Safety First, Agility comes: Challenges & Solutions to Fulfill IND Safety Requirements

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Abstract

Following the 2010 final rule (75 FR 59935), FDA has published various guidance regarding safety reporting requirements for IND and/or bioavailability /bioequivalence studies with clarifying sponsors' roles and responsibilities. Compliance with those requirements will allow the agency, investigators, and sponsors to focus on the most prominent safety issues and take necessary actions to reduce subjects' risk in participating clinical studies. In this paper, we discuss challenges and solutions for statistical programming to support fulfilling FDA's requests during unblinded aggregated analysis of anticipated Serious Adverse Events (SAEs), while maintaining trial integrity. We will first briefly outline Boehringer Ingelheim's (BI) safety reporting process and introduce BI's independent safety analysis team (iSAT). The focus will be on statistical programmers' tasks in setting up firewalls, handling/reviewing blinded data, accessing unblinded randomization/ medication kits information, and maintaining trial integrity. We will conclude by sharing experience/lessons learned from reporting aggregated anticipate SAEs to open further discussion.

Key words: final rule, SUSAR, expedited anticipated SAE reporting, unblinding, trial integrity

Skeleton of the paper:

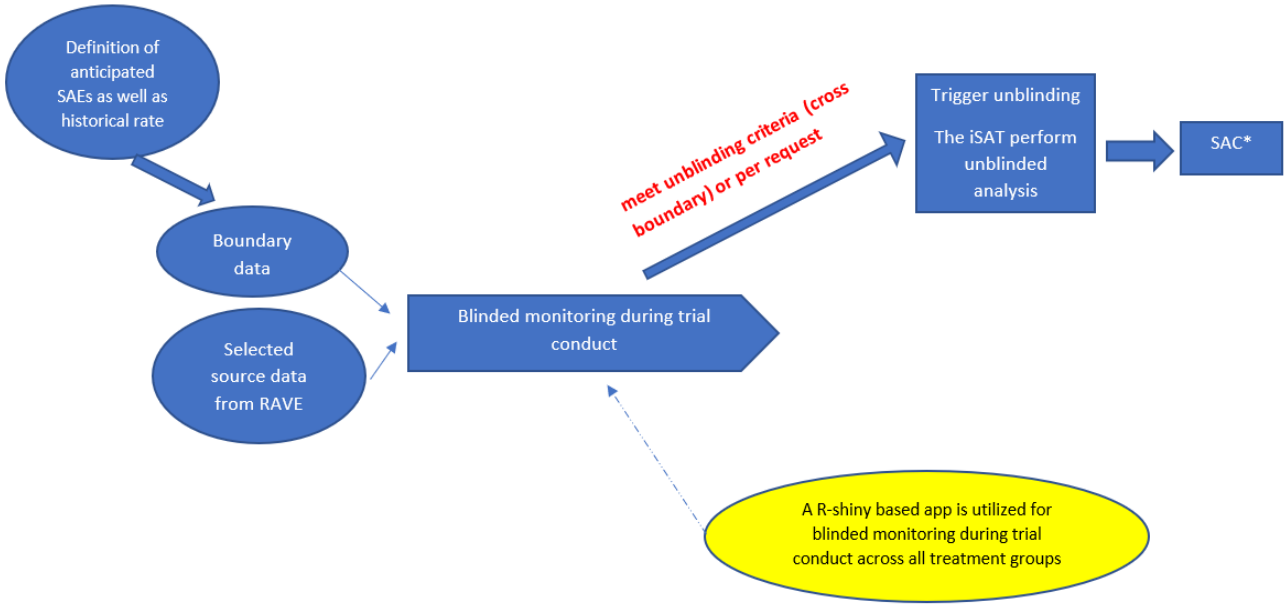
Background: challenges and solutions:

From programming perspective, to efficiently fulfill IND safety requirement during trial conduct, there are quite a few challenges. Among them, the biggest one is to maintain trial integrity while performing aggregated unblinded analysis. Furthermore, when it comes to safety aggregated data reporting, it is always crucial to review the freshest data in a timely manner. To overcome those hurdles, we are being agile and proactive: not only do we establish an independent team focusing on unblinded safety analysis, moreover, a dynamic R-shiny based monitoring tool, which has complex statistical algorithm built in, has been under development for regular blinded monitoring during trial conduct.

