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# **Good Clinical Practice in Children and Adolescents**

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## **Abstract**

Good clinical practice (GCP) is a series of systematically developed ethical and quality standard of designing, registering, running, recording, and reporting of the clinical trials. Good clinical practice is very important regarding the trials usually performed on the vulnerable populations especially children and adolescents. The sensitivity of the issue is even higher in the children with psychiatric disorders. Usually, these children have little legal protection. Hence, the safety of interventions and the ethical considerations are among the most important issues in this field. The purpose of this chapter is to deal with above problems and globally applicable standards for the conduct of clinical trials on the under legal age subjects especially those with psychiatric disorders. Selection of trial subjects, ethical principles, regulatory requirements, protection of trial subjects, monitoring (compliance with the protocol), responsibilities of the investigator, and other requirements to perform a clinically and ethically sound clinical trial in children and adolescents will be discussed in this chapter.

**Keywords:** children and adolescents, ethics, good clinical practice, monitoring

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## **1. Introduction**

While new medical products (drugs and vaccines) are being developed and asking for registration, their efficacy and safety should be assessed in a well-designed clinical trial, ultimately on human beings [1]. This process is costly, and ethical considerations are controversial. The history of developing of good clinical practice (GCP) goes back to the end of World War 2 following the Nuremberg trials on war victims. In Nuremberg Nazi, physicians were accused for performing inhumane trials on human beings in the name of medical research. After the

war, two American doctors who were present in Nuremberg invented a set of research ethics principles including 10 points which are in compliance to the human rights. These principles are known as Nuremberg Codes [2, 3].

Later in 1964, the elected medical representatives came from all over the world, attended the 18th General Assembly of the World Medical Association in Helsinki. They decided to improve the points asserted in the Nuremberg Code and create a more formal statement of ethical principles. Its attitude was to provide detailed directions for medical science researchers to conduct the trials on human subjects with scientifically sound methods and in accordance with basic ethical principles. This statement is known as the “Declaration of Helsinki,” and until now, several revisions have been released [4].

This history formed the basis for developing good clinical practice.

## **2. Good clinical practice definition**

Good clinical practice is an internationally accepted scientific and ethical standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials on human subjects which provides assurance that the reported results are credible and accurate; the rights, integrity, and confidentiality of trial subjects are protected [3].

The good clinical practice is a quality assurance system for the conduct of clinical trials. It is a legal requirement accepted by health systems in many countries. Hence, a new product will not be licensed by regulatory authorities if the rules of good clinical practice are not followed [5].

## **3. Selection of trial subjects**

Patient selection for any clinical trial is a very critical point. When choosing the inclusion criteria, the researcher should think that what factors are important to the research question and include the main characteristics of target population. The researcher should be careful that excessive exclusion may degeneralize the study. The caseness of pediatric subjects should be confirmed by a pediatrician. When working on pediatric psychiatric patients, the sensitivity is much more, the eligibility of subjects must be clearly defined in the inclusion and exclusion criteria. Furthermore, the diagnosis must be confirmed by a child and adolescent psychiatrist based on the latest version of diagnostic and statistical manual of mental disorders (DSM). In psychiatry trials, documentation and history of the diagnosis are usually required [6, 7].

## **4. Protection of trial subjects**

Childhood period comes with rapid growth and development and ends with puberty. Unfortunately, sometimes it is accompanied by harsh diseases like infection diseases, allergies, cancers, and psychiatric disorders. So, many advanced vaccines and medicines are

