

Investigator Initiated Trials: Turbulence ahead!

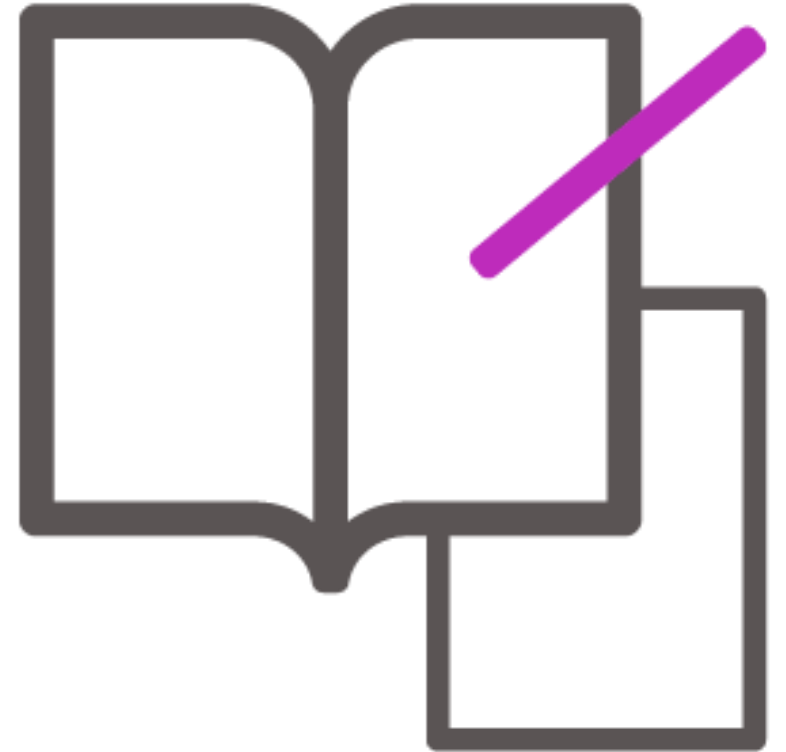
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Outline

- Introduction
- Investigator Initiated Trials (IITs)
- The Challenges faced
 - *Data collection and quality of data*
 - *Data analysis*
 - *Regulatory*
- Conclusion



Introduction

- Conducting robust clinical trials that produce decisive outcomes is always the goal of pharmaceutical companies.
 - But Pharma Cos. Have limits on how many trials they run
 - Sometimes they must acquire data from outside
- Investigator Initiated Trials(IIT)
 - In many respects are perfect to fill this gap
- *IIT in submission = Turbulence!*



Investigator Initiated Trials (IITs)

- What is Investigator Initiated Trials
 - Clinical trials proposed upon the initiative of clinical sponsor-investigators and without the company taking the role as a sponsor are termed Investigator Initiated Trials
- Purposes or motivations of IITs
 - To generate data on efficacy and safety of a drug in the real-world setting
 - To answer questions that clinical face in their face-to-face practice
 - To assist in developing hospital/state/nation-specific policies
 - *Seeking the drug approval is normally not their focus*

IIT in a Submission

- Pharmaceutical companies
 - Repurpose the IIT data for submission
 - Benefit from the findings if the results are positive
 - Add to the patient populations
- *Challenges*
 - *data collection,*
 - *data structure,*
 - *analysis & integration,*
 - *communications, and*
 - *regulatory submission etc.*

Data Quality Challenges - I

- Case Report Forms (CRFs)
 - Unique - Not submission-compliant
 - Paper CRFs:
 - ✓ *Easily* result in human errors or inconsistency of recording of data
 - Difficult to map to CDISC standards
 - Need a lot of data-driven decision making for data handling
 - ✓ *Missing data, special characters, numerical data from free text fields, splitting or combining variables etc.*

Example of Unconventional CRF - Adverse Event

❖ Handling of worsening of the severity of an adverse event

❖ Requires special handling

- splitting the record into two

ADVERSE EVENT
Please complete since ICF signature, during treatment period and up to 30 days after the last study drug administration or during the follow-up period in case of study drug related SAE. All adverse events of all grades will be reported.

Adverse event Diagnosis :

Onset date of the AE (dd/mm/yyyy) :

Event Period : ☐ 1 = Before treatment
2 = Treatment period cycle 1 to 6
3 = Follow-up period

Onset grade (according to CTCAE V4.03) : ☐ 1 / 2 / 3 / 4 / 5

Onset action taken with drugs : With CHOP ☐ 1 = Drug withdrawn / 2 = Drug interrupted
3 = Dose reduced / 4 = Dose unchanged
With Romidepsin ☐ 5 = Drug interrupted and dose reduced
6 = Not applicable / 9 = Unknown

Dates when grades increase/decrease for same event (if applicable)

	Date (dd/mm/yyyy)	New Grade	Action taken with CHOP	Action taken with Romidepsin
1.		☐	☐ 1 = Drug withdrawn 2 = Drug interrupted 3 = Dose reduced 4 = Dose unchanged 5 = Drug interrupted and dose reduced 6 = Not applicable 9 = Unknown	☐ 1 = Drug withdrawn 2 = Drug interrupted 3 = Dose reduced 4 = Dose unchanged 5 = Drug interrupted and dose reduced 6 = Not applicable 9 = Unknown
2.		☐	☐	☐
3.		☐	☐	☐
4.		☐	☐	☐
5.		☐	☐	☐
6.		☐	☐	☐
7.		☐	☐	☐
8.		☐	☐	☐

