

CH-10.

1. Discuss GCP and its principles. [W-22 7(c)] [S-23 7(c)]
2. Write a note on ICH guidelines. [S-22 2(c)]
3. Discuss in detail about CDSCO guidelines [S-22 3(a)] [S-23 E-2(a)]

CH-11

4. Discuss the challenges in implementation of guidelines in clinical trial [W-22 4(c)].

CH-12

5. Write a note on compensation for clinical trial subjects as per ethical guidelines [S-23 7(b)].
6. ~~Q11/X3~~ What is the role of ICMR in regulation of clinical trials? [S-22 3(b)].  
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7. Note on constitution & responsibilities of IRB [W-22 4(a)] [S-23 5(a)]
8. Explain IEC review procedure of a research proposal and methods of review process of IEC [S-22 7(a)].

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9. Regulatory setup in Europe [W-22 4(b)] [S-22 7(b)]
10. Details about regulatory setup that governs the clinical research in India [W-22 7(a)]

11. Regulatory setup in USA [S.22 2(b)] [S.23 6(c)]

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12. Components of CR protocol and process of protocol preparation [W.22 5(a)]

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13. National Case record form [W.22 6(c)]



C.R.

## Q1 GCP &amp; principles.

Q1 GCP stands for: good clinical practice & it defined as GCP is a set of internationally recognised ethical & ~~sci~~ scientific quality requirements which must be observed for designing, conducting, reporting & recording clinical trial that ~~involve~~ involve human subject participation.

## + Principles.

- ① C.T should be conducted in accordance with ethical principles that follow Declaration of Helsinki.
  - C.T must be consistent, applicable & follow the GCP guideline.
- ② Before trial is initiated, focus must be on risk to benefit ratio.
  - The foreseeable risk should be weighed against the benefit for individual trial subject & society.
  - The trial should be ~~regulatory~~ requirements initiated only if benefit justify risk.
- ③ Consideration of trial subjects that should prevail over interest of science & society are rights, safety & well-being.



4) Continue

5) Consider available clinical & non clinical information on product as support to CT.

6) CT should be clinically & scientifically sound & has clear objective

7) Trial should be conducted in compliance to protocol that has reviewed prior to IRB.

8) Qualified physician has responsibility of medical care decisions for ~~good~~ wellness of human subject.

9) Individuals, conducting trials must be qualified by education, experience & trained

10) Every subject should obtain informed consent form

11) C.T should be recorded, handled & store in a way that allow it accuracy reporting, interpretation & verification.

12) The C.T data must be confidential as it consist trial subjects data & private information

13) Investigational-product should be mfg, handled & stored according to GMP guideline



(13) Systems & procedures that ensure quality of every aspect of total must be implemented.



Q2 write a S.N on ICH guideline.

→ ICH stands for international conference on Harmonization and it is a technical requirements for registration of pharmaceuticals for human use.

→ The purpose is to reduce or obviate the need to duplicate the testing carried out during the research & development of new medicine.

→ It recommending ways to achieve greater harmonization in the interpretation & application of technical guideline & requirement for product

→ ICH includes 4 categories of guideline

- 1) Quality
- 2) Efficacy
- 3) Safety
- 4) Multi-disciplinary

① Quality :- It refers to chemical and pharmaceutical quality assurance.

→ It has 12 sub guideline in quality

Q1 :- Stability guideline

Q2 :- Analytical validation



- Q3 → Impurities
- Q4 → Pharmacopoeies
- Q5 → Biotechnological product.
- Q6 → Specifications for new drug.
- Q7 → GMP.
- Q8 → Pharmaceutical development.
- Q9 → Risk.
- Q10 → Pharmaceutical Quality System
- Q11 → Development & manufacturing.
- Q12 → Technical & regulatory consideration.

② Efficacy :- It deals with clinical study in human subjects.  
e.g. Dose response studies, gap etc.

→ It consist 20 subguideline

→ It start as E-1 → Clinical safety for drug used in long term treatment.

