SPECT Weekly Question Forum

Week-1

Question: "If a clinical trial subject is illiterate and not able to sign informed consent document, who would sign the document: the legally acceptable representative or the impartial witness?"

Answer: Legally acceptable representative (LAR)* must sign if he/she is literate.

However, on the issue of signing of the informed consent document by an impartial independent witness*, in cases where a literate LAR of the subject signs it, parallel interpretations of the applicable laws, regulations and guidelines seem possible.

On one hand, in view of Schedule Y of the Drugs and Cosmetics Rules, 1945 ("Schedule Y"), it may be argued that the presence and signature of an independent witness are required only if the subject or his/her LAR is unable to read/write. The Ethical Guidelines for Biomedical Research on Human Participants by the Indian Council of Medical Research also specify that "when the written consent as signature or thumb impression is not possible due to sensitive nature of the project or the participant is unable to write, then verbal consent can be taken after ensuring its documentation by an unrelated witness".

On the other hand, it may be argued that the capacity to give consent is independent and not necessarily related to the capacity to read or write. In legal documentation, a personal mark on the paper, whether in the form of signature or by thumb impression, is indicative of the consent of the signatory to the contents of the document. However, mere signature or thumb impression is not a conclusive proof of the informed and free consent of the signatory. The impartial independent witnesses thus are deemed to assume a greater role of testifying amenable circumstances while signing of the documentation, and not merely that of witnessing the signing.

This principle is, to a large extent, inculcated in the regulations governing clinical trials, by explaining as to what all the witnesses attest by signing the consent form. In this regard clause 4.8.9 of the ICH-GCP Guidelines prescribes that:

"If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representatives, and after the subject or subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative."

From a perusal of the above, it appears that:

A. It is possible to interpret that an impartial witness should sign and personally date the consent form if the subject is illiterate. The clause here assumes that the LAR may be literate, and does not prescribe an exemption from signature of the witness in such cases.

B. The role of the witness in clinical trials is not limited to merely testifying signing of the consent document by the LAR. A witness also testifies accurate explanation to the subject about the trial, proper understanding thereof by the subject or his LAR, and the "free" condition of the LAR while giving the consent.

Even Schedule Y assumes that the purpose of witness is to testify in writing that the informed consent was properly and duly obtained. It is interesting to note that that the column provided in the format of the informed consent form in Schedule Y has not been marked as optional.

The apparently incomplete provision of the (Indian) Good Clinical Practice Guidelines (reproduces below) also adds to the possibilities of parallel interpretations.

Prior to the Subject's participation in the Study the written Informed Consent form should be signed and personally dated by

1.
(i) The Subject or
(ii) if the Subject is incapable of giving an Informed Consent for example children, unconscious or suffering from severe mental illness or disability, by the Subject's legal representative or guardian or
(iii) if the Subject and his legal representative or guardian is unable to read / write,

2. An impartial witness who should be present during the entire informed consent discussion

3. The Investigator.

By signing the consent form the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the Subject or the Subject's legal representative or the guardian, and that informed consent was freely given by the Subject or the Subject's legal representative or the guardian.

Without going into the complex principles of legal interpretation, a careful reading of clauses and sub-clauses would reveal that sub-clause (iii) is not completely written, leaving open the possibility of interpretations. However, even the GCP ascribe a greater role to the witness than merely witnessing the signature.

Suggestion: In view of the above discussion, it appears that the requirement of signature of a witness on the consent form in case of literate LAR may be analyzed and debated from various angles. However, in view of the fact that clinical trials remain an academically, socially and legally sensitive matter, the investigators may exercise caution by obtaining the signature of the impartial witness in cases of illiterate subject, irrespective of literacy of the LAR.

Terms Used:

* Legally Acceptable Representative (LAR): In view of the governing laws and regulations, the term LAR would include the natural guardian and the legal representatives of the subject, as well as any person entrusted with the responsibility of deciding for and on behalf of the subject. The LAR shall also be, in his individual capacity, competent to contract. Thus an LAR should also of a sound mind, of an age of majority, and not under any duress or coercion that would affect his free decision. For clarification, being illiterate is not considered an impediment under Indian laws on the capacity of the person to contract.

* Impartial Witness: In terms of the GCP Guidelines means “an impartial independent witness who will not be influenced in any way by those who are involved in the Clinical Trial, who assists at the informed consent process and documents the freely given oral consent by signing and dating the written confirmation of this consent”.

Week-2

Question: "Should intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization be considered as Serious Adverse Event?”

Answer: Yes. Such events should also be considered as serious. These are considered serious for other medical reasons and medical judgment has to be exercised in such situations.

