trial;	There is a need to clarify whether this can include the investigator, since the sponsor and investigator may be the same in some clinical trials. For instance, the GCP guidelines define a 'sponsor-investigator' separately from a 'sponsor' to mean: *"An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator."*	The definition of sponsor should be amended to clarify when an investigator may also qualify as a sponsor.
7(1)	Constitution of Ethics Committee. - The Ethics Committee shall have of a minimum of seven members from	The categories specified in this provision do not adequately clarify the qualifications of the EC members. For instance, how is a 'non-	Clause 7(4) should be deleted, and the qualifications under clause 7(1) should be clarified.

	the following areas,- (i) Medical Science; (ii) Scientific; (iii) Non-medical; (iv) Non-scientific; (v) One lay person; and (vi) One woman member.	medical' member different from a 'non-scientific' member or a 'lay person'? If one of the members from categories (i)-(v) is a woman, is category (vi) automatically satisfied? Further, there is repetition in clause 7(4), which states that "The committee shall include at least one member whose primary area of interest or specialization is non-scientific and at least one member who is independent of the institution."	
7(7)	Every member of the Ethics Committee shall be required to undergo such training and development programmes as may be specified by the Central Licencing Authority from time to time: Provided that any member, who has not successfully completed such training and developmental programmes, shall be disqualified to hold the post of member of the Ethics Committee and shall cease to be a member of such committee.	Once an EC member has been disqualified, there should also be an option for them to complete the required training and development programmes and resume their position as EC member.	The following proviso should be added: *"Provided that any member who has been disqualified under this Rule shall be eligible to re-apply for membership once they have successfully completed the training and developmental programme as specified by the Central Licensing Authority."*
7(10)	No person having a conflict of interest shall be the member of an Ethics Committee and all members shall sign a declaration to the effect that there is no conflict of interest in the clinical trial or	It is unclear what constitutes 'conflict of interest' in this context. This phrase must be clearly defined, and if possible, illustrative examples of conflict of interest should be provided.	At least three kinds of conflict of interest might occur and ought to be avoided. These are: ● A financial interest in the outcome of the trial ● A professional interest, for

	bioavailability or bioequivalence study protocol being reviewed by the committee.		instance, when a member is also part of the investigating team ● A personal interest, when a member has a relative or friend participating in the trial
10(2)	The Central Licencing Authority shall, after scrutiny of information furnished with the application and after taking into account the inspection report, if any, and after such further enquiry, as considered necessary and on being satisfied that the requirements of these rules have been:...	It is unclear what this inspection report is, who prepares it and what its contents are. These must be specified.	
12(1)	No clinical trial or bioavailability or bioequivalence protocol and related documents shall be reviewed by an Ethics Committee unless at least five of its members as detailed below are present, - (i) medical scientist (preferably a pharmacologist); (ii) clinician; (iii) legal expert; (iv) social scientist or representative of non-governmental voluntary agency or philosopher or ethicist or theologian or a similar person; (v) lay person from community	This provision contradicts clause 7. The requirements under both these provisions must be harmonised.	Since this clause is more specific and provides guidance on the composition of the Ethics Committee, it is recommended that this provision should be retained and clause 7 deleted.
13(1)	The Ethics Committee shall maintain data, record, registers and other documents related to the	It is unclear why the requirements to maintain data about clinical trials and BA/BE studies is limited to five years. A process	

