

Safety first, Agility Comes

Challenges and Solutions to Fulfill IND

Safety Requirements

KE XIAO, HONG WANG
BOEHRINGER INGELHEIM
02MAY2022, ATLANTA, GA

Disclaimer

The opinions expressed in this presentation and on the following slides are solely those of the presenter and not necessarily those of Boehringer Ingelheim. Boehringer Ingelheim does not guarantee the accuracy or reliability of the information provided herein.

Acknowledgements

- Advisor: Hans-Juergen Lomp
- iSAT peer colleagues: Joe Scherer, Matthias Trampisch
- Tong Zhu for review

Outline

- ▶ FDA has published updated guidance regarding safety requirements for IND and/or bioavailability/bioequivalence studies.
- ▶ There are emerging challenges for statistical programming to support fulfilling FDA's requests during unblinded aggregated analysis while maintaining trial integrity.
- ▶ Introduce dedicated independent safety analysis team(iSAT) as part of the solutions.
- ▶ Focus on statistical programmers' roles and responsibilities during the process of safety reporting and introduce a visualization tool that facilitates blinded monitoring.
- ▶ Share our experience/lesson learned and open for further discussion.

Background

- ▶ FDA has published various guidance regarding safety reporting requirements for IND studies with clarifying sponsors' roles and responsibilities:
 - ▶ *In September 2010, FDA published Final Rule addressing the IND safety reporting requirements; effective on March 28, 2011*
 - ▶ *In December 2012, FDA published a final Guidance describing the operationalization of this Final Rule*
 - ▶ *In December 2015, FDA published Safety Assessment for IND Safety reporting Guidance(draft)*
 - ▶ *In June 2021, FDA published Sponsor responsibilities - safety reporting requirement and safety assessment for IND and bioavailability/bioequivalence studies guidance for industry*

Emerging challenge – a reporting dilemma

- ▶ Reporting of aggregated data requires unblinding
- ▶ Exposure-adjusted estimates ideal, requires unblinding information of **all** treated patients
 - A full unblinding is against the principle/industry standard where trial sponsors should be blinded during trial conduct

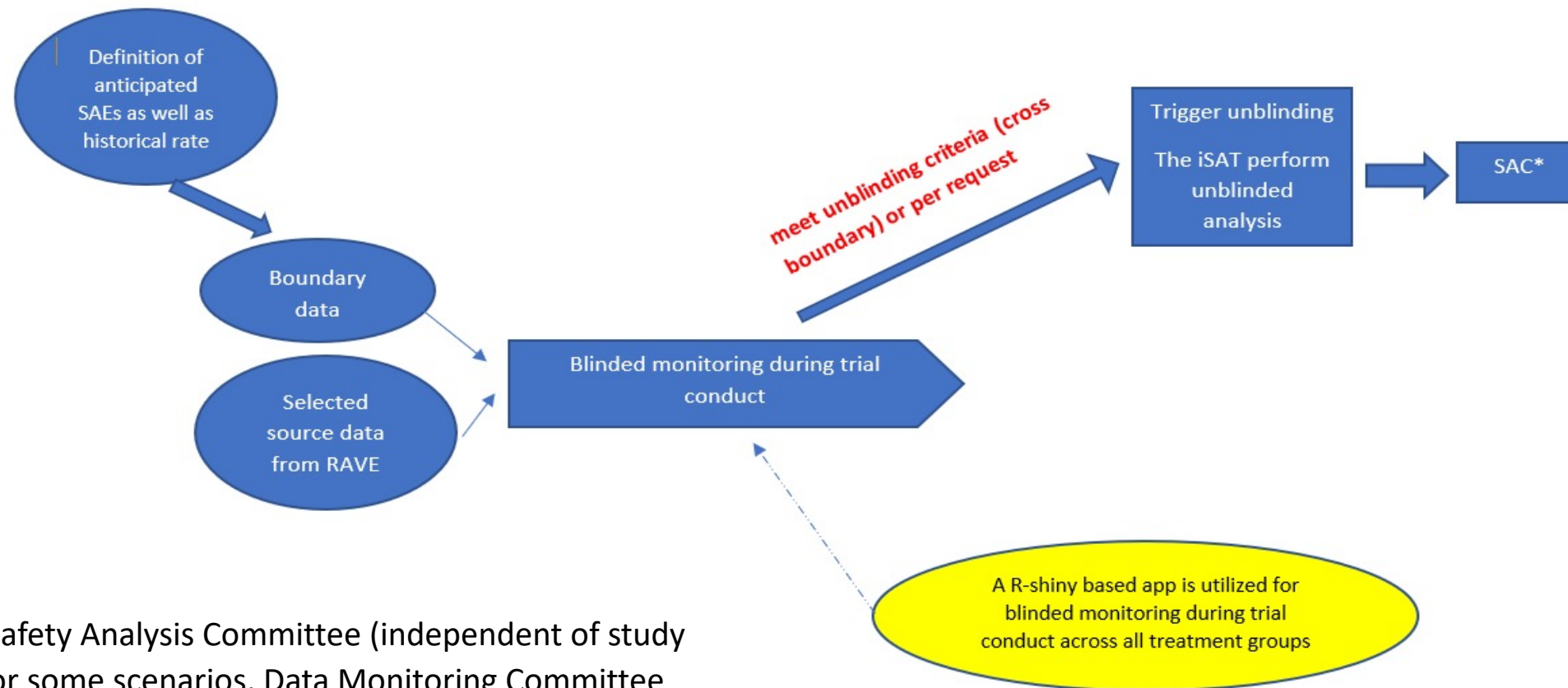
How to have a well-defined processes to allow compliance with FDA final rule, whilst protect the scientific credibility of their trials?

