Available online on 15 Mar. 2020 at https://ijdra.com/index.php/journal

International Journal of Drug Regulatory Affairs

Published by Diva Enterprises Pvt. Ltd., New Delhi
Associated with Delhi Pharmaceutical Sciences & Research University

Review Article

Impact of rules for New Drug and Clinical Trial in India

Akanksha Rani*,Vikesh Kumar Shukla

Department of Pharmacy, Amity Institute of Pharmacy, Amity University Noida (U.P.), Sector-125 Pincode-201303

Abstract

A good quality research requires the incorporation of good ethical practices throughout the conduct of the study. An efficient Ethics Committee will facilitate such a research at the site, and can achieve the major objective of ICH-GCP (International Conference on Harmonization-Good Clinical Practice) guidelines. Awareness of the changing rules among the stakeholders of clinical studies will ensure good clinical practice by safeguarding and protecting the rights, safety and well-being of the research participants. The draft of the New Drugs and Clinical Trials Rules was published in the Gazette of India by central government on March 19, 2019. Keeping abreast of the latest rules are essential for the uninterrupted conduct of clinical studies. We sought to give a summary of important changes in the new rules and to assess those rules from ethical perspective. India has a huge potential to attract drug discovery leader for the conducting clinical trials, in view of that the responsibility of the ethical regulation of clinical trial is a concern of Drug Controller General of India (DCGI). The DCGI takes all the decision regarding pharmaceutical-research and regulatory issues in India. The DCGI and their regularity team, ensures all the regulation for the clinical trial is taken with appropriate approval process. The present review will provide a platform to reader, about the approved trials in the past eight years and the current guidelines for the trial in India.

Keywords: Regulations, Approval, DCGI, Drug Controller General of India, Clinical Trial, India

Article Info: Received 11 Jan. 2020; Review Completed 27 Feb. 2020; Accepted 05 Mar. 2020

Cite this article as:
Rani A, Shukla VK Impact of rules for New Drug and Clinical Trial in India. International Journal of Drug Regulatory Affairs [Internet]. 15 Mar 2020 [cited 15 Mar 2020]; 8(1):25-30. Available from: http://ijdra.com/index.php/journal/article/view/379

DOI: 10.22270/ijdra.v8i1.379
*Corresponding author Tel.: +91-8445855253;
E-mail address: akankshachaudhary054@gmail.com (Akanksha Rani).

1. Introduction

Ethics Committee for Clinical Trial, Bioavailability and Bioequivalence Study in Chapter III in the gazette mentions about the changes in the EC constitution and training of ethical members. As per the rule at least 50% of the members should be non-affiliated and all the EC members should undergo timely mandatory training to continue as committee members. This is a welcome move as it empowers nonaffiliated members in EC deliberations. The non-affiliated members in the EC are lay person and chairperson exclusively, but it can be any members in the committee like legal expert, social scientist/philosopher/ethicist/ theologian, basic medical scientist and clinician. This is important because it facilitates a fairer and unbiased decision making in EC meetings. (1)

The increasing pressure from the higher hierarchy and 'publish or perish' attitude of many of the institutes/organization may influence the affiliated members to approve studies. Fixing the number of non-affiliated members may balance the discussion in the meetings. The rule also makes it mandatory that every member of EC should have training in Good Clinical Practice (GCP) and participate in the developmental Biomedical and Health Research in Chapter IV mentions about a separate EC for research involving basic, applied, operational or clinical research (Biomedical and health research). The institutes/organization should have a separate EC to be registered under the authority designated by the central Ministry of Health and Family Welfare. It also mentions about the functioning and proceedings of such an EC should be in accordance with the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants. This formation of a separate EC from EC's involved in new drug or investigational new drug studies, will certainly eases the work load and enhances efficiency of EC functioning. Clinical Trial, Bioavailability and Bioequivalence Study of New Drugs and Investigational New Drugs in Chapter V gives clarification regarding the conduct of research studies at a site which do not have ethics committee. If the site is not having the ethics committee of its own, the study can still be conducted at such sites after obtaining EC approval from another site, provided that such approving EC shall be responsible for the study at the trial site and it is located within 50 km radius from the clinical trial site.(2)