Reference:
According to ICH Topic E2A “Medical & scientific judgment should be exercised in deciding whether expedited reporting is appropriate in important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of outcome as follows:

- result in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

Week-3

Question: "Which SAEs (or ADRs) are required to be reported to Regulatory Agency (ies)?”

a) SAEs not related to Investigational Product (IP)
b) Expected serious ADRs
c) Unexpected SAEs not related to IP
d) Unexpected serious ADRs

Select only one answer to the question considered by you as the most appropriate or the correct answer:

i) All the above
ii) a, b & c
iii) d
iv) b, c & d

Answer: iii) i.e. Unexpected serious ADRs also known as SUSARs

Reference:
According to ICH-GCP Guidelines, Section 5.17.1: The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

ICHE2A, Section 3.A.1: Expedited reporting of reactions which are serious but expected will ordinarily be inappropriate. Expedited reporting is also inappropriate for serious adverse events from clinical

investigations that are considered not related to study product, whether the event is expected or not. Similarly, non-serious adverse reactions, whether expected or not, will ordinarily not be subject to expedited reporting.

Schedule-Y, Section 2.2.iv: Any unexpected adverse event (SAE) (as defined in GCP Guidelines) occurring during a clinical trial should be communicated promptly (within 14 calendar days) by the Sponsor to the Licensing Authority and to the other Investigator(s) participating in the study.

Indian GCP, Section 3.1.11: The sponsor should expedite the reporting to all concerned (including the ethics committee & the regulatory authorities) of all serious and/or unexpected adverse drug reactions.

Globally, only SUSARs are required to be reported to regulatory agency(ies). However, in India there is some ambiguity between different regulations. Schedule-Y mentions the reporting of unexpected adverse event (SAE) to the Licensing Authority with a further reference to GCP Guidelines. GCP guidelines mentions expedited reporting of all serious and/or unexpected adverse drug reactions. Use of words "and/or" poses reporting requirement even if any one of the two events happens. Hence, if strict compliance of the Indian provisions is sought, it would be appropriate to report all serious and/or unexpected adverse drug reactions to Indian Regulatory Agency.

Week-4

Question: "Which SAEs (or ADRs) are required to be reported to EC/IEC/IRB/ERB"

a) SAEs not related to Investigational Product (IP)
b) Expected serious ADRs
c) Unexpected SAEs not related to IP
d) Unexpected serious ADRs

Select only one answer to the question considered by you as the most appropriate or the correct answer:

i) All the above
ii) a, b & c
iii) d
iv) b, c & d

Answer:

i) As per ICH GCP: Unexpected serious ADRs

According to ICH-GCP Guidelines, Section 5.17.1: The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are **both serious and unexpected**.

ICHE2A, Section 3.A.1: Expedited reporting of reactions which are serious but expected will ordinarily be inappropriate. Expedited reporting is also inappropriate for serious adverse events from clinical investigations that are considered not related to study product, whether the event is expected or not. Similarly, non-serious adverse reactions, whether expected or not, will ordinarily not be subject to expedited reporting.

ii) As per Schedule Y: Serious and unexpected adverse events

Adverse event may include both AEs and ADRs

Schedule-Y, Section 2.2.iv: Any **unexpected adverse event** (SAE) (as defined in GCP Guidelines) occurring during a clinical trial should be communicated promptly (within 14 calendar days) by the Sponsor to the Licensing Authority and to the other Investigator(s) participating in the study.

iii) **As per Indian GCP: All adverse drug reactions and adverse events that are serious and/or unexpected**
Indian GCP, Section 3.1.11: The sponsor should expedite the reporting to all concerned (including the ethics committee & the regulatory authorities) of all **serious and/or unexpected** adverse drug reactions.

Section 3.3.4: The investigator should promptly report to the ethics committee, the monitor and the sponsor, all the adverse drug reactions and adverse events that are serious and/or unexpected.

Globally, only SUSARs are required to be reported to Ethics Committee(s). However, in India there is some ambiguity between different regulations. Hence, if strict compliance of the Indian provisions is sought, it would be appropriate to report all serious and/or unexpected adverse drug reactions/adverse events to Ethics Committee(s).

Week-5

Question: "Which SAEs (or ADRs) are required to be reported to Sponsor"

a) SAEs not related to Investigational Product (IP)
b) Expected serious ADRs
c) Unexpected SAEs not related to IP
d) Unexpected serious ADRs

Select only one answer to the question considered by you as the most appropriate or the correct answer:

i) All the above
ii) a, b & c
iii) d
iv) b, c & d

Answer: i) All the above

Reference:

According to ICH-GCP Guidelines, Section 4.11.1: All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting.

Schedule-Y, Section 3: Investigator(s) shall report all serious and unexpected adverse events to the Sponsor within 24 hours.

Indian-GCP, Section 3.3.4: The investigator should promptly report to the ethics committee, the monitor and the sponsor, all the adverse drug reactions and adverse events that are serious and/or unexpected.