E-2 Pharmacovigilance. etc & ends with

E-19 :- Safety data.

E-20 Adaptive clinical trial.

③ Safety :- It deals with in-vivo & in-vitro preclinical studies.

→ It consist 11 subguideline.

→ It start as S1 :- carcinogenicity

S2 :- Genotoxicity etc & ends with

S10 :- Photo safety evaluation of pharmaceutical.



S. II :- Non clinical safety - testing in pediatric medicine

4. Multidisciplinary :- It consist 8 subguidelines

M1 :- MEDRA terminology

M2 :- Electronic standard for transfer of regulatory information

M3 :- Non. Clinical safety study

M4 :- CTD (Common technical document)

M5 :- Data elements & 3rd drug ~~standards~~ dictionaries

M6 :- Virus & gene therapy

M7 :- Genotoxicity impurities.

M8 :- Electronic CTD.

Q3) Discuss in detail about CDSCO guideline.

↳ CDSCO Stand for central drug standard control organization & it is the central drug authority for discharging functions assigned to the central government under the drug & Cosmetic Act.

↳ To protect and promote health in India is the objective as CDSCO

↳ It has 4 main guideline



2) Investigational pharmaceutical product

3) Preclinical supporting data

3) Protocol :- It has 2 sub guideline.

(a) Relevant component of protocol.

① Objectives & justification

② Ethical considerations

③ Study design.

④ Inclusion, exclusion criteria

⑤ Handling product etc.

(b) Supplementaries & appendices

4) Ethical & safety consideration :- It has 7 sub guideline

(a) Ethical principles

① Essentiality

② Voluntariness, informed consent

③ Non exploitation

④ Privacy & confidentiality

⑤ Risk minimization etc.

(b) Ethics committee

① Basic responsibilities

② Composition

③ Terms of reference etc.

(c) Informed consent process

① Informed consent of subject.



(d) Confidentiality for prospect to research

(e) Compensation for publication

(f) Selection of special group

① Pregnant

② Children

③ Vulnerable groups

(g) compensation for accidently injury

Q4) Discuss the challenges in implementation of guidelines in clinical trial.

→ There are mainly 10 challenges in the implementation of ICHG guidelines are as follows.

①. Professional training on ICHG: There is a lack of professional training on ICHG across various stakeholders.

- The major challenge is to be trained competent.

②. Infrastructure: Majority of hospitals in India are not geared up to meet the infrastructure requirement as per ICHG guidelines.





### ③ Regulatory Environment

- In spite of well defined guideline on clinical trial, the biggest challenge in their implementation & adherence.

### ④ IRB / IEC / ERB.

- GCP guideline require a written standard operating procedures (SOP) for IRB / IEC / ERB.
- However, there are no standard guideline on what should be the content of an ideal SOP, so that there is uniformity across various hospital.

### ⑤ ICD Administration.

- Administration of ICD is a major challenge in a country like India, when the patient / legally acceptable representative has such an immense faith on treating doctor that, they insist on signing the document, & even reading it after reading it superficially.

- They feel that if the treating doctor is suggesting something, it would definitely help them.

### ⑥ Safety Reporting

- It is a joint responsibility of investigator & sponsor to report the entire serious & unexpected



adverse event to IRB/ERB & the regulatory authorities.

- The regulatory pharmacovigilance presently is not optimally implemented for adverse event handling and review.

### ⑦ Investigational product:

- Investigational product storage, handling and access control is a major challenge in the implementation of GCP guideline.
- It is difficult to produce any evidence of temperature chain being maintained during shipment of investigational product from sponsor's facility to investigation site.
- There is no validation and regular standardization of thermometer provided by sponsor.

⑧ Record keeping :- Data ~~not~~ ~~not~~ ~~not~~ lakhi devar

⑨ Grant & payment

⑩ Trial report / publication.





Q5) Write a note on compensation for clinical trial subjects as per ethical guideline.

→ CT play imp role in advancing medical research & discovering new t/t.

