1

Good clinical practices

5 2

- GCP are a set of internationally recognized ethical and scientific quality requirements which must be observed while conducting, designing, recording and reporting a clinical trial that involves participation of human subjects.

- compliance to GCP assures that the rights, safety and well-being of the trial subjects is maintained & protected & the results of the clinical trial are credible.

- Purpose : To harmonise the regulations and guidelines for drug development.

- Participants : Regulatory agencies are the Industry representatives from Europe, US and Japan.

- Goals :

(1) To remove duplication in the development of review process

(2) For the new medical products, the data showed demonstrate :

- Safety
- Quality
- Efficacy.

1 2 3 4 5 6 7 8 9 10 11 12 13
EPRBRSW CNC SSC MC Q ICF S CF IP SYS

• Principles of GCP :

(1) Clinical trials should be conducted in accordance to the ethical principles (as per declaration of Helsinki)

Trials should also be conducted in harmony with GCP and other regulatory requirements.

(2) Before the trial is initiated, focus on the benefit & risk ratio.

Foreseeable risks and suspect inconviniences should be ~~out~~ weighed against the anticipated benefits for the trial and society

The trial should only be conducted if the anticipated benefits outweigh the risks.

(3) The rights, safety and well being of the trial subjects should prevail over the interests of science and society.

(4) Enough clinical and non-clinical info about the drug should be available to conduct the proposed trial.

(5) Clinical trials should be scientifically sound and described in clear, detailed protocol.

(6) Clinical trials should be conducted in compliance with protocol approved by the IRB/IEC.

(7) A qualified physician is responsible for the medical care and decisions made on behalf of the trial subjects.

(8) Each individual involved in the clinical trial should be qualified by education, training and experience to perform their respective tasks.

(9) Freely given informed consent form should be obtained from every trial subject prior to participation.

(10) All info of clinical trial should be recorded, handled and stored safely which can help in accurate reporting, interpretation and verification.

(11) Confidentiality of records should be maintained as per regulatory requirements.

(12) Investigational products should be manufactured, stored, and handled as per GMP guidelines.

(13) Systems with procedures that assure quality of every clinical trial should be implemented.

(2) EU - European Union
EFPIA - European federation of P'ceutical industries & association

(3) ICH guidelines
International conference on Harmonization of Technical requirements for registration of p'ceuticals for human use.

- Joint initiative of both regulators and industry representatives of the Europe, Japan and US ~~to~~ in scientific and technical discussion about the testing to ensure safety, quality and efficacy of new medicines.

- Participants. — (6) founder members in Europe, US and Japan.

EU | EFPIA | MHLW | JPMA | FDA | PhRMA

- ICH Guidelines. = Q1 Q5 Q12 E2 E21 M15

(1) Quality :
Q1A - Q1F : Stability
Q2 : Analytical validation
Q3A - Q3E : Impurities
Q4A - Q4B : Pharmacopoeias.
Q5A - Q5E : Quality of biotech products
Q6A - Q6B : Specifications
Q7 : GMP
Q8 : P'ceutical development.
Q9 : Quality risk management.
Q10 : P'ceutical quality system
Q11 : Devel. & Manuf. of drugs.

MHLW - Ministry
JPMA - Japan P
PhRMA - P'ceutico

Q12 · Lifec
Q13 · Cont
Q14 · Anal

(2) Safety :
S1A - S1C
S2 : Gen
S3A - S3
S4 : To
S5 : Re
S6 : Bi
S7A - S
S8 : Im
S9 : N

S10 :
~~S11~~ :

(3) Efficc

E1 :
E2 :
E3 :
E4 :
E5 :
E6 :
E7 :
E8
E9
E1

(4) Type

MHLW - Ministry of Health, Labour & welfare (Japan)
JPMA - Japan P'utical manufacturers assc.
PhRMA - P'ueticai Research & " of America

Q12. Lifecycle management
Q13. Continuous manuf. of drug substances.
Q14. Analytical procedure devel.

(2) Safety:
S1A - S1C: Carcinogenicity studies
S2: Genotoxicity stu.
S3A - S3B Toxicokinetics & P'cokinetics.
S4: Toxicity testing
S5: Reproductive toxicology
S6: Biotechno. products
S7A - S7B: P'cology studies
S8: Immunotoxicology studies.
S9: Non-clinical evaluation of anticancer products.
S10: Photosafety
S11: Non-clin. pediatric safety
~~S12~~:

(3) Efficacy:
E1: Clinical safety of long-term therapies
E2: P'covigilance
E3: Clin. study reports
E4: Dose response studies.
E5: Ethnic factors.
E6: GCP
E7: CT in geriatrics.
E8: General considerations of CT
E9: Statistical principles for CT.
E10: Choice of group control in CT.

or
eviation of
ties &

onization
egistration

s and
Europe,
and
esting
fficacy

s in
Japan.