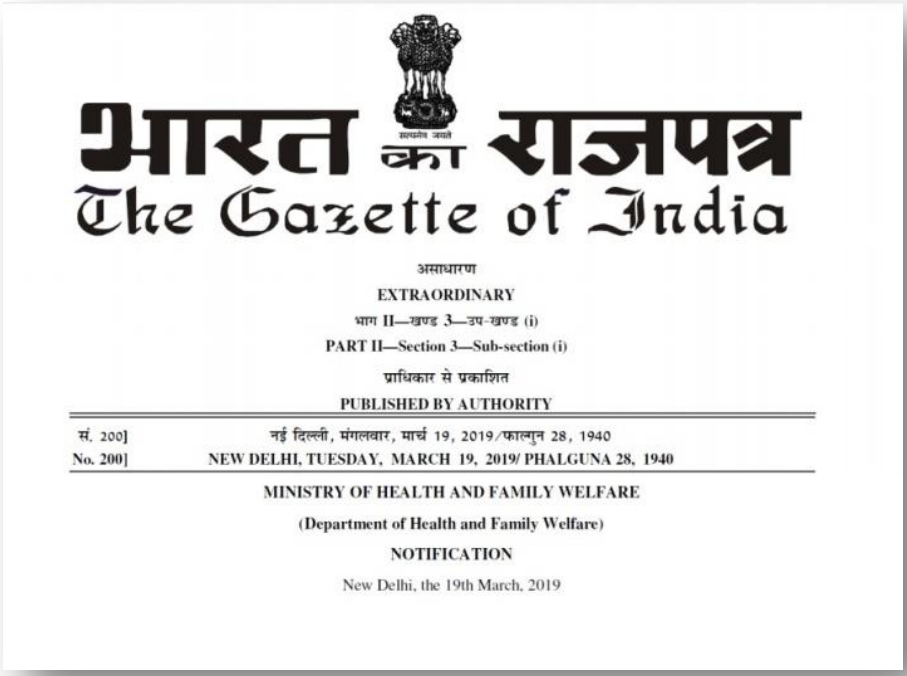
This is a welcome move as it ensures to an extent that the members from local ethnic community, who represents the actual population of the region, are represented as members and they will be reviewing the studies. This also eases the EC to competently monitor the study at the site regularly. Another incessant and highly debatable component in any study protocol is compensation. Newer rule in chapter VI emphasize on SAE and its compensation. It has significantly shortened the timeline of lengthy regulatory process involved in SAE. The timeline of independent expert committee to give its recommendation with respect to the cause of SAE and quantum of compensation to Central Licensing Authority is sixty days of receipt of SAE report. Earlier, it was 105 days for death as SAE and there was no clarity on timeline for SAE's other than death. It has also set the timeline for decision making by Central licensing Authority (CLA). The CLA should pass the order to the sponsor regarding the SAE by 90 days (earlier 150 days) of receipt of SAE report both in case of death or SAE's other than death. By this way the lengthy process of compensation path is shortened, which to some extent gives respite to the grief-stricken family. (3)

Import or Manufacture of New Drug for Sale or for Distribution in Chapter X mentions about waiver of local clinical trials if a person or pharmaceutical company intends to sell the new drug approved and marketed in the list of countries specified from time to time in rule 104. We welcome this rule, though some are critical about it. The rule explicitly specifies the type of studies which do not require repetition of clinical studies locally. However, the applicant in such cases must give an undertaking to CLA to conduct phase IV clinical trial to establish the safety and efficacy of such new drug. This rule is certainly praiseworthy from participants and sponsors perspective as it not only avoids unnecessary exposure of participants into study risks but also evades needless usage of resources. (4) Second schedule in the gazette provides provision for Accelerated approval to a new drug if it is intended for the treatment of a serious or life threatening condition or disease, where treatment in such cases is not addressed adequately by the available therapy.(5)

The efficacy observed in phase II for the investigational new drug may be considered for granting the marketing approval. This will encourage the sponsors to take-up more of such studies and enables early care of such needy patients in serious or life threatening conditions with promising drugs, without having to wait for long regulatory process.(6)

2. Highlights of the New Drugs and Clinical Trials Rules 2019:

New Drugs and Clinical trials Rules 2019 comprise thirteen chapters and eight schedules as per given notification from the Government of India. The official notification of the rule came out as extraordinary gazette (front page is in Figure 1) by ministry of health and family welfare on 19th March 2019