→ Ethical guideline for compensation clinical trial subject aim to strike a balance b/w acknowledging participants contribute & awarding undue ~~to~~ inducement.

→ The ethical guideline for compensation is needed due to it involve ~~exist~~ ~~of~~ human subject & must be compensated for the suffering, pain & fear there loss.

→ There are few points in ethical guideline to be consider during CT.

① Purpose of compensation :- Recognize participant vital role in advancing medical research

- Cover expenses such as travel cost & compensate of any other risk.

② Fairness & Equity :- Ensure compensation is fair & proportional to the level of involvement.

- Promote equitable t/t of participants regardless of demographics.



3. Informed Consent :- Clearly communicate compensation detail during the informed consent process.

- Provide an opportunity for participants to ask questions about compensation.

4. Avoiding Undue Inducement :- Set compensation at a level that acknowledges participation & is creating undue influence.

- Emphasize the voluntary nature of participation in the trial.

5. Risk - Benefit Analysis :- Align compensation to the level of risk associated to the clinical trial.

Consider the potential physical, psychological, and social risk participants may encounter.

6. Payment Timing :- Clearly define the schedule for compensation disbursement in trial protocol.

Consider providing compensation at regular interval to maintain participant motivation.

7. Regular Compliance :- Adhere to local and international ethics guideline and regulations.

- Ensure that compensation practices comply to institutional review Board (IRB).



Q6 = What is the role of ICMR in regulating CT.

→ The ICMR (Indian Council of Medical Research) play crucial role in regulating CT in India; ensure that research is conducted ethically.

→ The ICMR regulating CT & its role are explained as:

1. Guideline formulation: It is responsible for formulation of comprehensive guidelines that define the ethical & scientific std for conducting CT

2. Ethical Review Oversight: The ethical review process of CT protocol are overseen & ensured by ICMR by considering ethical norms.

3. Collaboration of ICMR: It collaborate & CDSCO aligning ethical consideration & regulatory requirement, this ensure safeguard of participant

4. Capacity Building & Training: It conduct training program for researchers, investigators & members of IECs.





- It aims to enhance understanding & compliance to ethical guideline among involved in CR.

⑤ Development of Ethical principle :- ICMR contribute to development and evolution of ethical principle governing CT.

- It addresses emerging ethical challenges & ensure the guideline remain robust & relevant to landscape.

⑥ Monitoring Ethical conduct :- ICMR monitor the ethical conduct of CT, this includes ensuring participation are treated to respect, that their rights are protected.

⑦ International Collaboration :- Engage in International collaboration to stay abreast of global ethics stds & practices.

⑧ Public Awareness :- It play a imp role in raising public awareness about the imp of ethical conduct in CT.

⑨ Policy advocacy :- It engage in policy advocacy, influencing the development of national policies related to CR. This measure ensure ethical consideration are embedded in broader landscape.





## Q7. Note on constitution & responsibility of IRB.

→ IRB stands for institutional review board and it is regulatory authority that regulate all research, carried on human subjects.

→ "Conduction of research should be in accordance with ethical principles" are the main objective of IRB.

→ In case of constitution of IRB.

- IRB should consist of reasonable number of members, collectively have qualifications to evaluate research work.
- It should have atleast 5 members.
- Atleast one member having primary area of interest in non-scientific area.
- Atleast one member independent of institution site.
- 1 Chairperson.
- 1 Secretary should be from same institute to ensure business committee.
- Maximum 7 & minimum 5 members required.

→ In terms of responsibility there are various responsibilities of IRB such as.

- ① To ensure safeguard of rights, safety & well being of human subject.



② To obtain the following document from trial such as.

- (a) Trial protocol.
- (b) Written information consent form
- (c) Subject recruitment procedure.
- (d) Patient information sheet.
- (e) Payment for subject.
- (f) Request for additional information
- (g) Qualification of investigator.
- (h) Approval of application of trial
- (i) Justification of compensation

③ IRB should ~~also~~ consider qualification of investigator & it intention

④ IRB should conduct continuous review on trials.