needed to be developed for children and adolescents. Furthermore, some supplements are targeted for this group of population [8–10]. Hence, performing clinical trials on children and adolescents is a critical mission sometimes inevitable. Children are vulnerable population in medical research; hence, inclusion of children in clinical trials always is a matter of great concern for parents, researchers, and ethic committees. Children and adolescents who will attend in the clinical trials should be selected carefully by a qualified physician. The physician should be qualified by sufficient education, training, and experience and should be in charge for optimum health of the participants. All diagnosis should be supported by the latest clinical guidelines [11]. Furthermore, inclusion and exclusion criteria should be carefully set on the basis of study objectives and previous studies. The processes of medical care and every decisions made here should be based on evidence and guarantee the maximum safety of the patients in a way that the rights and well-being of the children would be protected. Blood sampling in children is not ethical if the benefits of the study do not exceed the harms for children. When a specific group of children directly benefit from blood sampling or blood sampling is necessary for diagnosis, the documents should be presented to the institutional ethics committee and benefits should be described to the parents or legal guardians. The subjects or his/her parent or legal guardian should be adequately informed about the processes of research, the rights and responsibilities. The aims and methods of the research should brightly be described to them. Furthermore, the subjects and their legal guardian must be aware of anticipated benefits and potential hazards of the intervention. Then, informed consent must be signed by the parents or legal guardian of the subjects below the legal age. Moreover, the subjects should ascent to participate. Then, after obtaining sufficient ethical approvals and consent forms, blood sampling could be gathered by a trained client under the guidance of existing guidelines [12, 13]. In clinical trials on pediatric psychiatry, a team-based approach involving the laboratory physician would help the quality assurance of examination, diagnosis, and reporting, as well as patient safety [14, 15].

## 5. Safety reporting

In trials with the main objective of efficacy assessment, the safety assessment is usually the secondary objective. One of the responsibilities of the researcher is to carefully monitor the adverse effects and record immediately when a participant experiences any side effect [16]. Then, the investigator should report it in a suitable way. Furthermore, in respecting the privacy, the researchers should guarantee the confidentiality of records that could identify the subject. Another duty of the researcher is to provide best possible care available and follow until complete disappearance of adverse effect. Sometimes, it is necessary to stop the trial to protect one or more subjects. Sometimes, the subjects or the legal guardian themselves decide to stop medication. In pediatric psychiatry, loss to follow-ups happens due to adverse effects of the intervention, stigma, and lack of parent's knowledge about medicinal psychotherapy [17]. So, the researcher should conduct a thorough investigation and find the exact reason of each loss to follow-up and report it. Usually, identifying the barriers and reducing them would be helpful. Educating the parents and legal guardians to help reduce the stigma of referring to psychiatrist and fear of tacking psychiatry medications may support the children health [18].

## 6. Develop informed consent form

Consenting is the process by which participant voluntarily confirms his/her willingness to participate in the trial. The medical researchers should be careful and pay special attention when obtaining consent from vulnerable subjects, including children, the elderly, and psychiatric patients. Subjects with low perception may feel unable to make use of their right to judge the profits or hazards of the intervention and decide whether to consent or not. Child and adolescent psychiatrists should be careful about the decisional capacities of children and the role of the parents in medical decision making. Hence, obtaining informed consent form from the legal guardian of the subjects under legal age and the patients with severe psychiatric disorder is crucial. In addition, obtaining oral assents from the subjects with low perception or children who will participate in the medical research is essential. Full procedures, rights and responsibilities, potential hazards, and benefits should be described to each participant and the legal guardian. Then, informed consent must be dated and signed by the legal guardian before the subject participates into the trial. Then, a copy of informed consent form and related information should be delivered to the parents or guardian. The original informed consent must be kept in the investigator's file [19].

## 7. Ethical approval

The researcher should submit the sponsor-provided protocol document to the Institutional Review Board (IRB) or Research Ethics Board (REB) for approval before recruiting any case into the trial. The investigator should also submit consent forms and assessment tools, including questionnaires. During specific intervals, the researcher must report the progress of the trial and request re-approval of the research by the IRB/REB. The IRB/REB will ask for a summary of trial progress [20]. The responsibility of the ethics committee is to guarantee the protection of the rights and well-being of human subjects enrolling into clinical trials. The ethics board decisions are in line with the latest revision of the declaration of Helsinki and local pertinent regulations [21].

## 8. Quality of data

Every research study needs to have a written protocol which includes the plan of the study as detailed as possible. The design and method of the trial should be well-thought-out, and the protocol must be well-written and approved by a faculty council. Protocol includes the trial information in detail and should consist of the trial title, the name of the main investigator, supervisor/s and sponsor/s, literature review, materials and methods, characteristics of intervention, dosage, duration, randomization, blinding, allocation concealment, inclusion criteria, exclusion criteria, project schedule (Gantt chart), and budget of the project [22].