भारत का राजपत्र
The Gazette of India

असाधारण
EXTRAORDINARY
भाग II—खण्ड 3—उप-खण्ड (i)
PART II—Section 3—Sub-section (i)
प्राधिकार से प्रकाशित
PUBLISHED BY AUTHORITY

सं. 200] नई दिल्ली, मंगलवार, मार्च 19, 2019/फाल्गुन 28, 1940
No. 200] NEW DELHI, TUESDAY, MARCH 19, 2019/ PHALGUNA 28, 1940

MINISTRY OF HEALTH AND FAMILY WELFARE
(Department of Health and Family Welfare)
NOTIFICATION
New Delhi, the 19th March, 2019

Figure 1. Notification of New Drugs and Clinical Trials Rules 2019

The aim of implements was to felicitate ethical clinical research in India, because of the huge market potential in the India. The key points of new rules includes the rejuvenate some of the definition like as biomedical and health research, clinical trial, efficacy, good clinical practice guidelines, orphan drugs, post-trial access, a registered pharmacist, similar biologic, and trial subjects.

The need of the new rule was observed because of the wage identification feature of the Central Licensing Authority (CLA) in their previous amended rules. The amended rule clearly classifies the duties and responsibility of the CLA, which will be headed by Drug Controller General of India (DCGI). The DCGI will be appointed through the recommendation of Central Govt. and the CDSCO. The new rule clearly emphasize on the constitution of the ethical committee with their assigned duties. The major concern area of the committee is related to the clinical trials, bioequivalence studies and its role in biomedical research. (7)

Primary concern of the new rule is the compensations of clinical trial participants; where, they categorized the adverse effect on the term of severity. The serious concern of the participants may lead to the cancellation of the license, and prohibition of the trials in India further. The blacklisting of the trial centre and investigator with the penalty, imprisonment, penalty and imprisonment both can be possible in according to the new rule of India. The concept of orphan drugs is also introduced with the specific provisions for academic clinical trials and shortening of the approval timeline. (8-9)

3. Key points of Drugs and Clinical Trials Rules 2019

Table 1 Review of time line approval

Year	Approval time	Remark	Conclusion
2010	18 Months	Unethical practices followed and the scandals in 2012	Led down the number of clinical trials in India
2013	-	Three-tiered regulatory review process by DCGI	-
2017	8 months	Unattractive process for clinical trials	Demand for further reduction of approval time
2019	30 days for domestic and 90 days for global trials	Attractive market for clinical trials	for the betterment of the Indian population health

Clinical trials on drugs already approved outside India

The approved drug from countries like US, EU, Australia, Canada and Japan, will be exempted from the tedious phase-III; however the exemption will be only where the serious side effect is not the matter off consideration and in other case where no significant difference is in the metabolism of drug with the tried sample to the Indian sample.

This special clause regarding approved drug will be a healthy connection between the drug and needy population. It will also save the approaching time of the drug and recourses for conducting clinical studies on the new molecule. In spite of relaxation in phase-III study it gives special attention to the phase-IV of the drugs, which confirm the safety concern of the new marketed drugs. (10)

Timeline of approval:

This CDSCO took a great decision on the reduction of the time as given in table 1, will certainly have a significant impact on the Indian population for the betterment of the health. The reduction of time has a huge impact on the trial process time and cost. (11)

4. New drugs approval: Waivers for testing in India

When the aim is to bring into the market as many drugs as quickly as possible, waivers are a must. The New Rules give powers to the regulator to waive a wide range of pre-clinical studies (toxicological, teratogenic, reproductive, etc.) before conducting CTs. They also confer powers to waive CTs in India if a drug has already been approved in certain developed countries. This provision is one sided, as no developed country has given this status to Indian drugs approved by the Indian regulator. Indian regulators do not get this status because standards of regulation in India are lax. The present obsession with speed will make them even more lax. There may be one more reason for this provision: to bypass the question of the "ethnic factor", namely, the need for clinical trials to ensure the drug's safety and efficacy in different ethnic groups. The 59th Report of the PSC had dealt with this issue, and passed stringent strictures against the CDSCO for approving drugs in India without local CTs and without paying attention to ethnic factors. The report of the Prof Ranjit Roy Chaudhury expert committee, which was appointed by the government at the instance of the Supreme Court "to formulate policy and guidelines for approval of new drugs, CTs and banning of drugs", emphasized that "Ethnic differences affect the efficacy, safety and dose regimen of a medicine".(12)