	functioning and review of clinical trial or bioavailability study or bioequivalence study, as the case may be, for a period of five years after completion of such clinical trial.	should be put in place for the digitisation of these records so that they can be stored for a longer period and retrieved when required.	
18(1)	Subject to provision of rule 17, where the Ethics Committee fails to comply with any provision of these rules, the authority designated under sub-rule (1), may, after giving an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, take one or more of the following actions, namely, - (i) issue warning to the Ethics Committee describing the deficiency or defect observed, which may adversely affect the rights or well-being of the study subjects; (ii) suspend for such period as considered appropriate or cancel the registration issued under rule 18; (iii) debar its members to oversee any biomedical health research in future for such period as may be considered appropriate.	This provision must also give the Central Licensing Authority the power to issue notice to an EC, and ask for an action taken report based on the deficiencies or defects observed. Based on this action taken report, it may recommend further action with respect to the clinical trial or EC. This may include halting the trial if necessary. If halting the trial may lead to harm for the clinical trial participants, it should also be possible for the EC to direct the sponsor to take remedial measures or take over supervision of the trial itself.	After clause 18(1)(i), the following provisions should be added: *(ii) Issue notice asking for the submission of an action-taken report on the deficiency or defect observed in the warning in sub-rule (i).* *(iii) Notwithstanding anything contained in sub-rules (i) and (ii), suspend registration for such period as considered appropriate or cancel the registration issued under rule 18;* *(iv) Notwithstanding anything contained in sub-rules (i) and (ii), debar its members from overseeing any biomedical health research in future for such period as may be considered appropriate.*
18(2)	Where the Ethics Committee or its member, as the case may be, is aggrieved by an order of the authority designated under sub-rule	The provision does not impose a time limit within which the Central Government must pass its order.	This provision must specify the period within which the Central Government must pass its order.

	(1), it may, within a period of forty- five days of the receipt of the order, make an appeal to the Central Government in the Ministry of Health and Family Welfare, Government of India, and the Central Government may, after such enquiry, as deemed necessary, and after giving an opportunity of being heard, pass such order in relation thereto as may be considered appropriate in the facts and circumstances of the case.		
23(1)	Permission to conduct clinical trial of a new drug or investigational new drug as part of discovery, research and manufacture in India.- (1) Notwithstanding anything contained in these rules, where any person or institution or organisation make an application under rule 21 to conduct clinical trial of a new drug or an investigational new drug which fulfils the following conditions, namely,- (i) the drug is discovered in India; or (ii) research and development of the drug are being done in India and also the drug is proposed to be manufactured and marketed in India	This provision provides for an expedited decision making process with respect to drugs which have been developed in India. However, it is insufficient to state that the drug must be 'proposed' to be manufactured and marketed in India. An undertaking must be taken from the applicant to this effect to ensure that the drug will be available to patients in India.	Rule 23(1)(ii) should be replaced with the following: "*(ii) research and development of the drug are being done in India and also the applicant has given an undertaking that the drug will be manufactured and marketed in India subject to the necessary approval being obtained.*"
23(1) P	Provided that, where no	This provision indicates a lack of regulatory	It is recommended that this proviso

	communication has been received from the Central Licensing Authority to the applicant within the said period, the permission to conduct clinical trial shall be deemed to have been granted by the Central Licensing Authority and such permission shall be deemed legally valid for all purposes and the applicant shall be authorised to initiate clinical trial under these rules.	oversight over clinical trials that may pose high levels of risk to clinical trial volunteers. Therefore, such a provision with respect to deemed approval must be removed.	should be deleted.
25(viii)	in case of an injury during clinical trial to the subject of such trial, complete medical management and compensation shall be provided in accordance with CHAPTER VI and details of compensation provided in such cases shall be intimated to the Central Licencing Authority within thirty days of the receipt of recommendations made by Ethics Committee in accordance with CHAPTER VI;	Since the term 'injury' has not been defined, the term should be replaced with 'adverse event' in this rule. In the alternative, it must be clarified that the definition of an 'injury' shall be the same as defined in Rule 41(5).	This provision should be replaced with the following: *"in case of an adverse event occurring during clinical trial to a trial subject, complete medical management and compensation shall be provided in accordance with CHAPTER VI and details of compensation provided in such cases shall be intimated to the Central Licensing Authority within thirty days of the receipt of recommendations made by Ethics Committee in accordance with CHAPTER VI;"*
25(xii)	where the new drug or investigational new drug is found to be useful in clinical development, the sponsor shall submit an application to the Central Licencing Authority for permission to import or manufacture for sale or for	(i) In this provision, it is unclear what the term 'useful' means. This term should be replaced with 'therapeutic benefit' or a similar phrase. (ii) This requirement for the sponsor to make an application for import or manufacture	It is recommended that this provision be replaced with the following: *"where the new drug or investigational new drug is found to have therapeutic benefit in clinical development, the sponsor shall submit an application to the*