Introduction to the Independent Safety Analysis Team (iSAT)

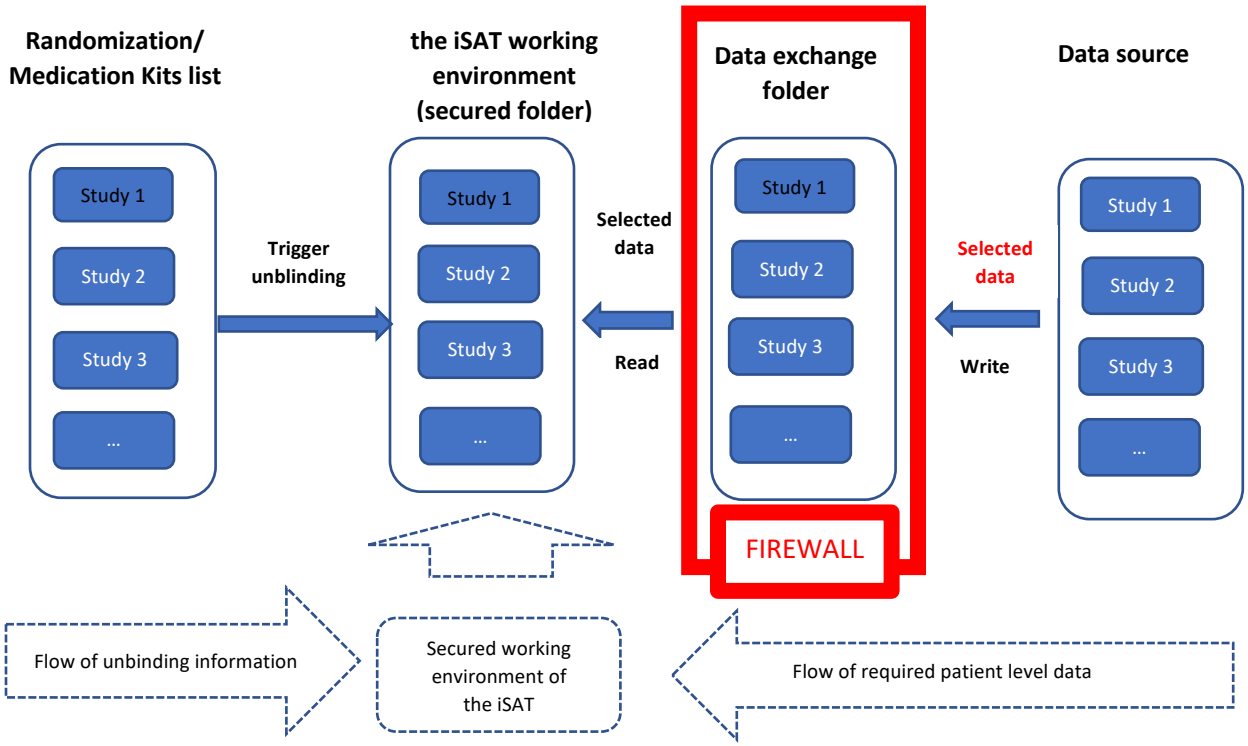
The primary task of the iSAT is functioning as a dedicated independent team, preparing unblinded data handling and analysis to fulfill FDAs requests for expedited safety reporting. From this perspective, the iSAT is independent of any study and project team within the sponsor organization and not involved in trial or project related tasks during conduct – except for tasks requiring strict confidentiality handling such as IND safety reporting, internal DMC support or internal Interim Analysis.