Week-6

Question: "Is FDA 1572 Form (Statement of Investigator) is mandatory to be signed by Indian Investigators participating is US-FDA registration trial?"

Select only one answer to the question considered by you as the most appropriate or the correct answer:

i) Yes
ii) No

Answer: No

There is no FDA requirements that study sites outside of the United States operate under a U.S. IND. FDA regulations (21 CFR Parts 312.120 and 314.106) establish the criteria under which the agency will accept non-U.S., non-IND studies/data for purposes of FDA review in support of applications (IND or NDA). The decision to operate under an IND at non-U.S. site(s) is discretionary on the part of the study sponsor.

Moreover the IND form (Form FDA 1571) explicitly gives sponsors the option of submitting either **Investigator data** [21 CFR 312.23(a) (6)(iii)(b)] **or** completed Form(s) **FDA 1572**.

Week-7

Question: "In case of accidental injuries leading to death of a clinical trial subject as a result of his/her participation in a trial, are the dependents entitled for material compensation:

i) Yes
ii) No

Answer: Yes

Reference:

According to Indian GCP Guidelines, Section 2.4.7: Research subjects who suffer physical injury as a result of their participation in the Clinical Trial are entitled to financial or other assistance to compensate them equitably for any temporary or permanent impairment or disability subject to confirmation from IEC. In case of death, their dependents are entitled to material compensation.

According to ICMR Guidelines, Chapter III, Section VI: Research participants who suffer physical injury as a result of their participation are entitled to financial or other assistance to compensate them equitably for any temporary or permanent impairment or disability. In case of death, their dependents are entitled to material compensation.

Week-8

Question: "Can a Sponsor directly interact with the EC/IEC/IRB/ERB for a trial related discussion?"

Select only one answer to the question considered by you as the most appropriate or the correct answer:

i) Yes
ii) No

Answer: It is important that a formal line of communication be established between the clinical investigator and the IRB. Clinical investigators should report adverse events directly to the responsible IRB, and should send progress reports directly to that IRB. However, FDA does not prohibit direct communication between

the sponsor and the IRB, and recognizes that doing so could result in more efficient resolution of some problems.

FDA does require direct communication between the sponsor and the IRBs for certain studies of medical devices and when the 21 CFR 50.24 informed consent waiver has been invoked. Sponsors and IRBs are required to communicate directly for medical device studies under 21 CFR 812.2, 812.66 and 812.150(b). For informed consent waiver studies, direct communication between sponsors and IRBs is required under 21 CFR 50.24(e), 56.109(e), 56.109(g), 312.54(b), 312.130(d), 812.38(b)(4) & 812.47(b).
http://www.fda.gov/oc/ohrt/IRBs/faqs.html

Week-9

Question: "What should be an ideal scenario to execute following Clinical Trial agreement with investigator site?"

i) Bi-partite agreement (Between the Principal Investigator and Sponsor/CRO)
ii) Tri-partite agreement(Between the Principal Investigator, Institution and Sponsor/CRO)

Answer:

i) Bi-partite agreement (between the Principal Investigator & Sponsor/CRO) should be executed **only** when the Principal Investigator (PI) is having an individual practice and he/she is **not attached** to any clinic/institution for the purpose of executing the clinical trial.

ii) Tri-partite agreement (between the Principal Investigator, Institution & Sponsor/CRO) should be signed when the PI **is associated with** an Institution/Clinic/Organization. As a golden rule Tri-partite agreement is the most transparent way of conducting a clinical trial where all the involved parties are aware of their roles and responsibilities.

Agreement with Institution **is must** simply because it is the institution that is responsible for retaining the patient's source files and other trial documents for the specified period of time. If the PI leaves the Institution in the mid of a trial or after the completion of trial it is the Institution only that holds the responsibility of retaining the trial documents at the site for the specified period of time. Hence there should be a **legal binding** in terms of a Clinical Trial Agreement.

Simply taking the PI's undertaking that he/she would prefer a Bi-partite agreement (or a Tri-partite Agreement is not applicable) is illegal unless the Institution endorses it. At the same time having two separate Agreements (one with the PI & Institution and other with PI only) is also illegal unless the Institution is aware of it or has approved it via a formal written communication. It is the responsibility of PIs, Sponsors & CROs to execute a trial legally & ethically.

Week-10

Question: "For the global/local clinical trials to be conducted in India what should be the composition of the 'quorum' of the IRB/ERB/IEC/EC* that reviews the trial proposal and grants its opinion"?

Answer: According to Schedule Y, Appendix VIII of Drugs & Cosmetics Act, the 'quorum' of the IRB/ERB/IEC/EC should contain a minimum of five persons with the following representations:

1) basic medical scientists (preferably one pharmacologist)
2) clinicians
3) legal expert
4) social scientist/ representation of non-governmental voluntary agency/ philosopher/ ethicist/ theologian or similar person
5) lay person from the community.

