Investigator Initiated Trials

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Agenda

• Introduction to Investigator Initiated Trials (IITs)
• FDA Guidances
• Big Pharma and IITs
Introduction to IITs

• Introduction to Investigator Initiated Trials (IITs):
  • After a 5 to 8 year decline, IITs are gaining renewed interest as more biopharmaceutical companies are using them as a creative and cost-effective way to innovate and further improve patient safety.

• Introduction to Investigator Initiated Trials (IITs):
  • Unlike industry-sponsored trials focused on regulatory approval of new medications, IITs are developed and executed under the direction of 3rd party investigators who are physician researchers, often within an academic institution.
Introduction to IITs

• Introduction to Investigator Initiated Trials (IITSs):
  • The Investigator is responsible for:
    • Study conception
    • Design
    • Operational execution
    • Data handling
    • Data analysis and interpretation
    • Subsequent publication
    • IRB approval
    • Annual Report
    • Complying with applicable country regulations

Can IIT results be kept confidential?
Introduction to IITs

• Introduction to Investigator Initiated Trials (IITs):
  • The Sponsor is responsible for:
    • A written contract covering:
      • Financial support and/or drug product
      • Communication and enforcement of all applicable regulations
      • Tracking and monitoring GCPs and/or GLPs
      • Trending safety reporting

Introduction to IITs

• Introduction to Investigator Initiated Trials (IITs):
  • The Risks:
    • Inexperienced or unqualified investigators which impacts the resulting data
    • Per Cutting Edge Information, a Research Triangle Park-based business management and consulting firm, the average cost for an IIT trial is about $115,000 per a study lasting 2 to 3 months (Note – these trials may last for up to 2 to 3 years, and so would be considerable more money)
    • Trial protocol complexity can also increase the cost

What are the comparative cost factors of an IIT vs. a more formal clinical trial?
FDA Guidances

- Good Clinical Practice, Including Human Subject Protection and IRB Review and Approval (CFR 312.40)
- Safety Reporting Requirements for INDs and BA/BE Studies

- What exactly is required for the FDA approval of an IIT?
- Are there different requirements for IITs that involve already FDA-approved drugs but for different indications (e.g., re-purposing) vs. use of NCEs?
- Can an IIT be done for initial safety/dosage work involving a generic drug?
- To what extent would a reformulated (e.g., an oral form of an injectable drug) generic drug be permitted as the subject of an IIT?

FDA Guidances


- This guidance is aimed not so much at the industry, but at the individual investigators doing studies on marketed drugs or drugs with an existing IND for a different indication (repurposing, generics)
FDA Guidances

  - The main sections include:
    - Acquiring information needed and communication with the FDA
    - Information required for an IND submission
    - The IND process and review procedures – including clinical holds, IND amendments, and import/export requirements
    - Other sponsor-initiated (SI) responsibilities

Key points:

- The SI must handle the responsibilities of both the sponsor and the investigator.
- Definition of SI – Defined as “an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed”
FDA Guidances - SIs

  
  • Key points:
  
  • As the name suggests, a sponsor-investigator assumes the responsibilities of and must comply with FDA regulations applicable to both a sponsor and an investigator
  
  • These responsibilities include the submission and maintenance of an IND
  
  • In most cases the SI “cross-references” the already open IND
  
  • The SI is the one who actually does the trial

Are there different requirements for an IIT that involves already FDA-approved drugs, but for different indications (e.g., re-purposing) vs. use of NCEs?

Can an IIT involve more than one clinical site? Yes, put there is still a primary investigator that is the responsible party for the other sites with oversight from co-investigators

FDA Guidances

  
  • The SI has forms they are required to submit, for example:
  
  • 1571 – Basic registration form
  
  • 1572 – Safety form:
    • Requires the SI to conduct the trial in accordance with the protocol, meet all informed consent requirements, IRB requirements, and comply with record-keeping and adverse event reporting

What is the extent to which FDA must approve the IIT? Is their approval optional? What exactly is required for their approval of an IIT?
FDA Guidances

  
  • Note: Interestingly, the guidance says that an Investigator Brochure (IB) is not required for an IIT
  