General process for aggregated SUSAR reporting: a simplified example when taking triggering approach



*SAC: Safety Analysis Committee (independent of study team; for some scenarios, Data Monitoring Committee (DMC) could also be considered to serve the purpose)

Firewall Setup



- Both the iSAT and involved study teams have access to the data exchange folder, which provides the location where selected blinded study data can be stored. The iSAT will then copy the selected blinded data to the iSAT's own secured working environment for further use.
- The setup of firewall is bidirectional: the iSAT does not have access to the study data sources directly since the iSAT only need selected data for safety assessment monitoring. Other study data that are not relevant should not be available to the iSAT. By doing so, the integrity and confidentiality of the iSAT work can be well maintained. On the other hand, the study teams do not have access to the secured iSAT working environment.
- Once study teams have completed their interactions with the iSAT, their access to the exchange folder will be revoked and they will no longer be able to access the exchange folder until new requests.
- Randomization/medication kits information will be delivered to the iSAT based on company standard procedure via secured channel.

Limited access to selected study data: the iSAT does not have access to all the study data, but only selected ones based on analysis needs.

- Essential: AE, demographics, disposition, drug accountability and exposure.
- Optional: concomitant medication, medical history, lab and/or other data that are relevant to interpret SAEs under investigation.
- No access to any efficacy datasets by default.

Access to randomization and medication kits information for unblinding in aggregated reporting

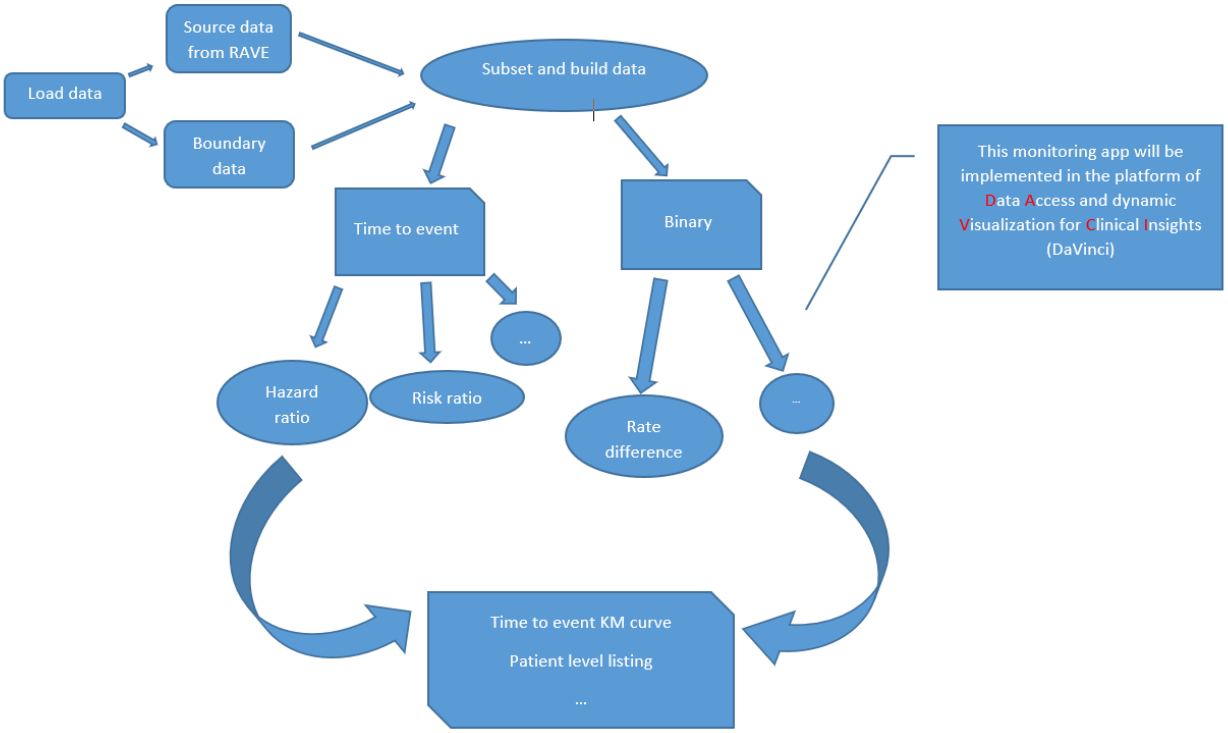
Unblinding is only triggered when pre-specified criteria is met or SAC (or other equivalent committee, e.g. DMC for some cases) requests to perform aggregated unblinding analysis. Randomization and medication kits information will not be released to the iSAT till then. The process to request unblinded information will follow company standard procedure.