Week-11

Question: "According to Indian Regulations how long **the IRB/ERB/IEC/EC* should retain it records"?**

Answer:

1. According to **Indian GCP Guidelines**; **Section 2.4.2.8** - It is recommended that all records must be safely maintained after the completion / termination of the study for at least a period of **5 years** if it is not possible to maintain the same permanently.

2. According to **ICMR Guidelines (2006) -** It is recommended that all records must be safely maintained after the completion / termination of the study for a period of **3 years** if it is not possible to maintain the same for more than that due to resource crunch and lack of infrastructure.

Hence the maximum period for which IRB/ERB/IEC/EC should maintain it records is **5 years** after the completion/termination of the study.

Week-12

Question: "Can a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject) be performed in illiterate subjects?**"**

Answer:

1. **According to ICH GCP Guidelines**; **Section 4.8.13** - A non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

   And in **ICH GCP Guidelines; Section 4.8.14 -** Non-therapeutic trials may be conducted in the subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

   a) The objective of the trial cannot be met by means of a trial in subjects who can give informed consent personally.
   b) The foreseeable risks to the subjects are low.
   c) The negative impact on the subject's well-being is minimized and low.
   d) The trial is not prohibited by law.
   e) The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favorable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in the patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

2. **<u>According to Indian GCP Guidelines</u>; <u>Section 2.4.3.3</u>** - In case of a non-therapeutic study the study must always be given by the subject. Non-therapeutic studies may be conducted in the subjects with consent of a legal representative or guardian provided all of the following conditions are fulfilled:

i) The objective of the study cannot be met by means of a trial in subject(s) who can personally give the informed consent..
ii) The foreseeable risks to the subject(s) are low.
iii) Ethics Committee's written approval is expressly sought on the inclusion of such subject(s).

Week-13

Question: "How frequently the Investigator's Brochure (IB) should be reviewed and updated**"?**

Answer:
<u>According to Section 5.12.2 & 7.1 of ICH-GCP</u>: "The Sponsor should update the Investigator's Brochure as significant new information becomes available. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information".

Week-14

Question: "In case of Investigator's Brochure (IB) amendment for an ongoing trial what is the responsibility of sponsor/CRO with regards to regulatory compliance:"

a) Forward the amendment IB to DCGI office & wait for permission
b) Make a notification (Along with amended IB) to DCGI office but need not wait for permission
c) No need of notification to DCGI office as the trial permission is already available on the basis previous version of IB

Answer: (b)
Make a notification (along with amended IB) to DCGI office but need not wait for the permission.

Week-15

Question: In case of Investigator's Brochure (IB) amendment for an ongoing trial should the ICD/ICF be amended accordingly?

Answer: In case of IB amendment for an ongoing trial ICD/ICF should be amended if significant new information becomes available that may affect the subject's decision to participate (new subjects) / continue participation (ongoing subjects in the trial). The significant new information may include data from:

- Adverse Events/Serious Adverse Events/SUSARs
- Safety & efficacy data from other completed studies/interim analysis
- Latest update on number of subjects exposed to the Investigational Product *etc.*

Week-16

Question: For amendment of Informed Consent Document (ICD/ICF) in an ongoing trial, which of the following is a correct sequence of event?

a) Submit the ICD/ICF to IEC/EC and DCGI in parallel and obtain approval from both,
b) Obtain the IEC/EC approval first followed by submission & approval by DCGI's office,
c) Obtain the DCGI approval first followed by submission & approval by IEC/EC,
d) Obtain the IEC/EC approval first followed by notification to DCGI's office and need not wait for permission
e) Submit to IEC/EC and DCGI's office in parallel; wait for IEC/EC approval but need not wait for DCGI's permission.

Answer: (d)
Obtain the IEC/EC approval first followed by notification to DCGI's office and need not wait for permission.

Majority of the responses that we received mentions, (e) as the correct sequence of events. However, only drawback for the option (e) is if IEC/EC suggests some changes in the ICD/ICF than the same needs to be amended and notified once again to DCGI's office. In addition the rate limiting step is IEC/EC approval as only a notification is required to DCGI's office hence there is no real benefit on timelines by submitting it in parallel to IEC/EC as well as DCGI's office.

Week-17

Question: During the ERB/IRB/IEC review of a Phase-III clinical trial proposal, the 'lay person' as stipulated in the 'quorum' requirement was absent. As a CRA/Monitor/Auditor which of the following options you would propose to the site:

a) The approval is invalid and requires a full 'quorum' approval once again in the next scheduled meeting,
b) The approval is valid however, requires an exemption/clarification from the Chairperson on the approval document,
c) A separate approval can be obtained in writing from the lay person and can be placed on records along with the initial approval.