  • However, the SI should obtain the IB if it does exist, in order to “ensure subject safety and to facilitate identification of serious and unexpected adverse reactions that may require expedited reporting to the FDA”
  
  • Comment: This makes sense if the drug is approved and the IB no longer exists

• Other things required in the SI’s submission to FDA:
  
  • A “description of the clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the investigational drug in human subjects and to minimize risk”
  
  • Also required are all materials relevant to the safety of the proposed trial
FDA Guidances - GCPs

• FDA Guidance – Good Clinical Practice, Including Human Subject Protection and IRB Review and Approval
  • This section states the SI should conduct the trial under good clinical practices (GCPs):
    • Monitoring of the investigation
    • Protection of human subject’s rights and well-being
    • Safety reporting to the sponsor and IRB

What about a repurposed drug with a new indication or mode of administration?

FDA Guidances

• FDA Guidance – Good Clinical Practice, Including Human Subject Protection and IRB Review and Approval
  • This section states the SI should conduct the trial under good clinical practices (GCPs):
    • Safety reporting to the sponsor and IRB:
      • Maintaining adequate case histories and records
      • Case report forms
      • Supporting data
      • Signed and dated consent forms
      • Source documents (i.e., patient reported outcomes)
FDA Guidances

• FDA Guidance – Good Clinical Practice, Including Human Subject Protection and IRB Review and Approval
  • This section states the SI should conduct the trial under good clinical practices (GCPs):
    • IND safety reports (CFR 312.32):
      • Unexpected fatal or life-threatening suspected adverse reactions (ADRs) within 7 calendar days

Other than IRB approval from the clinics involved, what regulatory approvals are required to conduct an IIT?

Can an IIT involve more than one clinical site?
Yes, but there is still a primary investigator that is the responsible party for the other sites who have oversight from co-investigators

Other than IRB approval from the clinics involved, what regulatory approvals are required to conduct an IIT?
FDA Guidances

• FDA Guidance – Good Clinical Practice, Including Human Subject Protection and IRB Review and Approval
  • This section states the SI should conduct the trial under good clinical practices (GCPs):
    • IND safety reports (CFR 312.32):
      • Safety reports are to be submitted in narrative format or using the MedWatch Form 3500A
      • If other IND safety reports of a similar AR have been submitted, the SI must identify these reports and analyze their significance
      • The SI also must notify the IRB of any unanticipated problems involving risk to human subjects

FDA Guidances – BA/BE

• FDA Guidance – Safety Reporting Requirements for INDs and BA/BE Studies
  • Adverse Event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related
  • An AE can be any unfavorable and unintended sign (e.g., an abnormal lab finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality

Can an IIT be done for initial safety/dosage work involving a generic drug? To what extent would a reformulated (e.g., an oral form of an injectable drug) generic drug be permitted as the subject of an IIT?
FDA Guidances

- FDA Guidance – Safety Reporting Requirements for INDs and BA/BE Studies
  - Adverse Event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related
    - An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose

Can an IIT be done for initial safety/dosage work involving a generic drug? To what extent would a reformulated (e.g., an oral form of an injectable drug) generic drug be permitted as the subject of an IIT?

FDA Guidances

- FDA Guidance – Safety Reporting Requirements for INDs and BA/BE Studies
  - Suspected Adverse Reaction (SAR) (CFR 312.32(a)):
    - SAR means any adverse event for which there is a reasonable possibility that the drug caused the adverse event
    - For the purpose of IND reporting:
      - “Reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE
FDA Guidances

- FDA Guidance – Safety Reporting Requirements for INDs and BA/BE Studies
  - Unexpected Adverse Event (UAE) (CFR 312.32(a)):
    - An AE or suspected adverse reaction (SAR) is considered “unexpected” if it is not listed in the investigator brochure (IB) or is not listed at the specificity or severity that has been observed in the “reference material”
      - What is the “reference material?”
        - General investigational plan submitted as part of the IND amendment (e.g., repurposing)
        - Safety profile found in the original IND
        - Past labeling of the product for another purpose
        - Literature
        - Published Risk Evaluation and Mitigation Strategies (REMS), if applicable