Maintenance of trial integrity after unblinding

- Involvement of the iSAT
    - The iSAT is a dedicated independent safety analysis team, independent of any study team and independent of any trial conducts within the sponsor organization. The fundamental philosophy and nature of the iSAT is being independent, which makes the iSAT capable to get involved in unblinding activities, perform unblinded analysis and prepare unblinded outputs.
- Data handling
    - Treatment assignment of subjects who experienced SAE(s) and unblinding of data pertinent to interpret those events.
    - Efficacy data, study endpoints, and other data that are not related nor instrumental to interpretate events under investigation will not be unblinded.

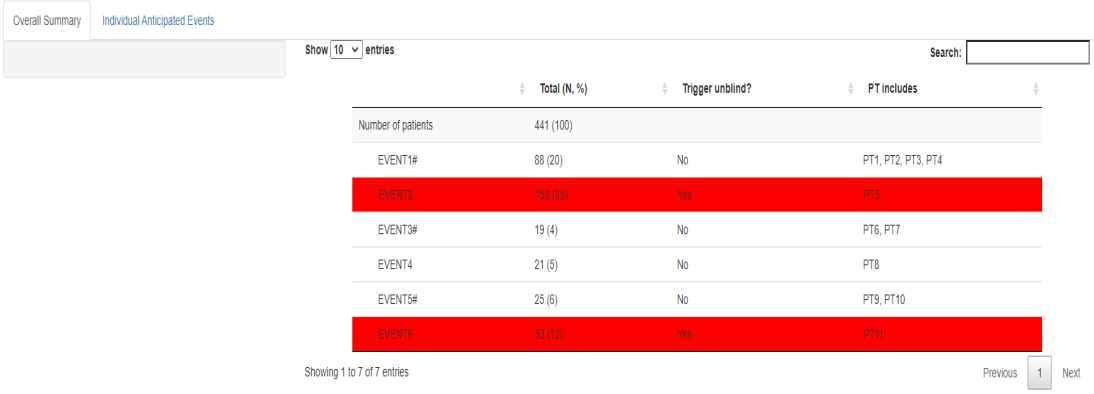
Blinded monitoring of pre-defined anticipated SAEs during trial conduct, using a R-shiny based monitoring tool: a sample workflow of blinded safety assessment monitoring to support aggregated triggering approach

- The main purpose of this app is for blinded safety assessment monitoring across treatment during trial conduct while taking the triggering approach.
- The primary targeted audience is study safety physician.
- The input study data, which are source data directly from data base (e.g. RAVE), are selected according to specific study needs.
- The boundary data are calculated based on the pre-defined anticipated SAEs and historical rate.
- The triggering algorithm(s) are built in the app and the calculation can be done dynamically.