The report calls for the need to collect data from different parts of India because of the wide variations in ethnic factors, and enumerates many of them. The report also argues that if some centers in India are part of international multi-centric trials, then regulatory authorities should ensure the inclusion of adequate numbers of Indian participants with ethnic variations in them. They must do so to ensure that there is statistical power, that those data are amenable to separate analyses, and that we are not required to do a repeat trial of that drug in India, if it is found to be efficacious. The New Rules, unfortunately, provide no details of the criteria for waivers as well as for consideration of ethnic factors. (13)

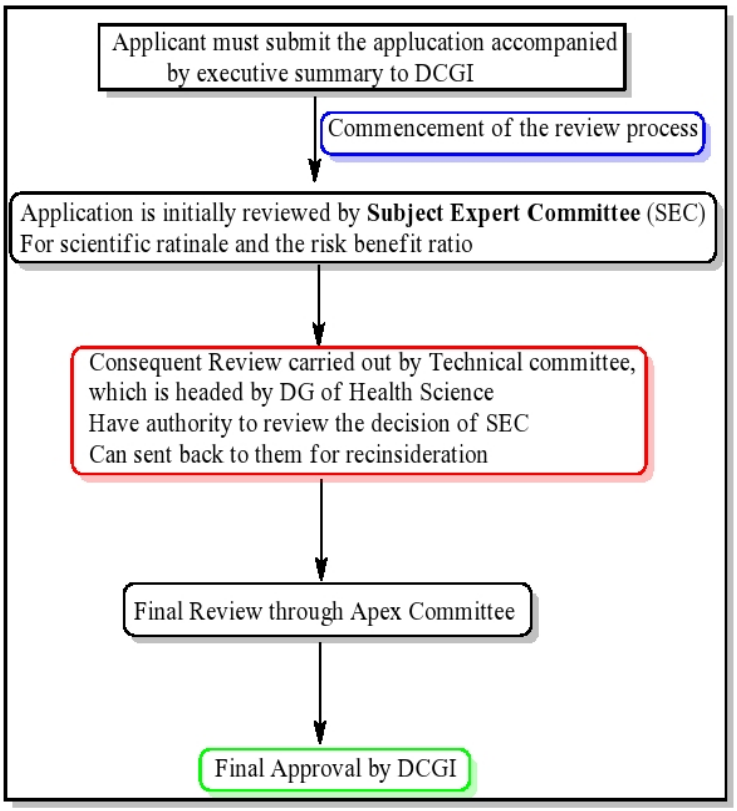


Figure2. The three-tiered regulatory process of approval process

5. Key Documents in clinical research

Drugs and Cosmetics Act (1940) and Drugs and Cosmetics Rules (1945)

The Drug and cosmetics acts came to the beginning of 1940 for the regulation of import, manufacture and distribution of drugs in the side the regime of country. It ensures the safety, effective and conforms to essential quality standards. This act was divided in to various Chapters, Rules and Schedules and it was amended at regular intervals to ensure greater safety, efficacy and drug quality. The Schedule Y along with rules 122A, 122B, 122D, 122DA, 122DAC and 122E is the key regulation descriptor that governs clinical research in the country. In accordance to the law, it was mandatory that all clinical research that falls under the ambit of Schedule Y complies with the necessary requirements. It has 12 appendices, formats for clinical trial protocols, informed consent forms, ethics committee (EC) approval templates and a format for serious adverse event (SAE) reporting. (14-15)

Indian Good Clinical Practice Guideline (2001)

A good clinical practice (GCP) guideline was released in 2001 by the CDSCO that attempted to be India specific, but unlike the ICH GCP guideline, has not been revised since. (16)

Improvements over the previous Rules

Arrangement

The original rules were arranged in a rather odd manner, with little logic. Take Rule 122 as an example. There were numerous sections of the rule, devoted to different aspects of clinical trials, but no logic is discernible. The sections of the rule were as follows:

122: Substances specified in Schedule C (1)

122 A: Application for permission to import new drug

122 B: Application for approval to manufacture new drug

122 C: Omitted

122 D: Permission to import or manufacture fixed dose combination.

122 DA: Application for permission to conduct clinical trials for New Drug/Investigational New Drug

122 DAA: Definition of a clinical Trial (now omitted)

122 DAB: Compensation in case of injury or death during clinical trial

122 DAC: Permission to conduct clinical trial

122 DB: Suspension or cancellation of Permission/ Approval

122 DC: *Appeal*

122 DD: Registration of Ethics Committee

There was no logical way to remember these rules and one had to depend on memory to do so.