independent Safety Analysis Team(iSAT) formed due to 2015 new guidance!

Introduction of iSAT

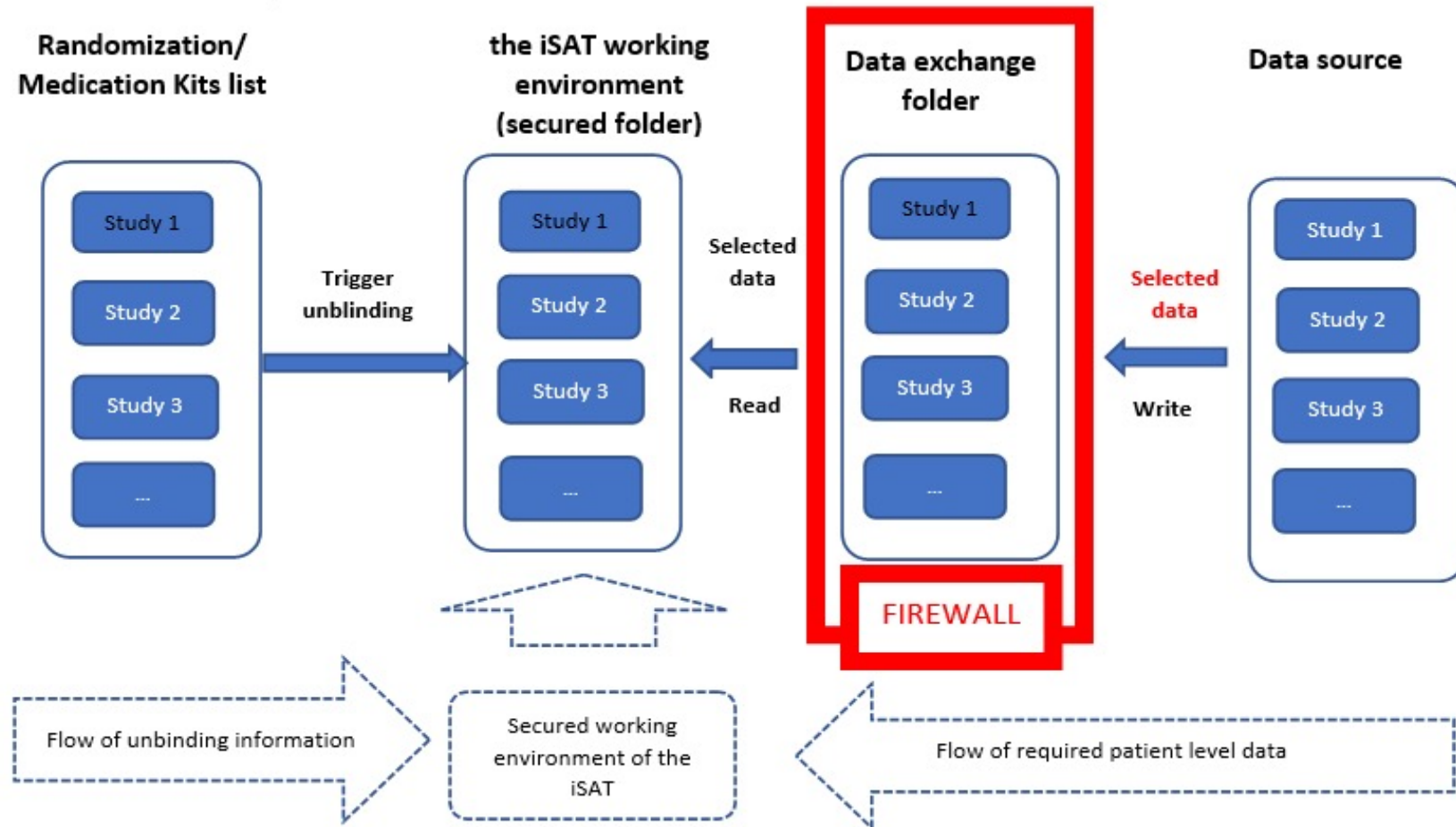
- ▶ Initially established in Nov. 2017 with 2 statisticians and 1 programmer
- ▶ Now iSAT has 2 statisticians and 4 programmers
- ▶ The primary task is functioning as a dedicated independent team, preparing unblinded data handling and analysis to fulfill FDAs requests for expedited safety reporting (majorly focus on **aggregated** analysis for **anticipated** Unexpected Serious Adverse Events)
- ▶ iSAT is independent of any study and project team within the sponsor organization
- ▶ iSAT is not involved in trial or project related tasks during conduct – except for tasks requiring strict confidentiality handling such as IND safety reporting and other unblinding activities