	distribution of new drug in India, in accordance with CHAPTER X of these rules, unless otherwise justified;	must be made time bound. (iii) There must be consequences for a failure to make an application in this manner.	*Central Licensing Authority for permission to import or manufacture for sale or for distribution of new drug in India, in accordance with CHAPTER X of these rules within a period of two years if the completion of clinical trials, unless otherwise justified"*
27	Post-trial access of investigational new drug or new drug.- Where any investigator of a clinical trial of investigational new drug or new drug has recommended post-trial access of the said drug after completion of clinical trial to any trial subject and the same has been approved by the Ethics Committee, the post-trial access shall be provided by the sponsor of such clinical trial to the trial subject free of cost	There are several possible justifications to provide post-trial access to INDs and new drugs to trial volunteers. Point 34 of the Declaration of Helsinki on Ethical Principles for Medical Research involving Human Subjects states that "In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process." The possibility of exploitation and side-stepping of the regulatory process has led to advanced jurisdictions introducing strict safeguards. For example, in the United States, a monitoring plan is developed for adverse events and the response (compensation and medical care). If access will be provided, this is included in the initial consent document. Similarly, safeguards must be put in place to ensure that vulnerable subjects are not	To ensure the safety and well-being of trial subjects, at least the following safeguards should be introduced: 1. Post-trial access must only be available after the completion of phase III trials. This eliminates the risk of the misuse of this process to conduct a de-facto clinical trial. 2. Post-trial access to the drug should be provided only until the drug has received marketing approval, or for a period of two/three years after the completion of the clinical trial, whichever is earlier. This period of two-three years has been allowed just in case the sponsor takes longer than 2-3 years to receive marketing approval for the drug. Alternatively, registering the drug for marketing should be made compulsory within a specified time. 3. Further, there must be a positive

		exploited and that their rights, safety and well-being are ensured. There is a need for wider debate and consultation with all concerned stakeholders before such a provision is introduced. In the interim, we recommend the introduction of certain minimum safeguards.	obligation on the sponsor/investigator to inform the Central Licensing Authority about any significant information about the health effects of the drug and stop access to the drug if any harmful side-effects are discovered at any stage during or after the clinical trials. 4. The sponsor and investigator must be prohibited from collecting any clinical data from the trial subjects unless this done as part of a proper clinical trial. 5. Finally, they must also be prohibited from submitting this data to any regulatory authority. This is because such submission would turn this process into a clinical trial and under the current provisions, there is no scope for granting compensation to persons receiving post trial access.
27(i)	if the clinical trial is being conducted for an indication for which no alternative therapy is available and the investigational new drug or new drug has been found to be beneficial to the trial subject by the investigator; and	It is recommended that the phrase 'no alternative therapy is available' be replaced with a requirement for there being an unmet need for the therapy. There are only very few indications for which no therapies currently exist, and limiting this provision in such a manner may result in the condition to invoke this provision never being satisfied. Here 'unmet medical need' must be defined in a similar manner as defined in the Second	It is recommended that this sub-rule be amended as follows: *"if the clinical trial is being conducted for an indication for which there is an unmet medical need and the investigational new drug or new drug has been found to be beneficial to the trial subject by the investigator; and* For the purpose of this Rule, an 'unmet