Relationship with drugs : With CHOP ☐ 1 = Related
2 = Unrelated
With Romidepsin ☐ 9 = Not applicable

Corrective treatment / Procedure ? ☐ 0 = No
1 = Yes

If yes, please fill in treatment(s) on concomitant treatments page

Data Quality Challenges - II

➤ Atypical EDC Systems

➤ Unusual data format & system

➤ Difficult to convert to SAS data

- ✓ *Entire data received is one Excel sheet without proper variable labels*
- ✓ *Multiple small text files in a different language*

Data Quality Challenges - III

- Data cleaning and data review
 - The data management group in the pharmaceutical companies don't lead the cleaning of IIT data
 - Limited data were shared by some organizations before database lock or some milestones

Example of Extra Data Cleaning of IIT data

- ❖ Contract amendment needed to have the cooperative group add resources for data cleaning



Data Analysis Challenges

- Different Analysis Methods/Conventions
- Mapping Variables and Codelists

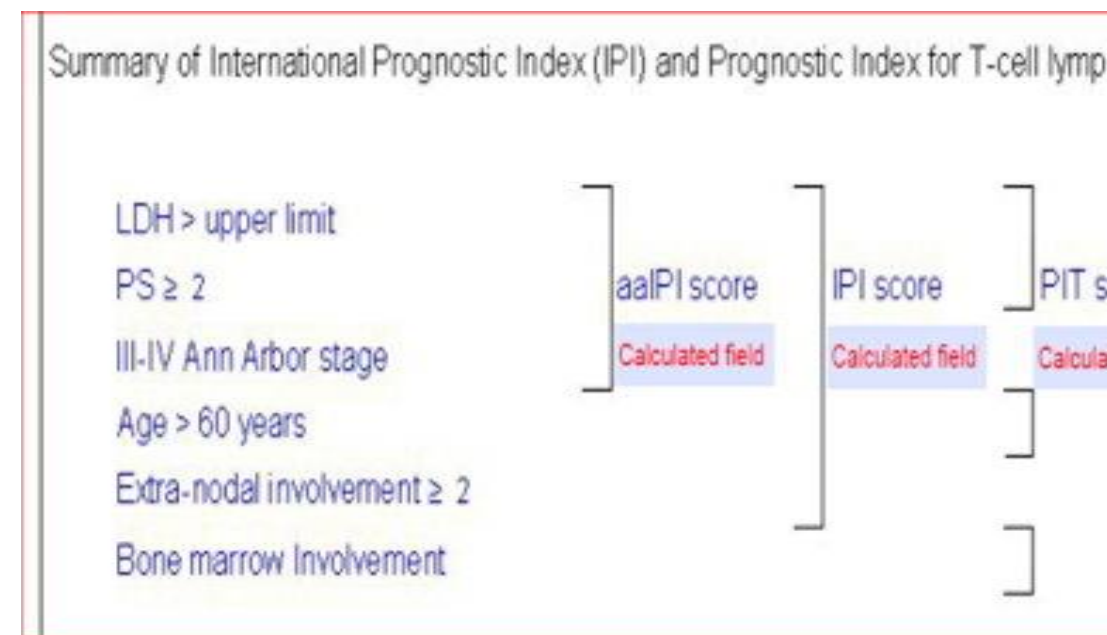
Example of Statistical Analysis Method Difference

- the Efron method for handling ties is to be preferred, particularly when the sample size is small either from the outset or due to heavy censoring

```
proc phreg data=OS2;  
  class &_trt(ref='2');  
  model AVAL*cnsr(1)=trt/risklimits ties=efron;  
  strata BIPIDCAN AGEGRP1N NODEXN;  
  
run;
```

Example of Convention Differences at Analysis of a IIT of Peripheral T-cell Lymphoma

Convention	The research Organization	Company
Baseline	Based on the value of the CRF visit = “Baseline” (in their data collection it was at screening)	The last non-missing observation on or before treatment day 1
Extra-Nodal Involvement	Also consider another CRF page bone marrow involvement	Based the location of system/organ involvement in that CRF page
Index for T-cell lymphoma(PIT score)	Re-derived based on their clinical experience by modifying the formula; If any of the parameters is missing, set to missing	CRF page; sum function of SAS



Regulatory Challenges - I

- Submission Data Package
 - The unconventional data may result in low P21E validation score
 - Mapping to CDISC standards takes a huge effort
 - Lot of documentation in reviewer's guide
 - data conversion
 - P21E warnings and errors

Regulatory Challenges - II

- Health Authority interaction
 - Sometimes difficult to convince
- Response to Information requests

Recommendations- I

- Timely and effectively communication
- Get cooperative group's help in converting data to familiar format
- Statistical Analysis Plan (SAP) review
- Exchange SAP and analysis data specification
- Prior discussion with Health Authorities

Recommendations - II

- Plan for extra resource / budget
- Manage expectations in submission team beforehand
- Get company's data review 'machine' involved
- Set-up communication channel with Stat/Programmer at Cooperative group

Conclusion

- IITs fill a critical need in improving patient outcomes
- Most IITs run for different purpose and follow different standards
- Huge effort may be needed to clean, map and analyze the IIT data to include in a submission
- Use of IIT data: Challenging but rewarding!

References, Acknowledgement and Q&A

References

[Investigator initiated trials \(IITs\) - PMC
\(nih.gov\)](https://pubmed.ncbi.nlm.nih.gov/)

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Q&A