Answer: (a)
The approval is invalid and requires a full 'quorum' approval once again in the next scheduled meeting.

Week-18

Question: "Can a member of ERB/IRB/IEC/EC who is unable to be present at the convened meeting participate by video-conference or conference telephone call to fulfill the 'quorum' requirements"?

Answer: Yes**,** a member who is unable to be present at the convened meeting may participate by video-conference or conference telephone call, when he/she has received a copy of the documents that are to be reviewed at the meeting. Such members may vote and be counted as part of the 'quorum'.

Week-19

Question: "If an Informed Consent Document submitted to ERB/IRB/IEC/EC contains fill-in-the-blank sections (to include information such as contact details of PI & ERB Chairperson; version date *etc.*) should the details (to be included in the fill-in-the-blank section), be submitted to ERB/IRB/IEC/EC in all the languages proposed to be used at site".

Answer: Yes, it can be followed as a good Industry practice so that ERB/IRB/IEC/EC is aware of all the information provided to the study subjects (in the relevant vernacular language) and ERB/IRB/IEC/EC can make recommendations as & where required. It would also standardized the fill-in-the-blank process followed by different site personnel involved in the same trial.

Week-20

Question: If an ICD/ICF is amended based on new safety information during the active enrolment period which one of the following should be followed:

a) Obtain ERB/IRB/IEC/EC approval of the amended ICD & its translations
b) Administer the amended ICD to the new subjects for enrolment in the study
c) Administer previous version along with the amended version to the new subjects for enrolment in the study
d) Obtain a re-consent from the subjects who have signed the previous ICD and are ongoing in active treatment
e) All the above
f) Both a & d above
g) Both a & b above
h) a, b & d above

Answer: (h) i.e. a, b & d above.

Week-21

Question: Is a Sponsor/CRO required to provide Insurance/Indemnity Coverage for the Post-Marketing Surveillance (PMS) study of a drug in approved indication?

Answer: Post-Marketing Surveillance (PMS) studies are non-interventional studies and do not expose the study subjects to any additional risk apart from the risks associated with routine medical care. Hence Insurance/Indemnity coverage is not required to be provided by the Sponsor/CRO.

Week-22

Question: Which of the following monitoring report is required to be placed in the file(s) located at Investigator's Site?

a) Pre-trial monitoring report (site assessment report)
b) Site/trial initiation monitoring report

c) Routine monitoring visit report(s)
d) Site close-out monitoring report
e) All the above
f) None of the above
g) a, b & c

Answer: (b) i.e. Site/trial initiation report.

Week-23

Question: With regards to the Investigational Product (IP) which of the following statement is correct?

a) 100% accountability of IP is required at all levels [Sponsor, CRO, Investigator site, patient (if applicable)
b) Certificate of analysis is required to be retained by Sponsor for all batches of IP
c) All transactions (receipt, dispensing, return, destruction etc.) are required to be documented at the level of Sponsor, CRO, Investigator site, patient (if applicable)
d) IP should be labeled as "Clinical Trial Material, Not for Sale"
e) All the above
f) a, c & d above

Answer: (e) i.e. All of the above.

Week-24

Question: According to ICH-GCP, what should be the location of "Subject Enrolment Log"?

a) In the files of Investigator/Institution
b) In the files of Sponsor
c) Both a & b

Answer: (a) i.e. In the files of Investigator/Institution.

Week-25

Question: "According to ICH-GCP, what should be the location of "Certificate of Analysis":

a) In the files of Investigator/Institution
b) In the files of Sponsor
c) Both a & b

Answer: (b) i.e. In the files of Sponsor.

Week-26

Question: Is it mandatory to submit the 'Undertaking by Principal Investigator' to ERB/IEC/EC?

a) Yes
b) No

Answer: (a) i.e. Yes
Reference: Schedule Y (Appendix VIII)

Week-27

Question: "How frequently the trial progress report should be submitted to EC/IEC/IRB?"

a) Once a year
b) Once in 6 months
c) As per EC/IEC/IRB Standard Operating Procedures (SOP) however at least once per year
d) At trial completion

Answer: (c) i.e. As per EC/IEC/IRB Standard Operating Procedures (SOP) however at least once per year.

Week-28

Question: "Should each Deviations/Violations be reported to EC/IEC/IRB?"