		Schedule. Another alternative that may be explored is to limit access to situations where there is 'no comparable or satisfactory alternative therapy', a standard that is applied by the USFDA in its regulations (21 CFR 312.305)	medical need' is as defined in the Second Schedule i.e. "a situation where treatment or diagnosis of disease or condition is not addressed adequately by available therapy. An unmet medical need includes an immediate need for a defined population (i.e., to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs)."
28(i)	Academic clinical trial.-(1) No permission for conducting an academic clinical trial shall be required for any drug from the Central Licencing Authority where,- (i) the clinical trial in respect of the permitted drug formulation is intended solely for academic research purposes including generating knowledge, knowing mechanism, advancement of medical science, determination of new indication or new route of administration or new dose or new dosage form; and	This definition contradicts, and is much broader than, the definition of academic clinical trials in clause 2(1)(a). The intended purpose of academic clinical trials, as listed in this provision, could include clinical trials usually conducted for regulatory purposes. The determination of new indication, new route of administration, new dose or new form, particularly, brings these studies within the definition of 'new drugs' on which clinical trials must be conducted to ascertain their safety and efficacy.	It is recommended that this sub-rule be deleted. Additionally, it must be specified that data generated from these studies cannot be used to market or promote the sales of a drug.
30(1)(ii)	Suspension or cancellation of permission to conduct clinical trial.- (1) Where any person or institution or organisation to whom permission has been granted under rule 22 in Form CT-06 fails to	It is unclear what it means to 'reject the results' of a clinical trial by the Central Licensing Authority. If this means that the trial will be taken off the Clinical Trials Registry and discontinued, this must be specified in the Rule.	It is recommended that Rule 30(1)(ii) be re-drafted to clarify what the rejection of the results of a clinical trial entails. Measures must be taken to ensure that the investigator and sponsor do not use the data for approval by regulators in

	comply with any provision of the Act and these rules, the Central Licencing Authority may, after giving an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, take one or more of the following actions, namely,- (ii) reject the results of clinical trial;	Additionally, this Rule must also give the Central Licensing Authority the power to ask for any rectifications of deficiencies noticed by it during the conduct of a clinical trial, and re-inspect the clinical trial site before allowing the clinical trial to proceed.	other countries. Additionally, the following sub-rule should be added after (ii): (iii) direct the person, institution or organisation to rectify any deficiencies observed in the clinical trial. If upon inspection it is found that these deficiencies have been rectified, the Central Licensing Authority may allow the trial to proceed. The following sub-rules are then to be numbered (iv) and (v).
39P	Provided that in case of death or permanent disability, as referred to in subrule (1), if an interim compensation has been paid under sub-rule (1), in such case, the quantum of compensation to be paid shall be an amount which is less the amount paid as the interim compensation.	It is unclear what is meant by 'less than the amount paid as the interim compensation'. If 60% of the compensation (as calculated under Schedule VII) is paid as interim compensation, then the remaining compensation amounts to 40% of the total compensation.	It is recommended that this proviso be deleted, to avoid confusion.
41(5)	Any injury or death or permanent disability of a trial subject occurring during clinical trial or bioavailability and bioequivalence study due to any of the following reasons shall be considered as clinical trial related injury or death or permanent disability, namely,-	The definition of 'injury' must also be expanded to include a claim for compensation arising out of a breach of the trial subject's health data and unauthorised use of the information collected from them. Health data is recognised as sensitive personal data, and its breach constitutes harm to the patient. The trial subject must therefore be	It is recommended that this provision be amended to include a breach of health data as constituting 'injury' under these Rules.

	(i) adverse effect of the investigational product. …	compensated for any breach, or unauthorised use of this data. Further, there must be a positive obligation on the sponsor and investigator to maintain patient confidentiality and protect any identifiable health information either through pseudonymisation/anonymisation or through the use of encryption that meets the minimum standards prescribed by the government. Correspondingly, the manner for computing the compensation to be paid for a breach of health data will also have to be prescribed. Recognising the breach of data in itself as constituting 'harm' to the trial subject, a base amount must be set, which may be increased based on aggravating factors.	
41(4)	Where the sponsor or the person who has obtained permission from the Central Licensing Authority fails to provide medical management, the Central Licencing Authority shall, after affording an opportunity of being heard, by an order in writing, suspend or cancel the clinical trial or bioavailability and bioequivalence study or restrict the sponsor including its representative, as the case may be, to conduct any further clinical trial or bioavailability and	If the sponsor or person who has obtained permission from the Central Licensing Authority does not provide medical management to the clinical trial subject, there is no mechanism prescribed to inform the Central Licensing Authority of this. The trial subject should be able to directly file a complaint with the Central Licensing Authority in case free medical management is not provided to them.	This provision may be re-drafted as follows: "*Where the sponsor or the person who has obtained permission from the Central Licensing Authority fails to provide medical management, the trial subject may file a complaint with the Central Licensing Authority in the format in Form [XX]. Based on this complaint, or suo motu, the Central Licensing Authority shall, after affording an opportunity of being heard, by an order in writing,* *(i) Order medical management to*