Where does this terminology come from?
FDA Guidances

• FDA Guidance – Safety Reporting Requirements for INDs and BA/BE Studies
  • MedDRA:
    • What is MedDRA?
      • MedDRA or Medical Dictionary for Regulatory Activities is a clinically validated international medical terminology dictionary (and thesaurus) used by regulatory authorities in the pharmaceutical industry during the whole regulatory process
      • From pre-marketing to post-marketing activities
      • For data entry and retrieval

FDA Guidances

• FDA Guidance – Safety Reporting Requirements for INDs and BA/BE Studies
  • MedDRA:
    • MedDRA is used to code the AEs reported on the MedWatch Form
      • MedDRA system organ class is defined as the level of MedDRA terminology, distinguished by anatomical or physiological system, disease origin, or purpose
      • Most of these describe disorders of a specific part of the body
        • For example, the term “cardiac disorders” describe heart problems
        • “Hepatic disorders” describe liver problems, and so on
FDA Guidances

• FDA Guidance – Safety Reporting Requirements for INDs and BA/BE Studies
  • Serious Adverse Events (SAEs) (CFR 312.32(a)):
    • An AE or SAR is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
      • Death
      • Life – threatening (putting the patient at immediate risk of death)
      • Impatient hospitalization or prolongation of existing hospitalization
      • A persistent or significant incapacity
      • Substantial disruption of the ability to conduct normal life functions
      • Congenital anomaly/birth defect
      • Medical events that result in the development of drug dependency, or drug abuse

Other SI safety reporting responsibilities:

• IND Annual Report (CFR 312.33):
  • This must be submitted to the FDA within 60 days of the IND anniversary date
  • In regards to safety, included in the annual report:
    • A narrative or tabular summary showing the most frequent and serious AEs by body system
    • A summary of all IND safety reports submitted during the previous year
    • A list of subjects who dropped out because of AEs and a description of the AEs
FDA Guidances – IIT Risks

• IIT risks as outlined in the guidances:
  • There must be written contracts between the sponsor (the one holding the
    original IND) and the potential SI
  • All required documents (IB, annual report, developmental safety update
    report (DSUR), etc.) must be supplied and revised, with updates sent out to
    sponsor and IRB
  • All SAEs must be sent to the sponsor immediately
  • Many companies and academic centers do not have adequate procedures,
    rules, restrictions, and oversight in place, which could put patients and the
    establishments at risk

• IIT risks as outlined in the guidances:
  • If a non-approved indication is being studied (i.e., in the 30-day window
    between registration and approval for trial), this trial should have oversight
    sufficient to protect the patients and all others involved
  • FDA can monitor an IIT, and place an IIT on hold
  • The company, the institution, the IRB, and all other players involved in an IIT,
    must treat these trials as seriously as they treat any other IND clinical trial
Big Pharma & IITs: Novartis IIT Guidelines

• The overarching principles that govern evaluation of IITs include:
  ● The validity of the scientific question being addressed, ensuring that any data generated by an IIT complement the existing body of evidence and not simply be a repetition of a previous study
  ● The robust nature of the IIT being conducted in terms of ethical and design elements
  ● A commitment by the SI to disseminate the findings in an appropriate, transparent and timely manner

Can IIT results be kept confidential?  What is the attitude of big Pharma toward IITs?

Big Pharma & IITs: Novartis IIT Guidelines

• It is important for the SI to be responsible for:
  ● Study conception
  ● Design
  ● Operational execution
  ● Data handling
  ● Data analysis/interpretation
  ● Reporting
  ● Publications
  ● Ensuring compliance with all rules, regulations, and laws

CRO can help with
Big Pharma & IITs: Novartis IIT Guidelines

• These guidelines lay out the principles Novartis is committing to on a worldwide basis for all 3rd party sponsored IITs:
  • Rigorous ethical and scientific standards when engaging and reviewing study proposals
  • Investigator qualifications
  • Institutional site credibility