In trials performing on children and adolescents, the investigators should be trained and interested in the scientific aspect and ensure that the study meets the needs of patient's health.

The researchers must also review up-to-date information, ensure the confidentiality of the data, and provide confidentiality agreement to sponsor. Furthermore, proper facilities, location, equipment, laboratory, product storage, and archive must be provided prior to study initiation [22, 23].

## 9. Resources

One of the requirements of good clinical practice is that the researcher has adequate access to resources to carry out a sound clinical trial. Resources include not only sufficient budget and materials, but also the ability to recruit adequate numbers of research subjects. Furthermore, the research team members must have adequate information about their specific roles, and they should have adequate time to deal with subjects and conduct the trial. In trials being conducted in children and adolescents, at least one of the team members should be specialized or trained previously to deal with the subject on this age span [24].

## 10. Randomization

Single-arm trials with historical controls for comparison may be biased by differences in subject characteristics (age, sex, prior therapy, phase of disorder, and supplemental care). Still, when matched controls can be selected, unknown confounding factors may be haphazardly distributed between two groups.

Designing a two-arm trial with distributing the subjects between two groups using randomization can help to minimize potential bias caused by unknown confounding factors. However, a placebo-controlled trial may be ethically defensible when the use of placebo would not add any risk or serious harm to the subjects. Sometimes, crossover design is more ethical and adheres to the principle of good clinical practice. In crossover studies, the subjects are randomly allocated to the treatment or control groups, after the first phase ends, the subjects will change the groups. In this design, all subjects receive all treatments. Of course, the priority of treatments should not harm the subjects.

When an uneven distributed factor between groups recognized, then controlling by statistics method at the analyses level may be considered. One strategy is to stratify the variable and discuss the results at different levels of the variable. A better solution is stratification process at the time of randomization using the permuted blocked randomize allocation. In this method, randomization will be performed using different age and sex blocks. Hence, the subjects will distribute evenly between treatment arms.

In a randomized clinical trial to control for the placebo effect and minimize the study bias, the subjects and researchers should be blinded using placebo, coding, and allocation concealment. In the case of a blinded trial, the protocol must declare who and in what conditions is allowed to break the codes (for example, the supervisor and in emergencies). Breaking the codes must be justified and must be reported [21].



## 11. Reports

Moving in accordance with protocol allows its accurate reporting, interpretation, monitoring, and verification of the trial. Furthermore, it assures the quality of every aspects of the trial. The data obtained from the trial must be handled, analyzed, synthesized, and reported in a sound approach. In addition, the sponsor or the research institute should be able to carry out on-site inspections of the validity of reported results. Hence, brilliant documentations and reporting are very important as well as the monitoring processes. For this purpose, the research institute should have easy access to all patient files and raw data during the trial [21].

## 12. Monitoring

Monitoring is an important part of good clinical practice. Monitoring is the process of auditing the trial based on compliance to the approved protocol, ethics, and regulation in a way that guarantee the optimum health and rights of the subjects, as well as timely submission of high-quality data. The objectives of monitoring are to prevent, detect, and correct careless errors, neglect, fraud/misconduct, and violations. Monitoring will guarantee the quality of medical care, quality of data, quality of trial, and quality of product. The monitor is a person who has been chosen by the sponsor or research institute for the monitoring and reporting of progress of the trial and for the confirmation of data. The monitor should have enough medical, scientific, and/or pharmaceutical qualifications, and clinical trial experience [21].