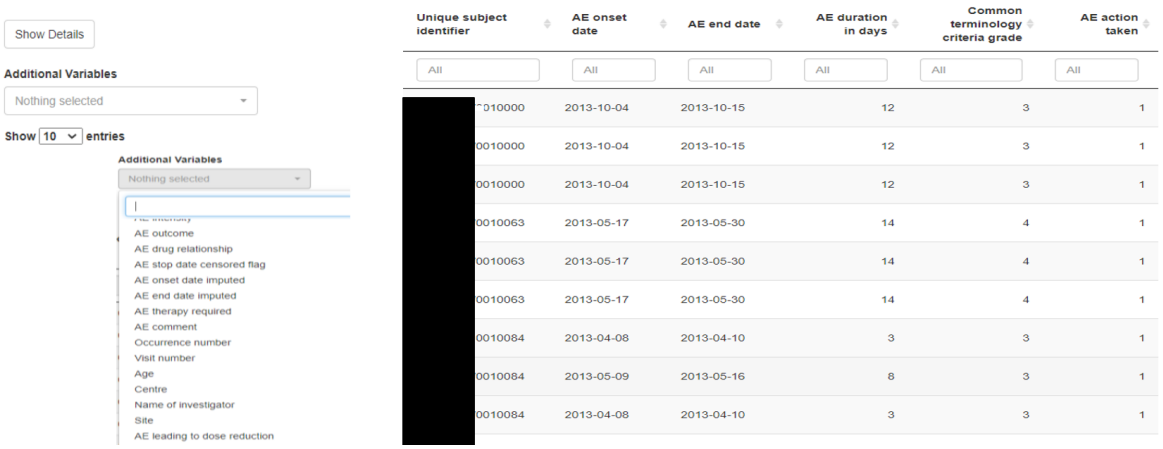


Sample selected outputs from the monitoring R-shiny based app

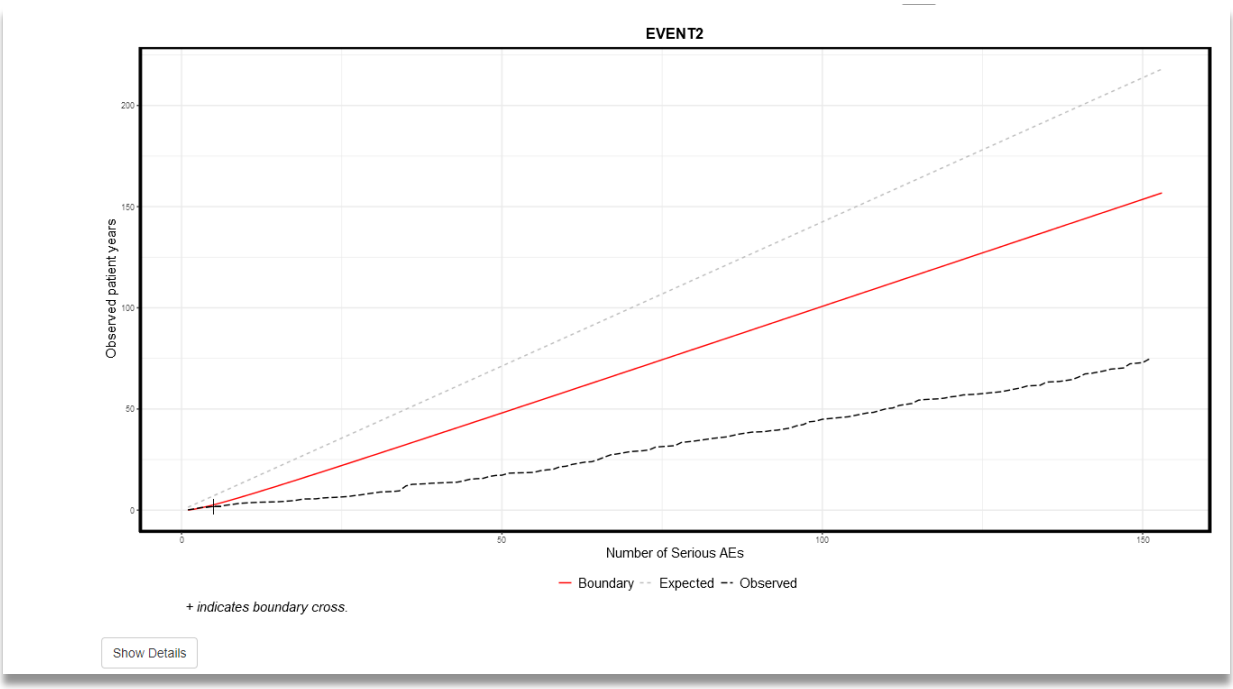
Overview: if certain category of anticipated serious adverse events meets the triggering criteria, the corresponding row will be highlighted in red. One click will be directed to the "individual anticipated events" page.