⑤ IRB should ensure the privacy & safety of data of clinical trial.

⑥ IRB review both amount & payment made to human subject.

⑦ IRB ensure the payment received by subject at specific interval.





Q8 Explain IEC review procedure of a research proposal & methods of review process of IEC.

→ Following procedure of IEC are:

1. Determination of composition and the authority under which it is established.
2. They schedule, notify their members & conduct meeting.
3. They conduct initial & continuing review of trial.
4. They determine frequency of continuing review as appropriate.
5. They should be specifying that no subject should be admitted to trial before IRB/IEC issue.
6. They should be specifying of protocol & should not initiate trial before IRB/IEC approval.
7. They should specify deviation & changes of protocol, report to IRB:-

ca) Deviation or changes of protocol to eliminate hazard





(b) changes increasing the risk of subject or affecting significantly

(c) All ADR that are serious & unexpected

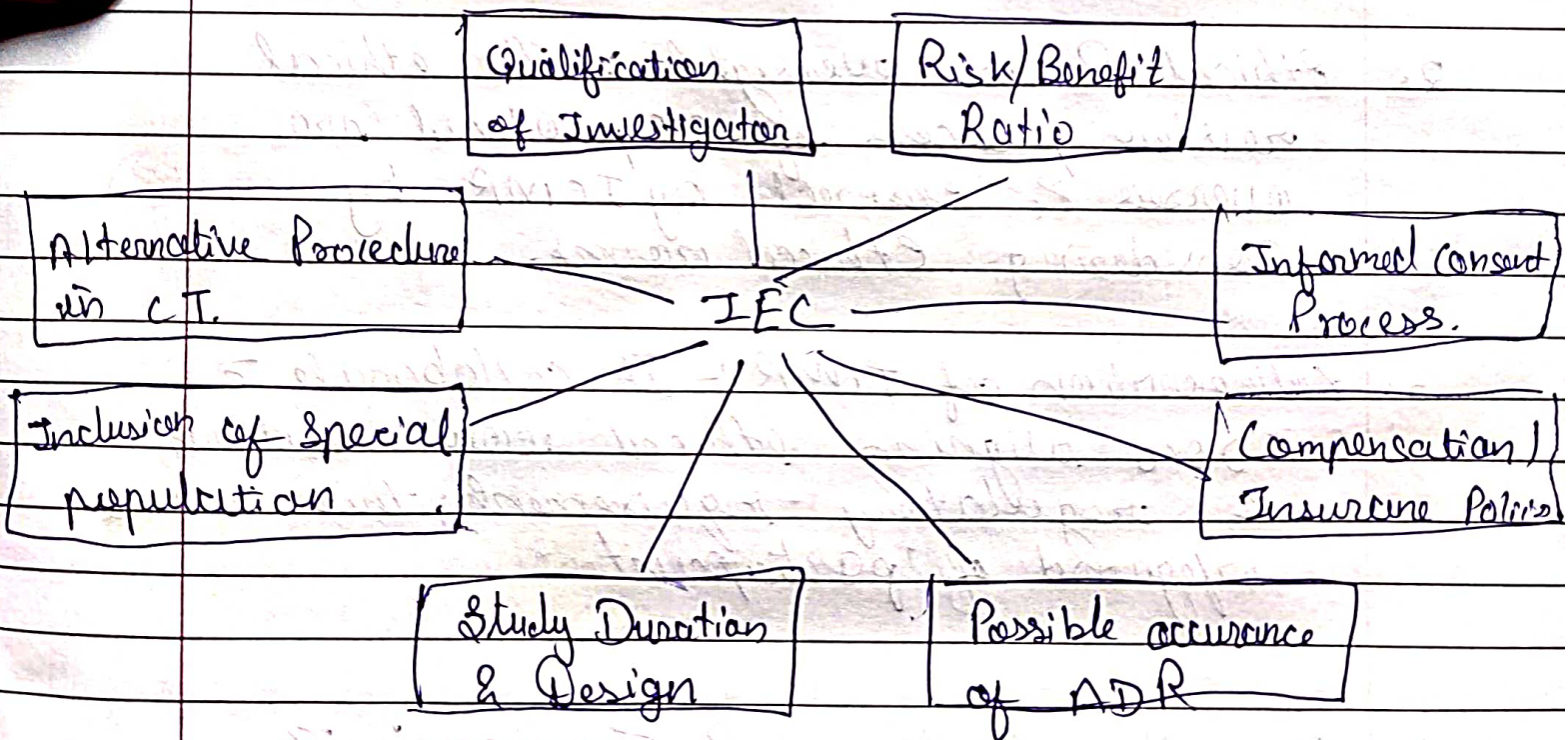
(d) New information that may affect ADR safety of subject & conduct of trial