Answer: The investigator should promptly report to the ethics committee & the sponsor of deviations from or changes of, the protocol to eliminate immediate hazards to the subject. Ideally investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazards to trial subjects, or when the changes involves only logistical or administrator aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).
Process related deviations/violation that has an impact on the safety, efficacy or integrity of trial data should be reported to EC/IEC/IRB

Week-29

Question: What should be the minimum number of members in an Ethics Committee that evaluates clinical trial projects in India?

a) 5
b) 7
c) 10
d) 12

Answer: (b)

The number of persons in an Ethics Committee should have atleast 7 members. However, for review of each project the quorum of Ethics Committee should be atleast 5 members with the following representations:

a. basic medical scientist
b. clinicians
c. legal expert
d. social scientist/representation of non-governmental voluntary agency / philosopher / ethicist / theologian or similar person
e. lay person from the community

Week-30

Question: With regards to vernacular language translations of ICF for multicentric trials, which of the following statement is correct?

a. All vernacular languages to be used at a site should be approved by respective EC of the site
b. Vernacular language approved by one site's EC can be used at other site without respective EC approval
c. Only English versions of ICF requires EC approval & vernacular language can be simply notified to the respective site's EC
d. All vernacular languages to be used in the site should be submitted to all site's EC irrespective of its usage at a particular site
e. All of the above
f. (a) & (b) above
g. (a) & (d) above
h. Only (a)

Answer: (h) i.e. Only (a)

Week-31

Question: With regards to Animal Toxicology, what type of Toxicity Studies Data needs to be submitted along with the application to conduct Clinical Trial in India?

Answer: The following are the toxicity studies data that needs to be submitted:

a. Systemic Toxicity Studies
b. Male Fertility Studies
c. Female Reproduction & Developmental Toxicity Studies
d. Local Toxicity
e. Allergenicity/Hypersensitivity
f. Genotoxicity
g. Carcinogenicity

Week-32

Question: In how many & what type of animal species Single Dose toxicity studies should be carried out?

a) one rodent species
b) two rodent species

c) At least two mammalian species of which one should be non-rodent
d) At least two mammalian species of which both should be non-rodent

Answer: (b) i.e. Two rodent species

Week-33

Question: In how many & what type of animal species Repeated-Dose Systemic toxicity studies should be carried out?

a) One rodent species
b) Two rodent species
c) Atleast two mammalian species of which one should be non-rodent
d) Atleast two mammalian species of which both should be non-rodent

Answer: (c) i.e. At least two mammalian species of which one should be non-rodent

Week-34

This week we provided an update regarding 'Declaration of Helsinki' (Amended Version) to update all working professionals and those who are in the field of Clinical Research.

Week-35

Question: Is it mandatory for the Investigator to personally sign the laboratory reports, patient's medical notes and other documents or he can delegate all these responsibilities to co-investigator(s)?

Answer: There is no explicit regulatory requirement for the Investigator to **personally sign the laboratory reports, patient's medical notes and other documents** however it certainly is a good clinical practice which will justify Investigator's involvement/supervision in the Clinical Trial. Indian-GCP and Schedule Y also states that Investigator should personally conduct and/or supervise the clinical trial at his/her respective study site.

Week-36

Question: Which of the following is the appropriate method for documenting lost to follow up for a Clinical Trial Subject?

a) By documenting the information obtained through telephonic calls made to the subject along with the outcomes, if any
b) By documenting the information obtained through letters sent to the subject's corresponding address along with the outcomes, if any
c) By documenting the information retrieved through contacting subject's relatives along with the outcomes, if any
d) By documenting the information retrieved by making personal contacts through social workers at subject's residence along with the outcomes, if any

e) a & d
f) a, b & d
g) a, b & c
h) a, b, c & d

Answer: (h) i.e. a, b, c & d.

Week-37

Question: "Can a study subject should be continued in the trial if his/her scheduled visit is delayed more than the time specified in the protocol during the active study period?"

Answer: The basic premise of a protocol is to collect the data in a uniform fashion at all the participating sites so that there is homogeneity at the time of data analysis. During the active study period if the scheduled visit of a study subject is delayed more than the time specified in the protocol than he/she **should be discontinued** from the study by making as assessment of what impact this delay has made on the safety and/or efficacy data. As a protocol is designed by taking into account of all the safety and efficacy issues, a delay beyond the protocol specified time-period should be considered as having an impact on the safety and/or efficacy data.

Week-38

Question: "In a clinical trial evaluating the overall survival of study subjects if a participant becomes lost to follow-up during the follow-up phase and later on turns up after several months while the trial follow-up is still on, can his/her participation in the trial be continued from that point onwards?"

Answer: As the primary objective of the trial is to evaluate the overall survival of study subjects the survival information is of great importance in reaching a conclusion. If a subject becomes lost to follow-up during the follow-up phase and later on turns up after several months while the trial follow-up is still on and is interested in continuing in trial follow-up, his/her participation in the trial can ideally be continued and a protocol deviation in this regard can be generated describing the rationale for the decision to continue.

Week-39

Question: Is it mandatory for the Principal Investigator to personally complete and sign the Serious Adverse Event reporting form (Appendix XI format) or he can delegate this responsibility to co-investigator(s)?