### 12.1. Monitor's responsibilities

Monitor's responsibilities are listed below:

- To act as a soother between the sponsor and the investigator

*The inspector is chosen by sponsor and is responsible for corresponding between sponsor and investigator.*

- To help the investigators on all aspects

*Helping investigators in providing supplies and solving problems is among the responsibilities of the inspector.*

- To help protection of study subjects

*Confirming obtain of informed consent for all subjects prior to their participation in the trial is one of the monitors responsibilities.*

- To verify adequacy of trial resources

*Monitor check for adequacy investigators, staff, and facilities before and throughout the study period.*

- To verify supply, control, storage, and disposition of investigational product/s

*Turning back additional materials after the trial is finished is one of the inspector's duties.*

- To verify adherence to the approved protocol/amendments

*Adherence to the approved protocol ensures that data are correctly gathered and reported. Any changes to the protocol should be documented and reported.*

- To verify adherence to good clinical practice and standard operating procedures

*Standard operating procedure (SOP) is a standard comprehensive framework for administration of clinical trials.*

- To monitor recruitment rate, safety evaluation, and compliant observations

*Validity and quality of data gathered and safety of patients are monitored by the inspector during the trial.*

- To check the accuracy and completeness of all trial data and case report forms

*Case report form is a paper-based or computer-based sheet that is used to record and gather the data on each trial subject during the trial, as defined by the protocol. The documentation should allow easy access for verification, audit, and inspection.*

- To discuss study plan and problems with main investigator and staff

*Monitors are trained in clinical trial and medical research and may collaborate to improve the quality of trial. They may also verify that trial documents are complete and up-to-date [25].*

## 13. Monitoring visits

### 13.1. Pretrial monitoring visit

During prestudy visit, the monitor ensures feasibility of trial in the center and interest of the investigator. Also he/she makes sure that the investigator understands the required "trial procedures" and sufficient site staff, proper facilities, location, equipment, laboratory, product storage, and archive exist to support the study.

The inspector may discuss with investigator(s) about

- The protocol in detail
- Consent form
- Assenting children (if present)
- Case report form and documentation of findings including adverse effects, standard operating procedures



The audit may clarify any issues that remain uncertain, regulatory requirement and fulfills the sponsor expectations. He/she may document any changes in the protocol to eliminate practical defects.

### 13.2. Trial initiation visit

Deliver study material, documents, and products, and make sure the investigational team understands the protocol and good clinical practice requirements.

The responsibilities of the inspector in trial initiation visit are listed below:

- Revise team training
- Ensure understanding of protocol
- Ensure understanding of case report form
- Ensure ethical requirements
- Ensure safety reporting procedure

*Discuss in detail:*

- Enrollment and exclusion criteria
- Endpoints
- Patients safety
- Criteria for grading adverse effects
- Handling of patient samples
- Handling of test product
- Standard operating procedures

### 13.3. Monitoring visit

In approach to help the investigational team in solving problems, the trained audits would make sure that the study is conducted in accordance with the requirements of the protocol and good clinical practice principles. Also they make sure that investigators are available during the visits.

*Discuss:*

- Problems
- Modifications
- Obtaining informed consent from legal guardian
- Obtaining assent from the children and adolescents (process by which patient/subject voluntarily confirms his/her willingness to participate)

- Protocol compliance: strictly follow protocol procedures, alteration
- Sponsor approval

#### 13.4. Close-out visit

Make sure the investigator file is archived properly and collects back all unused materials, documents, or products.

### 14. Responsibilities of the investigators after approvals

- Sign the final copy of protocol

*The main investigator should sign and hereby accept the responsibility of trial.*

- Submit the requested document

*The main investigator should provide the requested form including budget, Gantt chart, and consent forms to the sponsor, the research institute and ethics committee.*

- Registering the protocol of the trial in one of the clinical trial registries

*Now most high-quality journals necessitate researchers to submit their work in one of clinical trial registries before patient's enrollment into the trial and provide its code at the time of submission to the journal. He/she must also agree with publication policy of journal and publisher.*

- Work according to the protocol and good clinical practice guidelines

*The investigator must ensure that he/she acts in accordance with the sponsor-approved protocol and globally accepted standard of GCP.*

- Collaborate with monitor

*The investigator should collaborate in on-site inspections and in corresponding.*

### 15. Responsibilities of the investigators during study

- Adherence to the protocol and good clinical practice principles

*The investigator should adhere to the inclusion and exclusion criteria mentioned in the approved protocol. He/she has overall responsibility for ensuring the accuracy and completeness of data gathered.*