8. IRB/IEC ensure that notify in writing the investigator or institution concerning

(a) trial related opinion / decisions

(b) Reason behind opinion / decisions

(c) Procedure for appeal of opinion / decisions





## Q9 Regulatory setup in Europe

- ↳ Regulatory Authority in Europe is European Medicines Agency (EMA)
- ↳ EMA relies on result of CT carried out by pharmaceutical company to reach its opinion on authorization of medicines
- ↳ EMA ensure that GCP must be followed
- ↳ EMA is first regulatory authority that issue guidelines for biosimilars in 2005
- ↳ The guideline clearly differentiate generic & biosimilars





→ It includes quality, safety & efficacy of biosimilar guideline.

→ By 2 procedures the medicine is authorized  
(a) Centralized authorization procedure  
(b) National " " "

→ This procedure result in single marketing authorization, which is valid across Europe Union.

→ Centralized procedure is compulsory in human medicine such are,

(a) must be derived from biotechnology like genetic engineering.

(b) Intended for trt of HIV, AIDS, Cancer, DM, N.D.D or any immune dysfunction.

(c) Some medicines are officially designated as orphan medicines.

→ EMA only accept application through a centralized procedure.

→ 210 days taken by agency to decide the medicines should be marketed or not.

→ Once a community marketing grants the permission then the medicine ~~available~~ make available for patients & healthcare professionals.





→ In national authorization procedure, the every state has its own authorization procedure & it has 2 method of authorization

(a) Decentralized :- companies can apply for ~~simultaneous~~ simultaneous authorization in more than one European country of medical product that not yet been authorized in centralized procedure.

(b) Mutual recognition procedure :- Medicine is first authorized in one EU member state in accordance to the National procedure of country.

Following this, further marketing authorization can be brought from other European countries in procedure whereby countries agree to recognize the validity of original, national authorizations.



Q10 Detail about regulatory setup that governs the CR in India.

→ India has well defined regulatory framework governing CR to ensure the ethical conduct of trials & safety of participant.

→ The regulatory setups involve various agencies such as

① CDSCO :- central drug std control organisation. is the primary regulator authority for C.T under the ministry of Health & family welfare.



- It has duty to regulating & ensuring quality of medicines. & pharmaceutical product.

- ② ICMR :- Indian Council of Medical research provide guide-line. & ethical & tds fees. conducting clinical trials in biomedical products
- ③ SEC :- Subject Expert committee that review & evaluate CT protocol, provide recommendation for approval based on scientific & ethical consideration.
- ④ CDL :- central drug laboratory that regulate the control of drug quality. with collaboration with CDSCO.
- ⑤ DCGI :- drug controller general of India responsible for granting approval for import, mfg. & marketing of drug in CT & other various levels.

→ The regulatory Process in India are followed as.

CTA (Clinical Trial Application):

↓  
CDSCO

↓  
Approval of trial

↓  
Ethical consideration & Approval





Initiation of trial



Final Protocol Submission



Inspection, Monitoring & Trial conduction by CDSCO.



CDSCO approval for publication.

→ Mainly 2 bodies governs major part of Trials are CDSCO & DCGI.



