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Investigator Initiated Trials: Turbulence ahead!

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ABSTRACT

With a push to get therapies to expanded patient populations quickly, reduce cost of bringing drugs to patients and improve the efficiency of trials, chances are you have worked on some Investigator initiated trials (IIT) in your career in Pharma industry. These IITs are not your 'garden variety' company sponsored trials. They do not conform to many of the standards and conventions commonly followed in the industry. You need to be prepared to tackle regulatory, data structure, integrity & analysis, contractual, and communication challenges among others. However, if you successfully crack the code to mapping/cleaning the data and put in the effort (…lots of it!), they can lead to huge rewards. In this paper we will share our experience on some of the IITs- The challenges and how to mitigate them.

INTRODUCTION

Conducting robust trials that produce decisive outcomes is the goal of pharma companies involved in research and development. For a variety of reasons, however, sometimes they must settle for acquiring or buying trial or real-world data from outside. IITs are one possible source of such data which could help increase the sample size for an integrated analysis, play a more central role in efficacy analysis or support medical affairs goals. In this paper we will mainly discuss IIT data being repurposed for submission.

These days the Biometrics and Data Management departments in pharmaceutical companies rely on data, programming, and analysis standards to meet efficiency goals. More standardization means more efficiency and opportunity to automate. The decision to include an IIT in a submission however can introduce *a whole lot of turbulence into the mix*!!

Based on a variety of factors IITs may take several different forms and pose many challenges for the company, especially for the biostatistics & programming teams. There are some common themes of IITs through - non-standard data collection and CRFs, unique and unconventional electronic data capture systems and limited data review etc.

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[1]. The academic institutions and the Cooperative groups who sponsor the IITs have a variety of motivations for running these trials, broadly centered around patient wellbeing. These trials may help to expand the patient population for the medicine or to characterize certain risks. Investigators at the academic institutions and cooperative groups that run these trials lend credibility due to their perceived unbiased position. Many pharmaceutical companies can benefit from the findings of these IITs when results are positive or show the therapy to benefit additional patient populations. However, such IITs can also result in unexpected findings, e.g., potential risk of new malignancy etc.

DATA QUALITY CHALLENGE

The IIT CRFs, which may not be submission compliant, are difficult to map to CDISC standards and need a lot of decision making on missing fields, splitting, and combining variables etc. In addition, the database may reside in an uncommon system that is difficult to convert to SAS datasets. We encountered cases such as the entire database sent in one Excel sheet or multiple small text files in a different language without proper variable labels. Some other instances include receiving free-text fields instead of choices from picklist making comparing baseline to post-baseline difficult or the response categories not matching the industry criterion making integration challenging, and only preferred term present with no verbatim in Adverse event data making up-versioning tricky.

These institutions apply varying levels of rigor in data review and cleaning, but they rarely match the effort that a pharma company would put in. The problem can be compounded because the data management group at the pharma company does not play the traditional role of receiving the IIT data and leading data cleaning. In fact, some cooperative groups are deeply averse to engaging extensively in a pharma company driven data cleaning process. It undermines their own efforts, hints at the influence the company may be exerting on the trial results and burns out their limited resources.

In one such trial, the pharma company determined that the regulatory risk without doing any additional data checking and data cleaning was way too high. Since the original data sharing agreement with that cooperative group did not allow for extensive data cleaning budget, it was decided to amend the contract to allow the cooperative group to hire additional data managers to support the cleaning efforts. It was all documented and explained and ultimately lead to a successful submission.

ANALYSIS CHALLENGE

Downstream, there are issues of a different kind. We may have a reasonably clean IIT database but if the external investigator and the pharma company end up with different analysis results then there may not be an easy solution. In one instance a cooperative group published some results and presented them at conferences. But when the pharma company analyzed that data for one of their submissions the results came out differently. What ensued were months of teleconferences and some in-person meetings to get to the bottom of the differences. The fact that the two groups spoke different languages did not help much. The difference in results were ultimately determined to originate from differences in conventions. It was, however, not simple to agree on how to address them and it delayed the submission by months.

The other common challenge with using IIT data is mapping variables and codelists. Because of many different conventions and practices, it requires a special effort to understand the source and codes behind the variables and to map them correctly to the integrated data.

To avoid difficult situations the company could explore if the investigator and their organization are aggregable to having one set of analysis. Example – the Statistical Analysis Plan prepared by the company and reviewed and approved by the investigator. Another approach is if the two groups exchange statistical plans and analysis specifications early on and document differences in conventions and analysis approaches the results from the two groups could be handled relatively smoothly. In addition, effective and timely communication from statistics & programming groups between the research organizations and pharm company plays a critical role in ensuring the consistency of analysis results. In one Lymphoma IIT, meetings were set up early and regularly, key analysis datasets and outputs were shared and compared at two agreed dry-run times, and major discrepancies were identified, explored and all addressed through multiple meetings. The topline tables achieved 100% match at the database lock.

REGULATORY CHALLENGE

Since the IITs are mainly initiated for publication and presentation purposes and not for submission to regulatory authorities, the methods and tools that are used follow different standards. The CRFs and data capture technology utilized may be very different. But most of all using the data from an IIT whose study design and objective is different can pose regulatory challenges. Some of them are for Clinical and Regulatory groups to address, but there are some that Programmers and Statisticians must be prepared to resolve. They may need to work with external partners to produce matching data packages or sometimes may need to produce it themselves. But probably the most challenging is responding to health authorities' information requests. The Stat & Programming team need to be ready to quickly generate the analysis regardless of how familiar they are with this data.

CONCLUSION

Cooperative groups and academic institutions that run these IITs are doing a great service in expanding clinical knowledge and providing relief to patients. Their mission is not to seek drug approvals for the most part. So, the data standards applied by them are different from what are commonly established in pharma companies. If we need data from these trials for getting drugs approved, we need committed and motivated programmers working closely with statisticians to clean, map, and analyze this data. That will pave the way for improving the data and analysis quality for submission that contain IIT data.

REFERENCES

1. Investigator initiated trials (IITs) - PMC (nih.gov).

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