Answer: The Principal Investigator (PI) should personally sign the Serious Adverse Event reporting form (Appendix XI format) to comply with the commitments made by him/her in the Undertaking by the Investigator (Appendix VII). However, if a PI is not available at the time of reporting to regulatory agency the same can be done by a designated site personnel and PI can counter sign it whenever he/she becomes available.

Week-40

Question: In an Investigators' Meeting (IM), if, all the participating Principal Investigators are unable to attend then which of the following action(s) should be taken?

a) Send the training material/IM binder to the site.
b) Conduct a site specific IM before site initiation visit.
c) Allow the site to participate through video conferencing.
d) Waive-off the training requirement if the site has already participated in other studies.
e) Exclude the site from study participation.
f) b or c
g) a or d
h) b and c

Answer: (f) i.e. b or c

Week-41

Question: For a clinical trial patient if a scheduled investigation (as specified in the protocol schedule of events) is missed at a particular visit, which of the following is a best approach:

a) Prepare a deviation file note describing the root cause of the deviation and its impact on the safety/efficacy data followed by an action plan & continue thereafter with the patient in the study.
b) Conduct the missed investigation on a later date and prepare a deviation file note to document the delay.
c) Exclude the patient from the study.
d) Stop the trial at the site.
e) b & c above

Answer: (a) i.e. prepare a deviation file note describing the root cause of the deviation and its impact on the safety/efficacy data followed by an action plan & continue thereafter with the patient in the study

Week-42

Question: In a randomized double blind clinical trial if premature unblinding of the Investigational Product happens (e.g. accidental unblinding, unblinding due to a serious adverse event) then which of the following is the correct option?

a) Site co-ordinator handling the project can break the code & should promptly document and explain the premature unblinding to the investigator and sponsor
b) Investigator can break the code in accordance with the protocol
c) Site co-ordinator can break the code in accordance with the protocol
d) Investigator handling the project can break the code in accordance with the protocol & should promptly document and explain the premature unblinding to the sponsor
e) Premature unblinding cannot be done before the completion of the trial
f) a or d
g) b or c

Answer: (d) i.e**.** Investigator handling the project can break the code in accordance with the protocol & should promptly document and explain the premature unblinding to the sponsor

Week-43

Question: Can a Sponsor transfer **any** or **all** of the sponsor's trial related duties & functions to a CRO (Contract Research Organization)?

a) Yes
b) No

Answer: (a) i.e. Yes.

Week-44

Question: During a routine monitoring visit it becomes evident to the monitor that one of the trial subject meets the exclusion criteria but has been enrolled in the study and trial drug has been administered. What would be the best possible action for the monitor?

a) Prepare a deviation file note describing the root cause of the deviation and its impact on the safety/efficacy data & discontinue the patient.
b) Prepare a deviation file note describing the root cause of the deviation and its impact on the safety/efficacy data & continue with the patient.
c) Exclude the patient from the trial
d) Stop the trial at the site
e) Wait for some time to see the response and take a decision at that time-point.

Answer: (a) i.e**.** Prepare a deviation file note describing the root cause of the deviation and its impact on the safety/efficacy data & discontinue the patient.

Week-45

Question: During a routine monitoring visit it becomes evident to the monitor that one of the ongoing trial subjects meets the discontinuation criteria (as defined in the protocol) but has been continued in the study. What would be the best possible action for the monitor?

a) Prepare a deviation file note describing the root cause of the deviation and its impact on the safety/efficacy data & discontinue the patient.
b) Prepare a deviation file note describing the root cause of the deviation and its impact on the safety/efficacy data & continue with the patient.
c) Exclude the patient from the trial
d) Stop the trial at the site
e) Wait for some time to see the response and take a decision at that time-point.

Answer: (a) i.e**.** Prepare a deviation file note describing the root cause of the deviation and its impact on the safety/efficacy data & discontinue the patient.

Week-46

Question: Can an Investigator approach an Independent Ethics Committee for review of his/her study projects despite of having Institutional Review Board (IRB)?

a. Yes.
b. No, this is violation of GCP Guidelines.
c. Yes, after obtaining permission from the IRB/Management if there is a specific reason for doing it (IRB not in compliance with applicable regulatory guidelines or defunct for the time being etc.).
d. This situation is quite remote and does not happen in routine practice.

Answer: (c) i.e. Yes, after obtaining permission from the IRB/Management if there is a specific reason for doing it (IRB not in compliance with applicable regulatory guidelines or defunct for the time being etc.).

Week-47

Question: In case of studies prematurely discontinued for any reason including lack of commercial interest in pursuing the new drug application, what is the timeframe to submit a summary report to regulatory authorities (DCGI's office)?

a) Within 3 months after discontinuation
b) Within 6 months after discontinuation
c) Within 12 months after discontinuation
d) No specific timeframe, can be submitted any time

Answer: (a) i.e within 3 Months after discontinuation.