General process for aggregated SUSAR reporting – a simplified example if using 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 set up – flow



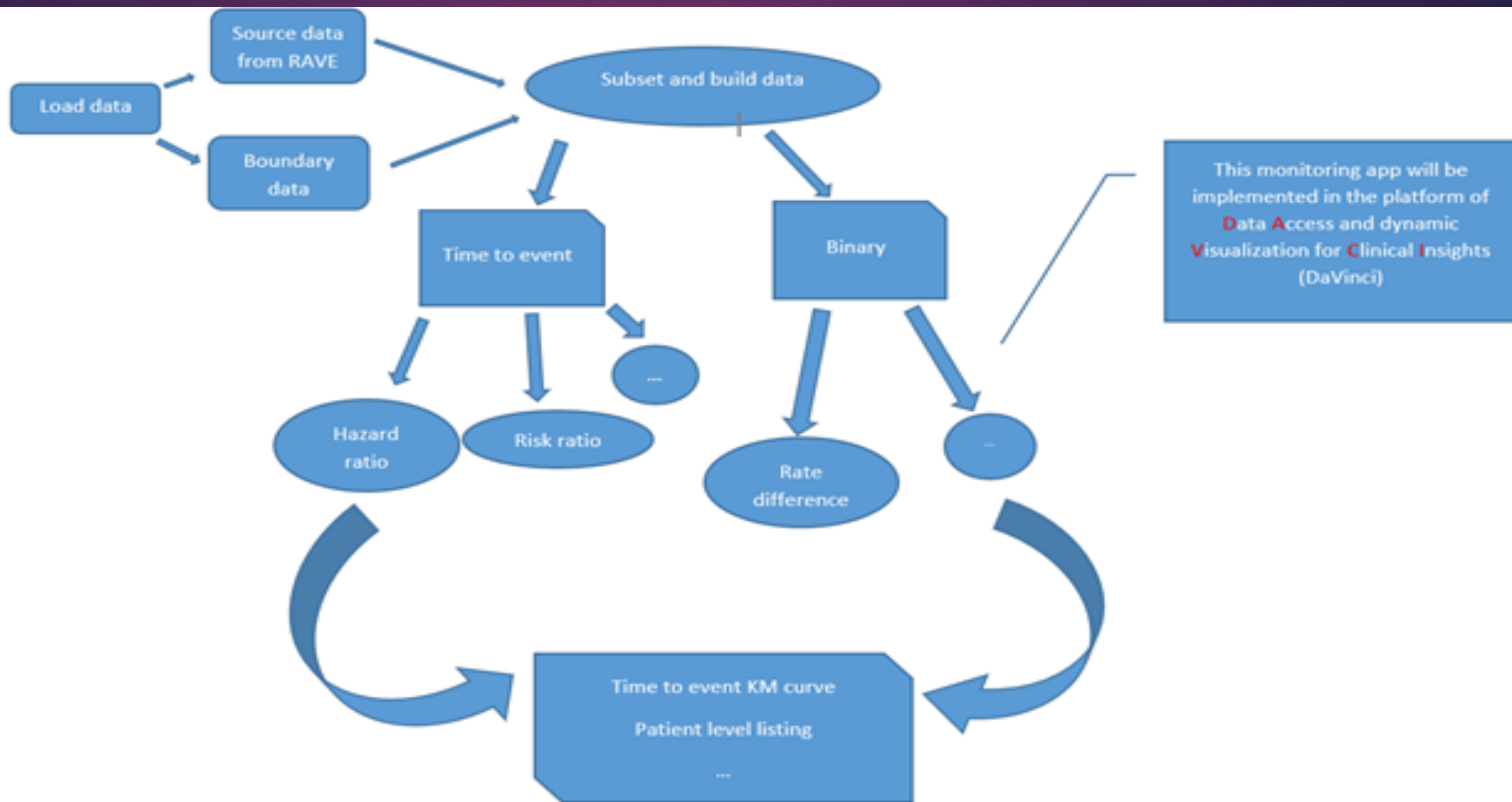
Firewall set cont'd

- ▶ **Bi-directional:** regular trial/project team have no access to iSAT working environment; iSAT have no access to trial/project team working environment neither.
- ▶ **Exchange folder:** for document and blinded data transfer. Both involved trial team and iSAT have access.