## ① Regulatory setup in USA.

↳ There are 6 regulatory setup in USA.

① The USFDA is a scientific, regulatory & public health agency.

② Responsible for regulating & supervising the safety of most of food products, human & animal drug, therapeutic agent of biological origin.





③ The scientists in agency are responsible for evaluation of application for new human drug and biologics, complex medical device, food & color additives, inject formulations & animal drugs.

④ The FDA is responsible for monitoring the manufacture, import, transport, storage and sale of about 1 ~~trillion~~ trillion

⑤ There are worth of product annually.

⑥ The FDA is led by commissioner of food and drug, who is appointed by the President and confirmed by Senate.



## Q12 components of CR protocol & process of protocol preparation & amendment

→ There are various component of protocol

① Title page :- It should be precise, clear & certainly explain the Subjective of research

② Signature page :- It should consist name, profession & Signature of all participant, guide & professors.

③ ~~Content Page~~ ~~Table of Contents~~ :- It is one of page of index that guide to specific content.

④ list of abbreviation :- All abbreviation should be listed and defined on this page follow international abbreviation guideline

⑤ Introduction / Abstract :- It should be of 2-3 page long and provide sufficient information to the reader & examiner.





- ① **Rationale** :- It is a section detailing the scientific rationale for a protocol that justify in medical & scientific literature.
- ② **Inclusion & exclusion criteria** :- It defines characteristic of participant eligibility to participate & excluded in clinical trial.
- ③ **Endpoint** :- ~~Specific and~~ Specifies the primary & secondary endpoint, outlines how those will be measured & assessed.
- ④ **Statistical consideration** :- Describes various methods use to analyse the clinical research.
- ⑤ **Human subject protection** :- Describe the risk & benefit of clinical trial with detail note on compensation on risk.
- **Preparation of protocol & amendment.**
- ⑥ **Literature review** :- It is the 1<sup>st</sup> step of any clinical research to review of existing study or literature that help to develop accurate protocol & minimize the risk of error.



- ② Study design & Methodology :- It involve careful consideration of study design, methods & statistical approach that outlines the framework of data collection & analysing.
- ③ Ethical consideration
- ④ Inclusive & Exclusion criteria formation
- ⑤ Regulatory approval.
- ⑥ Identify needed Amendment.
- ⑦ Overall expense of Clinical research



## ①3) Note on case record form.

- ↳ CRF stand for case record form, it is a trial doc. for collecting & recording, patient related information in standardized & uniform manner.
- ↳ It play pivotal role in maintaining accuracy & consistency in data collection.
- ↳ Good CRF have facilitate in designing & creating clean database require minimum query & better approach.
- ↳ The structured approach ensure uniformity in information gathering, reduce risk of error.

② Source of document :- It serve as primary source of doc of evidence for each participant in study

- It should provide data in comprehensive manner as per provided protocol

③ Quality control :- CRF act as tool for quality control, facilitate consistency & ~~standardization~~ standardized data collection across multiple site or investigator.



(4) CRF development :- Good CRF consistently develop their own design & protocol to eliminate flaws.

- The development is

(a) CRF design

(b) medical recorder

(c) Clinical monitor

(d) Data manager

(e) Statistician etc.

(5) Data Analysis facilitation :- Researcher can easily extract relevant information for statistical analysis, contributing to robustness of study finding.

(6) Regulatory Compliance :- compliance  $\bar{c}$  regulatory std is critical aspect of CR. The CRF ensure that study aligns  $\bar{c}$  ethical guideline & regulatory requirements, covering aspects such as informed consent form & privacy.

(7) There are 3 main part of element of CRF

- (a) Header consist module
- (b) Safety related module
- (c) Efficacy.





## Sample Record form

Name

Date

Age

Gender

Any ADR event occur?

Yes

☐

NO

☐

If Yes then provide clear symptoms

⑧ There are 3 main CRF designs layout such as

i) Non-time dependent data

ii) Time dependent data

iii) Cumulative data