- Adhering to administrative and regulatory requirements

*Local regulations and administrative requirements should also be respected by the investigators.*

- Compliance with ethics

*Give adequate information to the subjects and legal guardians about study procedure, harms, and benefits of the intervention. Also, give adequate information to the subjects and legal guardians about responsibility and rights of each side. Then, obtaining freely signed informed consent form from legal guardian.*

- Obtaining oral assent from the children and adolescents

*The researcher should also spend sufficient time for participants and allow participants themselves to decide.*

- Unbiased selection/randomization, blinding, and allocation concealment

*The investigator should ensure that the subjects are correctly diagnosed and reduce the known kinds of biases including random bias and selection bias with adhering to clinically sound diagnosis, randomization, blinding, and allocation concealment. These processes are discussed before.*

- Be sure that dosage and instruction for use are correct

*The main objective of performing a clinical trial is usually assessing the effectiveness of a product at a specific dose. But, the phase II clinical trials are dominantly aim at the determination of appropriate or safe dose ranges. Hence, determining appropriate dose and timing of product intake based on previous studies and literature is very important.*

- Correspondence

*The main investigator is responsible to correspond with the sponsor, ethics committee, and research institute.*

- Monitoring and follow-up potential side effects

*Adverse effects must be reported and monitored until its removal.*

- Trial data documentation

*The researcher must make sure that the participant's identification, trial observations, findings, and also side effects are recorded correctly and completely in a paper-based or computer-based case report form (CRF). Furthermore, the investigator should fill and maintain investigator's file.*

- Laboratory quality assurance/quality control (normal lab values)

*Laboratory values within or outside the normal reference ranges, if possible together with the specificity and sensitivity of the methods used, should always be recorded on the CRF or be attached to it.*

- Secured storage and limited access to data

*Suitable place for archiving and confidentiality of the data should be guaranteed by the investigator.*

- Preparing the final report

*The project should be based on the Gantt chart and the sponsor-approved budget. Then, the final report of the trial should be prepared as defined in the protocol. The report should be signed by the sponsor, monitor, and investigator(s) as well as the responsible statistician, in accordance with the relevant regulations.*

## 16. Conclusion

Clinical trial in children and adolescents as a vulnerable population is a great concern to the legal guardians, medical investigators, and ethics committees. These trials must be planned, set up, conducted, documented, and reported in a great standard named good clinical practice. The data should be collected, synthesized, and documented with accuracy and consistency. Furthermore, researches involving humans especially those with low perception including psychiatric patients and children, and adolescents should be scientifically sound and conducted in accordance with high ethical standards. Obtaining written freely signed informed consent form from parents or legal guardians is mandatory in clinical trials performing on children and adolescents. Additionally, obtaining oral assent from the subject itself is essential too. Institutional ethics committees are responsible for approving the trial methodology and safety in a way that ensure protecting of patient's rights and health. Meanwhile, monitoring would help to guarantee the maximum quality of data and well-being of subjects. Monitoring the clinical trial is the process of auditing trials based on the sponsor-approved protocol and the standard of good clinical practice. In all, the concept of good clinical practice in children and adolescents necessitates medical researchers a binding statement: "Performing the trial with best possible standards and optimum health of my patient will be my first consideration."

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## References

- [1] Acosta CJ, et al. Implementation of good clinical practice guidelines in vaccine trials in developing countries. *Vaccine*. 2007;**25**(15):2852-2857
- [2] Kiouss BM. The Nuremberg code: Its history and implications. *Princeton Journal of Bioethics*. 2001;**4**:7-19
- [3] Vijayananthan A, Nawawi O. The importance of good clinical practice guidelines and its role in clinical trials. *Biomedical Imaging and Intervention Journal*. 2008;**4**(1):e5
- [4] The World Medical Association. Declaration of Helsinki [Internet]. 2004. Available from: <http://www.wma.net/e/policy/b3.htm>