The arrangement of the New Drugs and Clinical Trial Rules 2019 is very logical and easy to remember. The Rules are divided into Chapters and each chapter refers to one aspect of research.

Chapter I – Preliminary

Chapter II – Authorities and Officers

Chapter III – EC for Clinical Trials, BA and BE Studies

Chapter IV – EC for Biomedical and Health Research

Chapter V – Clinical Trials, BA and BE Studies on Investigational/New Drugs

Chapter VI - Compensation

Chapter VII – BA/ BE Centre

Chapter VIII – Manufacture of new drugs for CT, BA and BE studies

Chapter IX – Import of new drugs for CT, BA and BE studies

Chapter X – Import of new drug for sale or distribution

Chapter XI – Import or Manufacture of new drug for treatment in Government hospitals

Chapter XII – Amendment of Rules

Chapter XIII – Miscellaneous

All definitions have been grouped together and arranged alphabetically in section 2 of Chapter I. Similarly, there are seven schedules each dealing with a particular heading, making searching of information very easy. (17)

Post marketing studies

The rules lay down the requirements for post marketing studies of which three types are described in the Fifth Schedule. These include:

(A) Phase IV (Post marketing) trial

(B) Post marketing surveillance study

(C) Post marketing surveillance through periodic safety update reports

The schedule specifies that post marketing studies are to be done as per rule 77 and 82. Rule 77 deals with drugs imported for the purpose of sales and marketing while Rule 82 refers to drug manufactured for sales and marketing. Both these rules use the same language in sub-rule (iv), thus 77 (iv) and 82(iv) both state.

"As post marketing surveillance, the applicant shall submit Periodic Safety Update Reports as specified in the Fifth Schedule;"

The need for PSUR becomes clear, but when is the manufacturer supposed to do the Phase IV trial or the Post Marketing Study is not clear. Clarification on these issues will be helpful for sponsors, investigators and EC members. (17-20)

Revision in application fees for various licenses

According to the new rule for the clinical trials, some of the basic enhancements of trials have been which is mentioned in below figure. (21)

Type of application	Previous fees (INR)	New fees (INR)
Clinical trial –Phase I	50,000	300,000
Clinical trial –Phase II, III	25,000	200,000
Clinical trial –Phase IV	No fees	200,000
Reconsideration of clinical trial application	No fees	50,000 INR

Figure3. New Rate of trials according to rule**.**

6. Impact of New Drug and Clinical Trial

The framers of the New Rules seem to regard research participants as mere providers of their bodies for experimentation, having no say in the proceedings (save for cursory consent). Even when they suffer permanent injuries, or die, they or their representatives are provided no presence at any level of decision making on compensation. They are not even given a minimum right to be heard by an EC, an expert committee or the CDSCO. Another glaring omission is that of any mention of data transparency. The New Rules do not even make it obligatory for researchers and sponsors to bring into the public domain, within a stipulated time after the CT is completed, the primary and secondary outcomes of the CTs, let alone all anonyms data. This requirement is meant to prevent data manipulation and facilitate the meta-analysis of many such trials to generate scientific and clinical evidence.

7. Conclusion

Overall, the newer rules have made clearer on the roles and functioning of EC's and has tried to frame rules carefully without relegating the interests of participants involved in the clinical studies. The amended rules will attract more agencies to conduct clinical trial studies in India. The ease of conducting trials will boost up the trials arena in the faster rate as never happened before; moreover the reduction of approval time will be a key feature which will enhance the ranking of the trial study among the glove. The prosperity in the trial field will enhance the drug discovery sector as well the health situation of India.