- ▶ **Limited access to selected study data:**
 - Essential: AE, demographics, disposition, drug accountability and exposure;
 - Optional: Con meds, medical history, lab or other relevant data;
 - No access to any efficacy data by default.
- ▶ Randomization/medication kit information will not be released to iSAT till trigger unblinding.

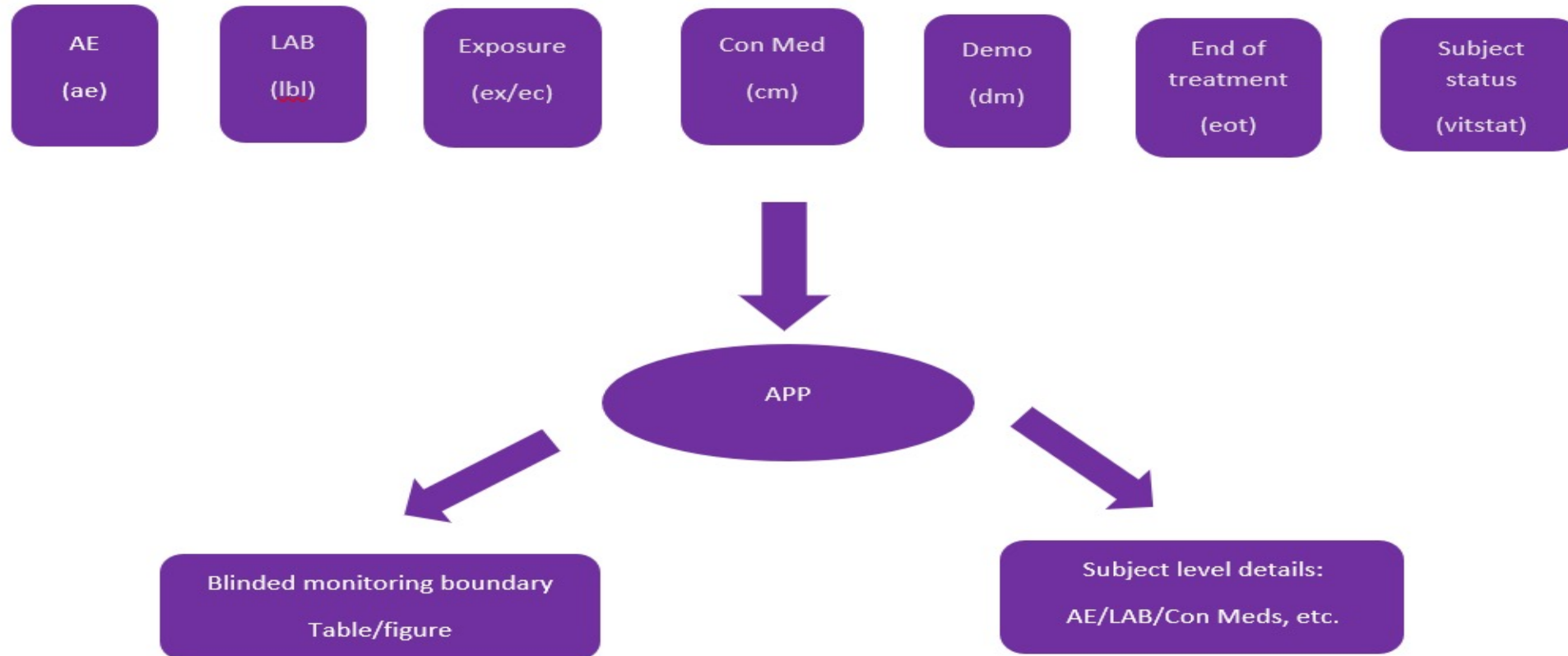
Blinded monitoring : utilization of R Shiny app taking triggering approach