	bioequivalence study or take any other action for such period as considered appropriate in the light of the facts and circumstances of the case.		*be provided, or where the treatment has already been obtained, provide reimbursement to the trial subject* *(ii) suspend or cancel the clinical trial or bioavailability and bioequivalence study* *(iii) restrict the sponsor including its representative, as the case may be, to conduct any further clinical trial or bioavailability and bioequivalence study* *(iv) take any other action for such period as considered appropriate in the light of the facts and circumstances of the case."*
42(1)	In case, the investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reasons for delay to the satisfaction of the Central Licencing Authority along with the report of the serious adverse event.	In addition to a requirement for the investigator to give reasons for not reporting a serious adverse event, there must be stricter consequences attached for non-reporting. It is recommended that a penalty provision be introduced for investigators who fail to furnish satisfactory reasons for a delay in reporting a serious adverse event. In case the investigator fails to report a serious adverse event, a provision must also be introduced for trial subjects to be able to approach the Ethics Committee or Central Licensing Authority themselves with their	The provision ought to be re-drafted as follows: *"In case, the investigator fails to report any injury within the stipulated period, he shall have to furnish the reasons for delay to the satisfaction of the Central Licensing Authority along with the report of the serious adverse event. If the Central Licensing Authority is not satisfied with the reasons for the delay, it may bar or temporarily suspend the investigator from conducting clinical trials or bioavailability or bioequivalence*

		grievances. Finally, the compensation provisions use the terms 'injury' and 'serious adverse event' at random, even though these terms have been defined differently. There is a need to clarify the use of these terms, and ensure that compensation is provided not just for serious adverse events but also for the different categories of 'trial related injuries' listed in Rule 41(5). Under this provision as well, the reporting requirement should extend to all injuries, not just serious adverse events.	*trials for a period as it deems fit.* *In case of any grievances with respect to injuries related to the clinical trials, clinical trial subjects may also directly approach the Ethics Committee through a complaint made in form [XX]."*
42(2)(i)	the Central Licencing Authority shall constitute expert committees to examine the cases which shall make its recommendations to the said authority for arriving at the cause of death or permanent disability, as the case may be, and quantum of compensation in case of clinical trial or bioavailability and bioequivalence study related death or permanent disability, as the case may be;	To ensure the legitimacy and reliability of the process of determination compensation, it is important that the expert committee should be independent. While the Central Licensing Authority may appoint the committee, its composition and functioning must be specified in the Rules. The different stakeholders and subject-matter experts must be represented on the committee. A judicial member (possibly a retired judge or legal expert) must also be present on the committee since determining relatedness and the quantum of compensation may involve judicial determination.	Additional clauses must be added outlining and specifying: (i) the composition and term of the expert committee (ii) the manner of appointment and removal of the members of the committee (iii) the functioning of the committee (iv) Transparency and accountability mechanisms must also be put in place
42(2)(ii)	the sponsor or its representative shall forward their reports on serious adverse event of death or permanent disability, as the case	Since the investigator is obligated to report any injury to the sponsor within 24 hours of its occurrence, the obligation on the sponsor must be to forward its report on the injury	The provision should be re-drafted as follows: *"the sponsor or its representative shall*