PhRMA

ds

E11: CT in Pediatrics.
E12: Clin. Eval. by Therapeutic category
E13: Clin. Eval of QT
E14: Definition in P'cogenetics/Genomics
E15: Qualification of genomic biomarkers
E16: MuHi. regional clinical trials.
E17: Genomic sampling
E18: safety data collection
E19: Adaptive clinical trials.
E20: inclusion of pregnant & Breastfeeding individuals.

Q (1) & Q (4) from phone.

(5)

(1) and (4) CDSCO guidelines.

- Central drug standard control organisation is the main regulatory body to regulation of p'ceuticals, medical devices and clinical trials in India.

Its guidelines are as following - 1234

(1) Investigational p'ceutical product

(2) Pre. clinical supporting data

(3) Protocol :

(a) Relevant components

1. Objectives and justification.
2. Ethical consideration.
3. Study design.
4. Inc., Exclu. and withdrawal of subjects
5. Handling of products
6. Assessment of efficacy.
7. Assessment of safety.
8. Statistics
9. Data handling & management
10. QA and Q control
11. Finance and Insurance
12. Publication policy
13. Evaluation

(b) Supplementaries & appendices.

VENP3 AMPITC

(4) Ethical and safety considerations.

(a) Ethical principles:

1. Principle of essentiality
2. Voluntariness, ICF & community agreement
3. Non exploitation.
4. Privacy & confidentiality
5. Precaution & risk minimization.
6. Professional competence
7. Accountability & transparency.
8. Maximization of public interest of distributive justice.
9. Institutional agreements.
10. Public domain
11. Nature of responsibility ~~and~~
12. principles of compliance.

(b) Ethics committee:

1. Basic responsibilities
2. composition
3. Terms of reference
4. Review procedure
5. submission of application
6. Decision making process
7. Interim review
8. Record keeping
9. special considerations

(c) In
1. I
2. E
M
3.

(d) Es
a p
sa

(e) C

(f) S
s
1
2
3

(g)
C

(c) Informed consent process:
1. Ic of subject
2. Essential info for a prospect to research an subjects
3. Ic in non-therapeutic study.

(d) Essential info an confidentiality for a project to research subjects safeguarding

(e) Compensation for participation.

(f) Selection of special groups as research subjects.
1. Pregnant
2. Children
3. Vulnerable groups.

(g) Compensation for accidental injury (obligation for sponsor to pay).

DO functions on Pg 104

VIN 23 AMPITC
BP
&
BCTRSDIRS

123 4 5 6 7 8 9 10
PIR IRB ICDA SR IP RR GP TR

4

Challenges in Implementation of ICH-GCP guidelines.

(1) Professional training on GCP:
- Scarcity of GCP-trained professionals; pose as a major challenge.
- Lack of GCP training in various stake holders (sponsor, investigator, ERB etc)

- Although, some companies have in-house training programs, it is not uniform across industry.

(2) Infrastructure:
- Majority of hospitals in India are not geared up to meet the infrast. requirements of GCP
- They lack labs and diagnostics upto the standard of GCP.

(3) Regulatory environment:
- Inspite of well-defined guidelines, the biggest challenge is their implementation and adherence".

- We do not have a regulatory inspection system in place to monitor the adherence to these guidelines. in majority of circumstances.

(4) IRB / IEC / ERB :

- GCP guidelines requires a written standard operating procedure for IEC/IRB.
- However, there are no standard guidelines on what should be the content of an ideal SOP.
  leading to non-uniformity across various hospitals / institutes.

(5) ICD administration :

- Administration of ICD is a major challenge in a country like India, where the patient has immense faith on the treating doctor that they insist on signing the document w/o even reading it or after reading it superficially!

(6) Safety reporting :

- It is the joint responsibility of the investigator & the sponsor to report the entire serious and unexpected adverse events to IRB/ERB and the regulatory authorities.
- But in most of the cases, the sponsor does not comply with the expidited safety reporting.

(7) Investigational product:

- The investigational product storage, handling and access control is a major challenge as it is difficult to produce any evidence of the temperature chain being maintained during the shipment of the product from sponsor's facility to the investigation site.

(8) Record keeping:

- Record retention and retrieval is always a major challenge in majority of hospitals.

- The documentation of patient disease, treatment and progress notes is not adequate to meet the standards of good documentation practices that ensure data completeness and correctness.

(9) Grants and Payments:

- Trial agreements are based on the institutional practices, where the research grant goes to a centralised research account, which in majority of cases remains un-utilized.

(10) Trial report:

- Negative trials (or) trials that get terminated prematurely, or narrowly published pose as a major threat toward the validity of evidence-based medicine as one gets to know the postive results only.

5

Compensation for participation

The compensation guidelines are given by the Drug controller general of India (DGCI).

These guidelines are classified as :
(1) Compensation for CT related Injury.
(2) Compensation for CT related death
(3) Compensation for CT related SAE (Serious adverse events)

(1) Compensation for CT related Injury :

Injury occuring due to any of the following reasons is considered as a CT. related injury an death and the nominees of the subject are entitled to a financial compensation.

(a) Adverse effect of Investigational product

(b) Violation of approved protocol an scientific misconduct.