Big Pharma & IITs: Novartis IIT Guidelines

• These guidelines lay out the principles Novartis is committing to on a worldwide basis for all 3rd party sponsored IITs:
  • In study sites where Novartis is not satisfied that GCP standards (i.e., emerging countries) exist, they will work with local policies and regulations
  • However, in countries where GCPs exist (i.e., US, EU, Japan), if the investigators do not practice GCPs, they are not permitted to do the trials
Big Pharma & IITs: Novartis IIT Guidelines

• These guidelines lay out the principles Novartis is committing to on a worldwide basis for all 3rd party sponsored IITs:
  • Robust medical and scientific governance systems in place at all levels of the Novartis organization (globally, regionally, locally) with no commercial funding or influences on any aspect of the IIT process
  • Under no circumstances will Novartis permit the involvement of sales and marketing associates in any aspect of IIT design, review and approval, operational execution, funding or transfer of value to a SI undertaking an IIT
  • The review/approval process focuses specific attention on ensuring that patient safety is of paramount importance in the proposed IIT

Big Pharma & IITs: Novartis IIT Guidelines

• These guidelines lay out the principles Novartis is committing to on a worldwide basis for all 3rd party sponsored IITs:
  • Worldwide training within Novartis on the policies and practices required for successful IIT support including:
    • SI study conception
    • Operational execution
    • Data management
    • Data handling
    • Data interpretation
Big Pharma & IITs: Novartis IIT Guidelines

• These guidelines lay out the principles Novartis is committing to on a worldwide basis for all 3rd party sponsored IITs:
  • Worldwide training within Novartis on the policies and practices required for successful IIT support including:
    • Financial transparency on amount of monies of value provided to any institution or investigator world-wide undertaking an IIT as part of a contractual agreement with Novartis
Big Pharma & IITs: Novartis IIT Guidelines

- These guidelines lay out the principles Novartis is committing to on a worldwide basis for all 3rd party sponsored IITs:
  - Worldwide training within Novartis on the policies and practices required for successful IIT support including:
    - High ethical and scientific standards as it relates to clinical research in human subjects as stipulated by ICH guidelines E6-GCP

Big Pharma & IITs: Novartis IIT Guidelines

- These guidelines lay out the principles Novartis is committing to on a worldwide basis for all 3rd party sponsored IITs:
  - Worldwide training within Novartis on the policies and practices required for successful IIT support including:
    - SIs undertaking non-clinical studies using animal subjects will have to provide equivalent evidence of ethical standards and/or Good Laboratory Practices (GLPs)

If NCE’s, I assume pre-clinical tox/safety work would be needed? What level of such work needed?
Big Pharma & IITs: Novartis IIT Guidelines

• These guidelines lay out the principles Novartis is committing to on a worldwide basis for all 3rd party sponsored IITs:
  • For clinical research in humans and before embarking on a contractual process of an IIT with an SI and co-SI, Novartis will require documentation that demonstrates the following:
    • Recent evidence (within previous 3 years) of the potential investigator and site personnel being trained in GCPs (e.g., a signed attestation of completed GCP training)
    • Evidence of a current medical license and good medical standing
    • Novartis will ensure the validity of the documentation
Big Pharma & IITs: Novartis IIT Guidelines

• These guidelines lay out the principles Novartis is committing to on a worldwide basis for all 3rd party sponsored IITs:
  • For clinical research in humans and before embarking on a contractual process of an IIT with an SI and co-SI, Novartis will require documentation that demonstrates the following:

  Novartis will not undertake a clinical IIT with an investigator that has not previously undertaken clinical research, either as a sponsor of clinical research themselves, or by participating in research sponsored by Novartis or another credible sponsoring organization

Summary

• The SI must handle the responsibilities of both the sponsor and the investigator
• Inexperienced or unqualified investigators will impact the resulting data
• The SI should conduct the trial under good clinical practices (GCPs):
  • Monitoring of the investigation
  • Protection of human subject’s rights and well-being
  • Safety reporting to the sponsor and IRB
• SIs undertaking non-clinical studies using animal subjects will have to provide equivalent evidence of ethical standards and/or GLPs
• Financial transparency on amount of monies of value provided to any institution or investigator is part of the contractual agreement for the trial