	may be, after due analysis to the Central Licencing Authority and the head of the Institution where the trial has been conducted within fourteen days of the knowledge of occurrence of serious adverse event of death or permanent disability, as the case may be;	following the investigator's notice. It should not be allowed for them to claim that they did not have knowledge of the injury, since the investigator is under an obligation to report it to them within 24 hours of the occurrence of the adverse event.	*forward their reports on serious adverse event of death or permanent disability, as the case may be, after due analysis to the Central Licencing Authority and the head of the Institution where the trial has been conducted within fourteen days* ***of the occurrence of serious adverse event of death or permanent disability, as the case may be****;"*
42(2)(vi)	in case of death or permanent disability, as referred to in clause (v), the sponsor or the person who has obtained the permission under rule24, shall pay an interim compensation of sixty percent of the compensation payable as per the formula specified in the Seventh Schedule, to the legal heir of the trial subject, in case of death and to the trial subject, in case of permanent disability, within a period of fifteen days from the date of receipt of the opinion of the Ethics Committee by that Sponsor or that person.	The Central Licensing Authority must be empowered to take action against the sponsor in case they fail to pay the ordered compensation to the trial subject or her heir within the time period prescribed. A provision should also be introduced which allows a trial subject to approach an Ethics Committee or the Central Licensing Authority claiming compensation in case of non-payment.	
42(2)(xi)	in case of clinical trial or bioavailability and bioequivalence study related death, the Central Licencing Authority shall, after considering the recommendations of the expert committee, decide the quantum of compensation, as	Currently, the quantum of compensation in case of a serious adverse event is determined by three different entities- the Ethics Committee, the Expert Committee and finally the Central Licensing Authority. This is an unnecessarily complicated process, and it is unclear whose decision will be final in case of	

	per the formula specified in the Seventh Schedule, to be paid by the sponsor, and shall pass orders as deemed necessary within ninety days of the receipt of the report of the serious adverse event.	a disagreement between these entities. It is recommended that this procedure be simplified. Further, it is recommended that a member with legal expertise should be a part of any committee making a recommendation with respect to the quantum of compensation or whether there has been a clinical trial-related injury.	
42(2)(x)	the Central Licencing Authority shall consider the recommendations of the expert committee and shall determine the cause of death with regards to the relatedness of the death or permanent disability, as the case may be, to the clinical trial;	Greater clarity and guidance is needed on the application of the 'relatedness' criteria, the burden of proof that must be discharged and by whom. It is recommended that the burden of proof should be on the investigator/sponsor to show that the injury is caused by something *other* than the clinical trial. If they can't find a definitive cause for the injury, then there should be a presumption that it is related to the clinical trial.	After this clause, the following explanation should be added: *"Explanation: To determine the relatedness of the injury with the clinical trial, the burden of proof shall be on the sponsor to prove that the injury was caused by something other than the clinical trial. If the sponsor fails to discharge this burden, it shall be presumed that the injury is related to the clinical trial."*
42(2)P	Provided that in case of death or permanent disability, referred to in clause (v), if an interim compensation has been paid under sub-rule (1), in such case, the quantum of compensation to be paid shall be an amount which is less the amount paid as the interim compensation.	The language used in this clause is unclear, and may lead to confusion. It is suggested that the clause be re-drafted for clarity.	The clause should be re-drafted as follows: *"Provided that in case of death or permanent disability, referred to in clause (v), if an interim compensation has been paid under sub-rule (1), in such case, the quantum of interim compensation may be deducted from the total quantum of compensation to be paid."*