Week-48

Question: With regards to single dose toxicity study, what type of Animal Toxicology Data needs to be submitted along with the application to conduct Clinical Trial in India?

a) Data of at least 3 animals of either sex
b) Data of at least 3 male animals
c) Data of at least 5 animals of either sex
d) Data of at least 5 female animals

Answer: (c) i.e Data of at least 5 animals of either sex

Week-49

Question: Can additional patient be recruited in a clinical trial to compensate for lost to follow-up and ineligible enrolments based on initial trial approval from EC & regulatory authority?

a) Yes
b) No

Answer: (b) i.e No.

Week-50

Question: With regards to Animal Toxicology study, data on which species of animal is required for male fertility study?

a) Two rodent species
b) One rodent and one non-rodent species
c) One rodent species
d) Two non-rodent species

Answer: (c) i.e one rodent species

Week-51

Question: With regards to the protocol amendment involving administrative and logistics changes or inclusion of additional safety assessment, which of the following is true in Indian context?

a) Requires approval of the institutional ethics committee
b) Requires prior permission of the regulatory authority
c) Requires notification to the regulatory authority but need not wait for permission
d) a & b above
e) a & c above

Answer: (a) i.e. requires approval of the institutional ethics committee

Week-52

Question: With regards to the protocol amendment involving addition of investigator site or change of investigator, which of the following is true in Indian context?

a) Requires prior permission of the regulatory authority
b) Requires notification to the regulatory authority but need not wait for permission

Answer: (b) i.e. requires notification to the regulatory authority but need not wait for permission

Week-53

Question: According to ICH-GCP, for blinded trial what should be the location of decoding procedure?

a) Investigator Site
b) Sponsor/CRO office
c) a & b above

Answer: (c) i.e. a & b above

Week-54

Question: With regards to the protocol amendment involving additional subjects to be recruited, which of the following is true in Indian context?

a) Requires prior permission of the regulatory authority
b) Requires notification to the regulatory authority but need not wait for permission

Answer: (a) i.e. requires prior permission of the regulatory authority

Week-55

Question: With regards to the amendment to Investigator Brochure or Informed Consent Form, which of the following is true in Indian context?

a) Requires prior permission of the regulatory authority
b) Requires notification to the regulatory authority but need not wait for permission

Answer: (b) i.e**.** requires notification to the regulatory authority but need not wait for permission

Week-56

Question: According to ICH-GCP, what should be the location of final report by Investigator to Institutional Ethics Committee?

a) Investigator Site File
b) Sponsor/CRO's File
c) a & b above

Answer: (a) i.e. Investigator Site File

Week-57

Question: With regards to the protocol amendment involving change in study design, inclusion/exclusion criteria, dose and treatment option, which of the following is true in Indian context?

a) Requires prior permission of the regulatory authority
b) Requires notification to the regulatory authority but need not wait for permission

Answer: (a) i.e. requires prior permission of the regulatory authority

Week-58

Question: According to ICH-GCP, if the investigational product is destroyed by the Sponsor, what should be the location of documentation of investigational product destruction?

a) Investigator Site File
b) Sponsor's File
c) a & b above

Answer: (b) i.e. Sponsor's File

Week-59

Question: Financial Disclosure by Clinical Investigator is meant to disclose:

a) Financial arrangements whereby the value of the compensation could be influenced by the outcome of the study.
b) Significant payments of other sorts, excluding the costs of conducting the study or other clinical studies.
c) A proprietary or financial interest in the test product such as a patent, trademark, copyright, or licensing agreement.
d) A significant equity interest in the sponsor of the study.
e) a & b above
f) c & d above
g) All of the above

Answer: (g) i.e. All of the above

Week-60

Question: In relation to the term SPOOS, which of the following is correct:

a) It means Significant Payment Of Other Sorts
b) It is one of the Financial Disclosure line item to be disclosed by the clinical investigators
c) It includes the cost of conducting the clinical study.
d) a & b above
e) All of the above

Answer: (d) i.e. a & b above

Week-61

Question: What is the maximum limit of Significant Payment of Other Sorts that an investigator can receive from the sponsor of the study?

a) $25,000
b) $50,000
c) $100,000
d) No such limit to be classified as "inappropriately large"

Answer: (a) i.e. $25,000

Week-62

Question: What is the maximum limit of significant equity interest that an investigator can have in the sponsor of the study:

a) $25,000
b) $50,000
c) $100,000
d) No such limit to be classified as “inappropriately large”

Answer: (d) i.e**.** No such limit to be classified as “inappropriately large”

Week-63

Question: A layperson in context to an IRB can be defined as:

a) A person who is a non-expert in a given field of knowledge.
b) An average individual who does not have professional training in a subject area.
c) An illiterate person
d) All the above
e) a & b

Answer: (e) i.e. a & b