(c) Failure of IP. to provide therapeutic effect

(d) Use of placebo. in placebo. CT.
(e) Adverse effect due to concomitant meds.
(f) Injury to child in uterus.

(2) Compensation for CT related death:

- In case of death occuring in trial subjects, their nominees are entitled to financial compensation, which will be over and above any expenses incurred due to medical management of the subject.

- It shall be given by the sponsor of the clinical trial.

- Sponsor shall give an undertaking to the licensing authority along with application of permission for CT, to provide compensation in case of CT-related death.
- If the sponsor fails to do so, the licensing authority will suspend or cancel the CT or restrict the sponsor to conduct any further trial in the country.

(3) Compensation for CT related SAE:

(a) Permanent disability-

- 100% disability may not be considered as death of subject.
- Quantum of compensation for 100% disability shall be 80% of compen. of death of subject.

- compensation for <100% disability

$$C = \frac{(D \times 80 \times C)}{100} \times 100$$

(b) congenital anomaly -
Following situation can occur due to congenital defects:
(i) Still birth
(ii) Early birth due to anomaly.

In case of (i) & (ii), the QOC should be the half of the base amount for SAE resulting into death

= ₹ 4,00,000 / 2 = ₹ 2 Lacs

(iii) NO death but deformity which can be fully covered through appropriate intervention.
(iv) Permanent disability (Phy. or Mental).

In case of (iii) & (iv)
= ₹ 4,00,000 + Medical management as long as required.

(c) SAE causing life-threatning disease -

Compensation = N × W
W : Min. wage
N : No. of days subject was under treide.

(a) Reversible SAE in case it is resumed -

- compensation per day of hospitalization in such case should be ~~double~~ double the minimum wage.

$$C = 2 \times W \times N$$

ECRMRREC

(6) Role of ICMR (ICMR guidelines)

1. There should be an ethics committee of central drugs standard control organization for conducting clinical trials with involvement of human subjects.

2. Complete review of the protocol submitted to them.

3. It should meet periodically to calculate progress of the ongoing trials, review serious adverse events and take apt actions.

4. Research should be done on vulnerable subjects only when there is a direct benefit from it.

5. INFORMED CONSENT should be taken from the participant. In case, the individual is incapable, consent from a legal guardian should be taken.

6. Participants may be reimbursed for the inconvinience and time spent during research.
But payments should not be so large as to make prospective participants overwhelm their better judgements.

7

- If the drug is found to be effective on a patient, the sponsor should provide it to him after the clinical trial is over till it is marketed in the country, at a reduced rate.

8

- Participants who suffer physical injury should get financial or other assistance. In case of death, dependants are entitled to compensation.

(*) Ethics are a set of standards or principles.
- These standards are universal. They help in seperating the good from bad or desirable from undesirable

- In terms of CR,
Ethics refers to a statement of general principles of research involving human participation
- Also called as ICMR code
- It consists of:
(a) Statement of general principles on ~~BMR~~ Rsrch involving human subj in BMR.

(b) Statement of specific principles on Rsrch on human subj in specific areas in BMR

7

IRB | IEC | ERB

Institutional review board (IRB) is an independant body constituted of Medical, scientific and non-scientific professionals.

Their responsibility is to ensure the protection of rights, safety and well-being of human subjects involved in a trial.

It is also known as:
- Independant Ethics committee (IEC)
- Ethics review board (ERB.)

Compasition: (7 to 8 members)
- One member is selected from out of institution i.e. chair person.

- 2-3 members selected as basic medical scientists

- 2-3 members as clinicians from different institutes | hospitals.

- 1 social scientist
- 1 philosopher
- 1 legal expert.

FR CDMNM

Functions:

1. They should perform their functions on the basis of written procedures.
2. They should maintain records of its activities and minutes of meeting.
3. They should comply with GCP and its regulatory requirements.
4. They should take their desicions at announced meetings at which at least a quorum is present.
5. Only members who participate in IRB/IEC review should vote and provide their opinion.
6. IRB/IEC may invite non-members with expertise in special areas for assistance.

Responsibilities:

- An IRB/IEC should safeguard the rights, safety and well-being of all vulnerable subjects.
- Special attention should be paid in trials with vulnerable subjects.

2. IRB/IEC should attain the following:
(a) Trial protocol
(b) written info consent form.
(c) subject recruitment procedures
(d) written info for subjects
(e) Investigator's brochure
(f) info about payment & compensation available to subjects.
(g) Availabe safety info, investigators CV evidencing qualifications.

3. IRB/IEC should consider qualifications of investigator for the proposed withdrawal as documented by CV.

4. It should continue conducting review of each ongoing trial at intervals apt. to degree of risk to human subjects. at least once/year.

5. IRB/IEC may request more info to be given to the subjects.

6. IRB/IEC should review both amount and methods of payment to subjects to assure that neither presents problems of coercion or undue influence

7. They should ensure the info about the payment is set forth in the written ~~IC~~ ICF. The payment will be specified.