43	Medical management and compensation for injury or death relating to biomedical and health research. - Notwithstanding anything contained in these rules, medical management and compensation for injury or death relating to biomedical and health research shall be in accordance with the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants specified by the Indian Council of Medical Research from time to time.	It is important to state explicitly that the provisions on free medical management and compensation continue to be applicable to academic clinical trials as well.	The Rules must state that: (a) The provisions related to clinical trials shall apply to academic clinical trials unless otherwise specified and (b) Compensation for injury related to the academic clinical trial must be provided to the trial volunteer in accordance with the Seventh Schedule.
60(1)(ii)	(ii) in case, where the Central Licencing Authority considers that there are some deficiencies in the application and the same may be rectified, said Authority shall inform the applicant of the deficiencies **within the stipulated period referred to in clause (i)**;	Sub-clause (ii) here states that the Central Licensing Authority must inform the applicant of the deficiencies in their application within the period specified in clause (i). However, clause (i) does not specify any such time period.	Sub-clause (i) must be amended to specify the time period within which the Central Licensing Authority must reply to the applicant.
62(1)(ii)	(i) suspend the permission for such period as considered appropriate; or (ii) cancel the permission granted under rule 60 in Form CT-14 or Form CT-15.	In addition to suspending or cancelling permission to manufacture granted in this chapter, the Central Licensing Authority must also have the power to order any stock manufactured in contravention of these Rules to be destroyed.	After sub-clause (ii), it is recommended that the following clause be added: (iii) seize any stock manufactured in contravention of these Rules and order that they be destroyed.
67(1)	(1) No person shall import a new drug or any substance relating	It is unclear what the phrase “or any substance relating thereto” means in the	

	thereto for conducting clinical trial or bioavailability or bioequivalence study except in accordance with the licence granted by Central Licencing Authority.	context of new drugs. This must be clarified.	
72(1)	(1) Where the person to whom a licence has been granted under sub-rule (1) of rule 68, fails to comply with any provision of the Act and these rules, the Central Licencing Authority may, after giving an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, suspend or cancel the licence for such period as considered appropriate either wholly or in respect of some of the substances to which the violation relates and direct the imported new drugs to be disposed of in the manner specified in the said order	In addition to a violation of the provisions of the Act and these Rules, a violation of the conditions of the license must also be a ground for the suspension or cancellation of the import license.	The provision may be re-drafted as follows: *"(1) Where the person to whom a licence has been granted under sub-rule (1) of rule 68, fails to comply with the conditions of the license, any provision of the Act or these rules, the Central Licencing Authority may, after giving an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, suspend or cancel the licence for such period as considered appropriate either wholly or in respect of some of the substances to which the violation relates and direct the imported new drugs to be disposed of in the manner specified in the said order."*
75(7)(iii)	there is no probability or evidence, on the basis of existing knowledge, of difference in Indian population of the enzymes/gene involved in the metabolism of the new drug or any factor affecting pharmacokinetics and pharmacodynamics, safety and efficacy of the new drug;	It is possible that the reason that there is no probability or evidence of a difference in the Indian population is because the requisite studies have not been conducted. There must therefore be a positive obligation on the applicant seeking a local clinical trial waiver to demonstrate that the existing knowledge does not warrant the conduct of local clinical trials. If the existing knowledge is insufficient	This clause may be re-drafted as follows: *"On the basis of current evidence and knowledge, there is a low probability of difference in Indian population of the enzymes/gene involved in the metabolism of the new drug or any factor affecting pharmacokinetics and pharmacodynamics, safety and efficacy of*

		to make a conclusive determination, then the local clinical trial waiver must not be granted. The same comment is also applicable to clause 79(7)(ii).	*the new drug;* *Provided that in case of an absence of or insufficient evidence on genetic differences in the Indian population, the application for waiver of local clinical trial shall be rejected."*
75(7)(iv)	the applicant has given an undertaking in writing to conduct Phase IV clinical trial to establish safety and effectiveness of such new drug as per design approved by the Central Licencing Authority:	The requirement to conduct phase IV trials must be time-bound and a penalty must be attached in case an applicant fails to conduct these Phase IV trials and report the data from these trials to the Central Licensing Authority. Additionally, the Central Licensing Authority should be able to direct the sponsor/investigator to conduct Phase III trials in the local population. The same comment is also applicable to clause 79(7)(iii).	
86(1)	Notwithstanding anything contained in these rules, a medical officer of a Government hospital or a Government medical institution, may import new drug, which has not been permitted in the country under CHAPTER X of these rules, but approved for marketing **in the country of origin** for treatment of a patient suffering from life threatening disease or disease causing serious permanent disability or disease requiring therapies for unmet medical needs,	In this clause, the term 'country of origin' must be limited to the ICH countries notified in Rule 100.	This clause should be re-drafted as follows: *Notwithstanding anything contained in these rules, a medical officer of a Government hospital or a Government medical institution, may import new drug, which has not been permitted in the country under CHAPTER X of these rules, but approved for marketing **in a country of origin specified under Rule 100** for treatment of a patient suffering from life threatening disease or disease causing serious permanent disability or*