Future Perspective

The reduction of time will undoubtly enhances the health benefits, which will be a good platform for the

health professional to get the chance to work in. The safety concern will defiantly come in to picture, because of the fast approval rate; the question for safety will be a great concern for the drug discovery personnel. The role of DCGI will be more powerful to ensure the patient's safety and drugs quality.

Acknowledgements

We thank Amity Institute of Pharmacy for giving a learning space.

Financial Disclosure statement: The author received no specific funding for this work.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Abbreviations

DCGI- Drug Controller General of India
ICH-GCP- International Conference on Harmonization-
CLA- Central licensing Authority
GCP- Good Clinical Practice
US- United State of America
EU- European Union

References

1. Ministry of Health and Family Welfare. Govt of India. Notification. The Gazette of India: Extraordinary, Part II, Section 3, Subsection (i) [Internet]. New Delhi: 2019 Mar 19 [cited 2019 Dec 20]; p. 1-264. Available from: https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents / NewDrugs_CTRules_2019.pdf
2. Jesani A, Srinivasan S. New Drugs and Clinical Trials Rules, 2019: The market trumps ethics and participant rights. *Indian J Med Ethics* 2019; 4(2) NS: 89-91. DOI: 10.20529/ IJME.2019.020
3. Vaidyanathan G. India's clinical trials rules to speed up drug approvals. *Nature* [Internet]. 2019 Apr 03 [cited 2019 May 20]. Available from: https://www.nature.com/articles/d41586-019-01054-4.
4. Bhatt A. Evolution of clinical research: a history before and beyond James Lind. Perspect Clin Res. 2010; 1(1):6-10.
5. Gogtay NJ, Ravi R, Thatte UM. Regulatory requirements for clinical trials in India: what academicians need to know. Indian J Anaesth. 2017; 61(3):192-9.
6. Wandile P, Ghooi R. A Role of ICH- GCP in Clinical Trial Conduct. J Clin Res Bioeth. 2017; 8(1):1-5.
7. Otten A. The GATT TRIPS Agreement and health care in India. Natl Med J India. 1995; 8(1):1-3.
8. Choudhury K, Ghooi R. New rules for clinical trial-related injury and compensation. Indian J Med Ethics. 2013; 10(3):197-200.
9. Ghooi RB. Ensuring that informed consent is really an informed consent: role of videography. Perspect Clin Res. 2014; 5(1):3-5.
10. Ghooi RB. Accreditation - A solution for problems or a fresh problem? Perspect Clin Res. 2015; 6(3):123-4.
11. Ministry of Health and Family Welfare. GSR 104 (E) New Drugs and Clinical Trials Rules; 2018.
12. The Supreme Court Order of the Supreme Court of India regarding the Draft Drugs and Clinical Trials Rules. Available at:http://www.indiaenvironmentportal.org.in/content/458635/order-of-the-supreme-court-of-india-regarding-the-draft-drugs-and-clinical-trials-rules-2018-12092018/
13. World Medical Association, WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects [Internet]. WMA [cited 2019 Dec 23]. Available from: https://www.wma. net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
14. Indian Council of Medical Research. National Ethical Guidelines for Biomedical and Health Research involving Human Participants; 2017.
15. Chingarande GR, Moodley K. Disparate compensation policies for research related injury in an era of multinational trials: a case study of Brazil, Russia, India, China and South Africa. BMC Med Ethics. 2018; 19(1):8.
16. Urooj M, Husain GM, Khan MA, Kazmi MH. Compensation to clinical trial participants in India: A gap analysis. Int J Pharm Investig. 2017; 7(2):41-6.
17. Henry LM, Larkin ME, Pike ER. Just compensation: a no-fault proposal for research-related injuries. J Law Biosci. 2015; 2(3):645-68.
18. Gupta YK, Pradhan AK, Goyal A, Mohan P. Compensation for clinical trial-related injury and death in India: challenges and the way forward. Drug Saf. 2014; 37(12):995-1002.
19. Saxena R, Saxena P. Clinical trials: Changing regulations in India. Indian J Community Med. 2014; 39(4):197-202. doi:10.4103/0970-0218.143018.
20. Vijayananthan A, Nawawi O. The importance of Good Clinical Practice guidelines and its role in clinical trials. Biomed Imaging Interv J. 2008; 4(1):e5. doi:10.2349/biij.4.1.e5
21. Reference document: Ministry of Health GSR Notification#227