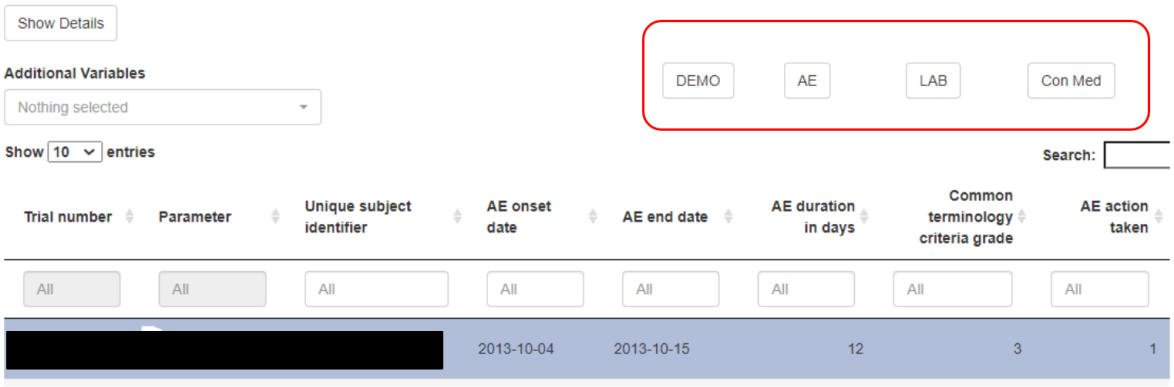
Individual anticipated events: this page gives the details of selected anticipated serious events, which can be searched from drop-down list on the left panel as well.



KM curve:

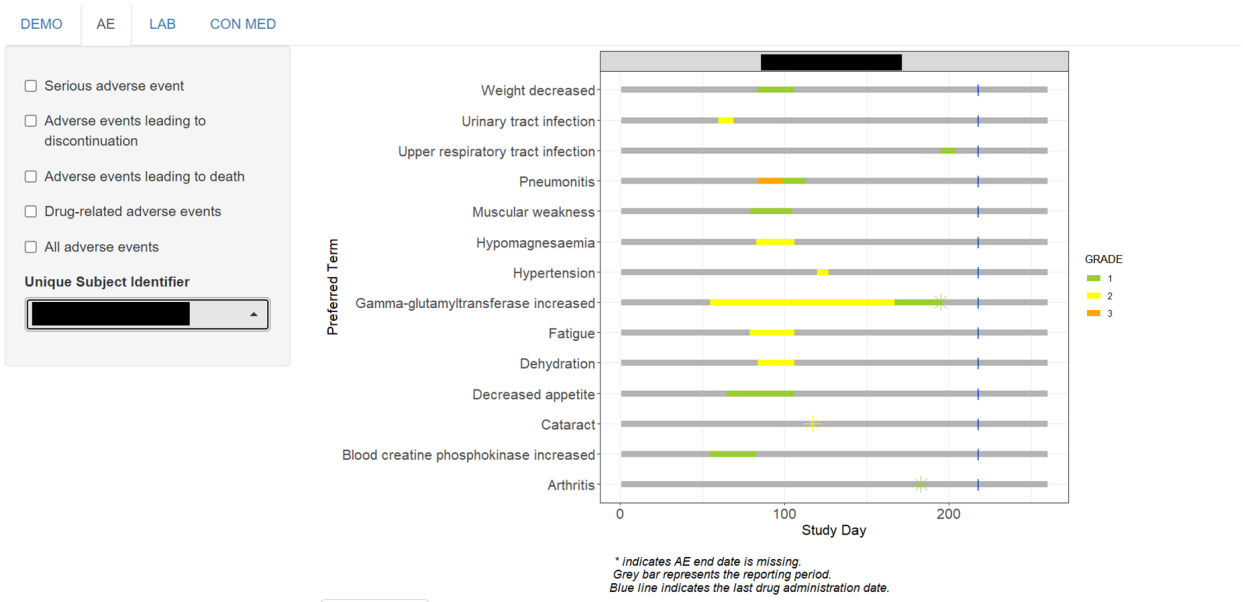


Click "Show Details" button, further information about the anticipated events under investigation will be displayed.

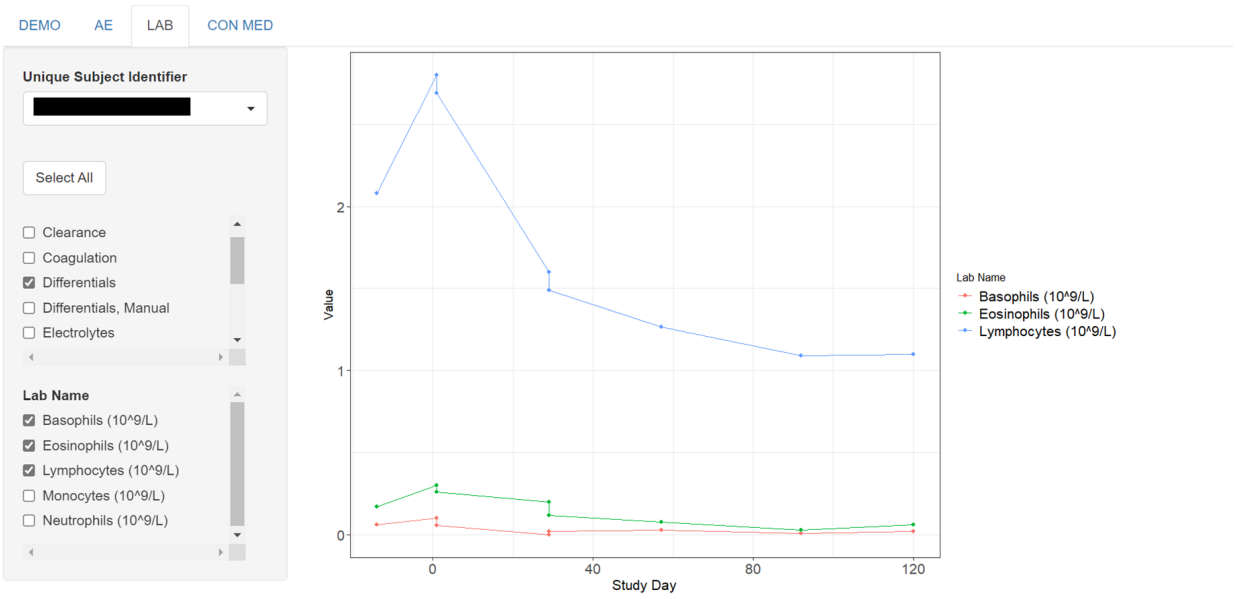


When click any adverse event in the listing, there will be another four options available: DEMO, AE, LAB and Con Med. After clicking those options, the reviewers will be directed to corresponding page for further patient level information. Below are examples from AE and LAB.

AE:



Lab:



iSAT – What is More?

The fundamental philosophy and nature of the iSAT is being independent, which also further expands the scope of the iSAT activities to most blinded non-pivotal phase II studies and under restricted condition to some open label phase III studies. For example, the iSAT can act as independent analysis team for interim analysis (IA) to support establishing proof of clinical concept in a double blinded non-pivotal phase II study or prepare unblinded analysis for Data Monitoring Committees (DMCs) in an open label phase III study.

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Reference:

FDA, *Sponsor responsibilities - safety reporting requirement and safety assessment for IND and bioavailability/bioequivalence studies guidance for industry*, June 2021