	by making an application duly certified by the Medical Superintendent of the Government hospital or Head of the Government medical institution, as the case may be, to the Central Licencing Authority in Form CT-24.		*disease requiring therapies for unmet medical needs, by making an application duly certified by the Medical Superintendent of the Government hospital or Head of the Government medical institution, as the case may be, to the Central Licensing Authority in Form CT-24.*
91(1)	Where any medical officer of a Government hospital or Government medical institution prescribes in special circumstances any new drug for a patient suffering from serious or life threatening disease for which there is no satisfactory therapy available in the country and which is not yet approved by the Central Licencing Authority but the same is under clinical trial in the country, then, such new drug may be approved to be manufactured in limited quantity subject to provisions of these rules	This provision provides easy access to drugs that are still in the clinical trial stage, which poses a risk to the safety and well-being of patients. It is therefore important that strict safeguards be put in place to prevent the misuse of this provision. Guidance may be sought from the law in the United States, where 21 CFR part 312 subpart I specifies how expanded access to experimental drugs may be provided to patients. Some of the safeguards incorporated in this law are as follows: (i) All access is mediated through a Risk Evaluation and Mitigation Strategy. (ii) Before access is provided, the USFDA must determine whether: *"(1) The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;* *(2) The potential patient benefit*	It is recommended that this provision be deleted till wider consultations are held with stakeholders. Sufficient safeguards must be incorporated into the provision to prevent its misuse.

		justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and *(3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use."* (iii) The physician who prescribes the drug is considered an investigator and must perform all the duties of an investigator. Investigators are responsible for reporting adverse drug events to the sponsor, ensuring that the informed consent requirements are met. (iv) In all cases of expanded access, sponsors are responsible for submitting IND safety reports and annual reports (when the IND or protocol continues for 1 year or longer) to the FDA.	
7th Sch Rule 1	Compensation = (B x F x R) / 99.37 Where, B = Base amount (i.e. 8 lacs)	The minutes of the expert committee that drafted the Compensation Formula, on page 4, states as follows: *"After detailed deliberation the committee decided that base amount should be such that if the nominee of the subject keeps that amount of compensation in bank by way of fixed deposit, he or she will get an*	It is recommended that the formula for the calculation of compensation in this Rule be revised as follows: Compensation = (B x F x R) / 99.37 Where, B = Base amount (which is the monthly minimum wage of an unskilled workman in Delhi)

		monthly interest amount which is at least approximately equivalent to the minimum wages (reference: *Minimum wages of Delhi) of the unskilled workers.* *It was deliberated that the minimum wages as on date is Rs. 7722.00 per month and accordingly a base amount (rounded) of Rs. 8.0 Lakhs would be appropriate. It was also decided that this base amount should refer to the age of 65 yrs which corresponds to the factor of 99.37 of the table of Workmen Compensation Act. It is evident that the base amount will increase /change with the revision of minimum wage."* Thus, the base amount of 8 lakhs was decided on the basis of the minimum wage for unskilled workers in Delhi at the time, which was Rs. 7,722. However, the minimum wage has now been revised, and is currently Rs. 13,350. The base amount must therefore be revised to reflect this change. Further, instead of specifying the base amount in the formula, it is recommended that it should be made a variable factor which is equal to the minimum monthly wage of an unskilled worker in Delhi. This will ensure that the updated amount is taken into account while calculating compensation automatically without having to amend these Rules.	

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