- [5] Ray S, et al. Maintaining good clinical practice: Publication of outcomes and handling of outliers. *Heart*. 2016;**102**(19):1518-1519
- [6] Stein DJ, Lund C, Nesse RM. Classification systems in psychiatry: Diagnosis and global mental health in the era of DSM-5 and ICD-11. *Current Opinion in Psychiatry*. 2013;**26**(5):493-497
- [7] Bathgate F, et al. Good practice guidelines for clinical psychologists working in paediatric cochlear implant teams. *Cochlear Implants International*. 2013;**14**(Suppl 4):S32-34
- [8] Mostafavi SA, et al. Role of melatonin in body weight: A systematic review and meta-analysis. *Current Pharmaceutical Design*. 2016;**22**. (E-pub Ahead of Print) DOI: 10.2174/1381612822666161129145618
- [9] Mostafavi A, et al. Melatonin decreases olanzapine induced metabolic side-effects in adolescents with bipolar disorder: A randomized double-blind placebo-controlled trial. *Acta Medica Iranica*. 2014;**52**(10):734-739
- [10] Mohammadi MR, et al. Melatonin effects in methylphenidate treated children with attention deficit hyperactivity disorder: A randomized double blind clinical trial. *Iranian Journal of Psychiatry*. 2012;**7**(2):87-92
- [11] Zimlichman E, Meilik-Weiss A. Clinical guidelines as a tool for ensuring good clinical practice. *Israel Medical Association Journal*. 2004;**6**(10):626-627
- [12] Howie SR. Blood sample volumes in child health research: Review of safe limits. *Bulletin of the World Health Organization*. 2011;**89**(1):46-53
- [13] Loebstein R, Koren G. The ethics of multiple blood sampling in children for research. *Therapeutic Drug Monitoring*. 1997;**19**(3):251
- [14] Asai S, Miyachi H. Good practice of clinical physiology examination for patient safety with a team-based approach: Quality practice in ultrasonographic examination. *Rinsho Byori*. 2015;**63**(7):847-854
- [15] Ezzelle J, et al. Guidelines on good clinical laboratory practice: Bridging operations between research and clinical research laboratories. *Journal of Pharmaceutical and Biomedical Analysis*. 2008;**46**(1):18-29
- [16] Good efficacy and safety profile in clinical practice. *MMW Fortschritte Der Medizin*. 2015;**157**(20):66-67
- [17] Mohammadi MR, Mohammadzadeh S, Akhondzadeh S. Memantine versus methylphenidate in children and adolescents with attention deficit hyperactivity disorder: A double-blind, randomized clinical trial. *Iranian Journal of Psychiatry*. 2015;**10**(2):106-114
- [18] Gust DA, et al. Risk factors for non-adherence and loss to follow-up in a three-year clinical trial in Botswana. *PLoS One*. 2011;**6**(4):e18435
- [19] Neilson G, Chaimowitz G. Informed consent to treatment in psychiatry. *The Canadian Journal of Psychiatry*. 2015;**60**(4):1-11

- [20] Kavar LN, Pugh DM, Scruth EA. Understanding the role and legal requirements of the institutional review board. *Clinical Nurse Specialist*. 2016;**30**(3):137-140
- [21] Idanpaan-Heikkila JE. WHO guidelines for good clinical practice (GCP) for trials on pharmaceutical products: Responsibilities of the investigator. *Annals of Medicine*. 1994;**26**(2):89-94
- [22] Goodarzynejad H, Babamahmoodi A. Project management of randomized clinical trials: A narrative review. *Iranian Red Crescent Medical Journal*. 2015;**17**(8):e11602
- [23] Stevens W. Good clinical laboratory practice (GCLP): The need for a hybrid of good laboratory practice and good clinical practice guidelines/standards for medical testing laboratories conducting clinical trials in developing countries. *Quality Assurance*. 2003;**10**(2):83-89
- [24] Devine S, et al. Good clinical practice and the conduct of clinical studies in pediatric oncology. *Pediatric Clinics of North America*. 2008;**55**(1):187-209, xi-xii
- [25] Grainger A. Clinical audit: Shining a light on good practice. *Nursing Management (Harrow)*. 2010;**17**(4):30-33