- ▶ **Main purpose**: blinded safety assessment monitoring across treatment during trial conduct.
- ▶ **The primary targeted audience** is study safety physician.
- ▶ **The input study data** : source data (selected based on specific study needs) directly from data base (e.g., RAVE)
- ▶ 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.
- ▶ Trigger based using an estimated background rate
 - ▶ Idea: monitor blinded data and compare against a background rate
 - ▶ Advantage: maintain blind as long as there is no indication of an increased risk

App flow



Overview input data: an example



Data load

Home

Data Load

Data Monitoring

Patient Data

Session Info

Please select Study ID:

Study Selected: *

Data loaded for study :

Dataset_name	Domain	Nrow	Ncol
ae	Adverse event	2124	113
ec	Exposure	3171	92
eot	End of treatment	305	58
vitstat	Subject status	292	68
dd	Death date	13	69
lbl	Labs	54899	33
cm	Concomitant medications	2656	173

Data monitoring – overall summary

Overall Summary

Individual Anticipated Events

Show 10 entries

Search:

	Total (N, %)	Trigger unblind?	PT includes
Number of patients	441 (100)		
EVENT1#	88 (20)	No	PT1, PT2, PT3, PT4
EVENT2	153 (35)	Yes	PT5
EVENT3#	19 (4)	No	PT6, PT7
EVENT4	21 (5)	No	PT8
EVENT5#	25 (6)	No	PT9, PT10
EVENT6	53 (12)	Yes	PT11

Showing 1 to 7 of 7 entries

Previous 1 Next

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.

Data monitoring – individual anticipated events

Overall Summary

Individual Anticipated Events

Anticipate event

EVENT2

Show 10 entries

Search:

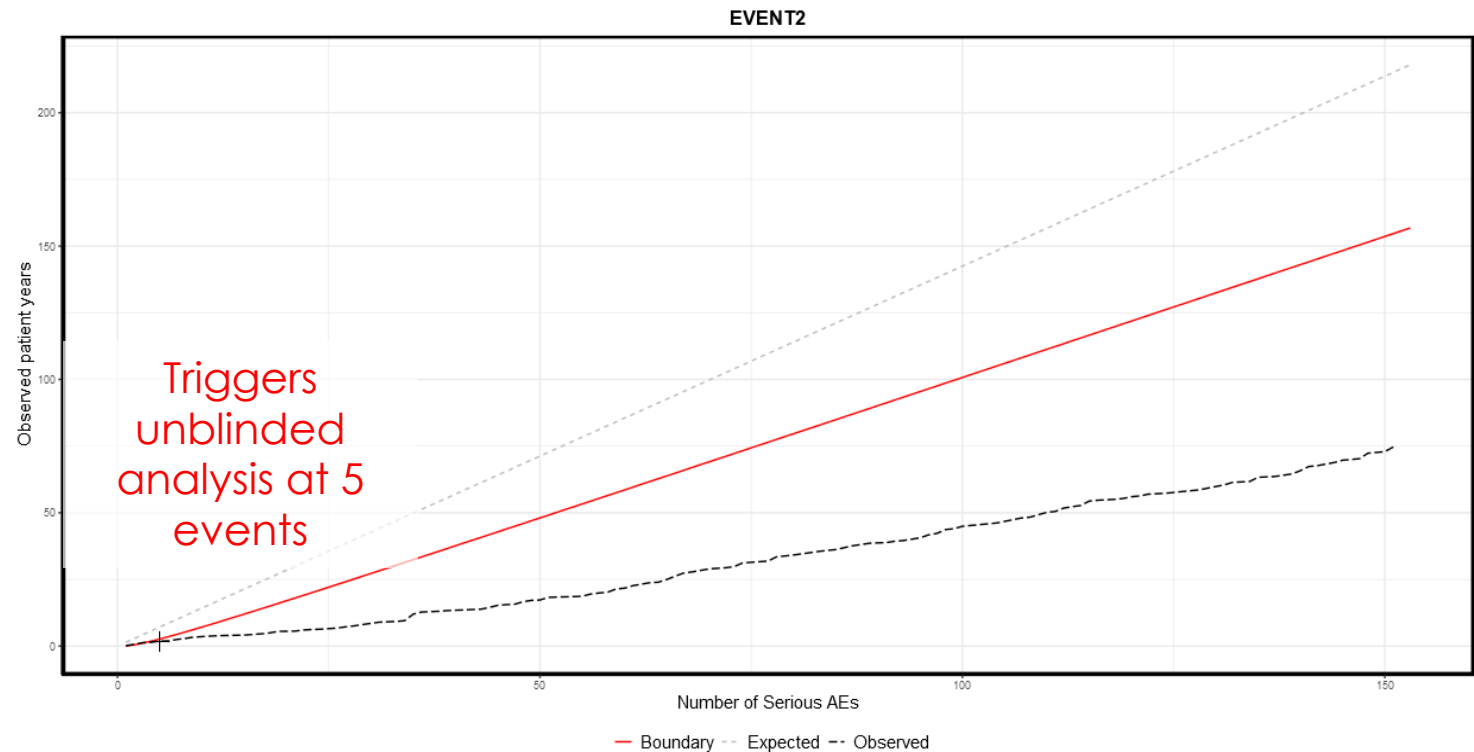
Anticipated Event	Number of SAEs	AE Onset Date	Exposure (PY)			Below Boundary?
			Observed	Expected	Boundary	
All	All	All	All	All	All	All
EVENT2	1	2013-03-19	0.1697	1.4248	0.0709	No
EVENT2	2	2013-04-08	0.6407	2.8496	0.4863	No
EVENT2	3	2013-04-25	1.2868	4.2744	1.1102	No
EVENT2	4	2013-04-28	1.4428	5.6992	1.8432	No
EVENT2	5	2013-05-06	1.8891	7.124	2.643	Yes
EVENT2	6	2013-05-07	1.9466	8.5488	3.4883	Yes
EVENT2	7	2013-05-17	2.4695	9.9736	4.3665	Yes
EVENT2	8	2013-05-24	2.8775	11.3984	5.2697	Yes
EVENT2	9	2013-05-31	3.3648	12.8232	6.1925	Yes
EVENT2	11	2013-06-05	3.7454	15.6727	8.0826	Yes

Showing 1 to 10 of 125 entries

Previous 1 2 3 4 5 ... 13 Next

Data monitoring : visual presentation of crossing boundary

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



Show Details

Data monitoring: more details about a particular event

Show Details

Additional Variables

Nothing selected

Show 10 entries

Additional Variables

Nothing selected

AE outcome
AE drug relationship
AE stop date censored flag
AE onset date imputed
AE end date imputed
AE therapy required
AE comment
Occurrence number
Visit number
Age
Centre
Name of investigator
Site
AE leading to dose reduction

Unique subject identifier	AE onset date	AE end date	AE duration in days	Common terminology criteria grade	AE action taken
All	All	All	All	All	All
0010000	2013-10-04	2013-10-15	12	3	1
0010000	2013-10-04	2013-10-15	12	3	1
0010000	2013-10-04	2013-10-15	12	3	1
0010063	2013-05-17	2013-05-30	14	4	1
0010063	2013-05-17	2013-05-30	14	4	1
0010063	2013-05-17	2013-05-30	14	4	1
0010084	2013-04-08	2013-04-10	3	3	1
0010084	2013-05-09	2013-05-16	8	3	1
0010084	2013-04-08	2013-04-10	3	3	1
0010084	2013-05-09	2013-05-16	8	3	1

Data monitoring: link to other data of interest

Show Details

Additional Variables

Nothing selected

DEMO

AE

LAB

Con Med

Show

10

 entries

Search:

Trial number	Parameter	Unique subject identifier	AE onset date	AE end date	AE duration in days	Common terminology criteria grade	AE action taken
All	All	All	All	All	All	All	All
			2013-10-04	2013-10-15	12	3	1

Patient level details: AE

DEMO

AE

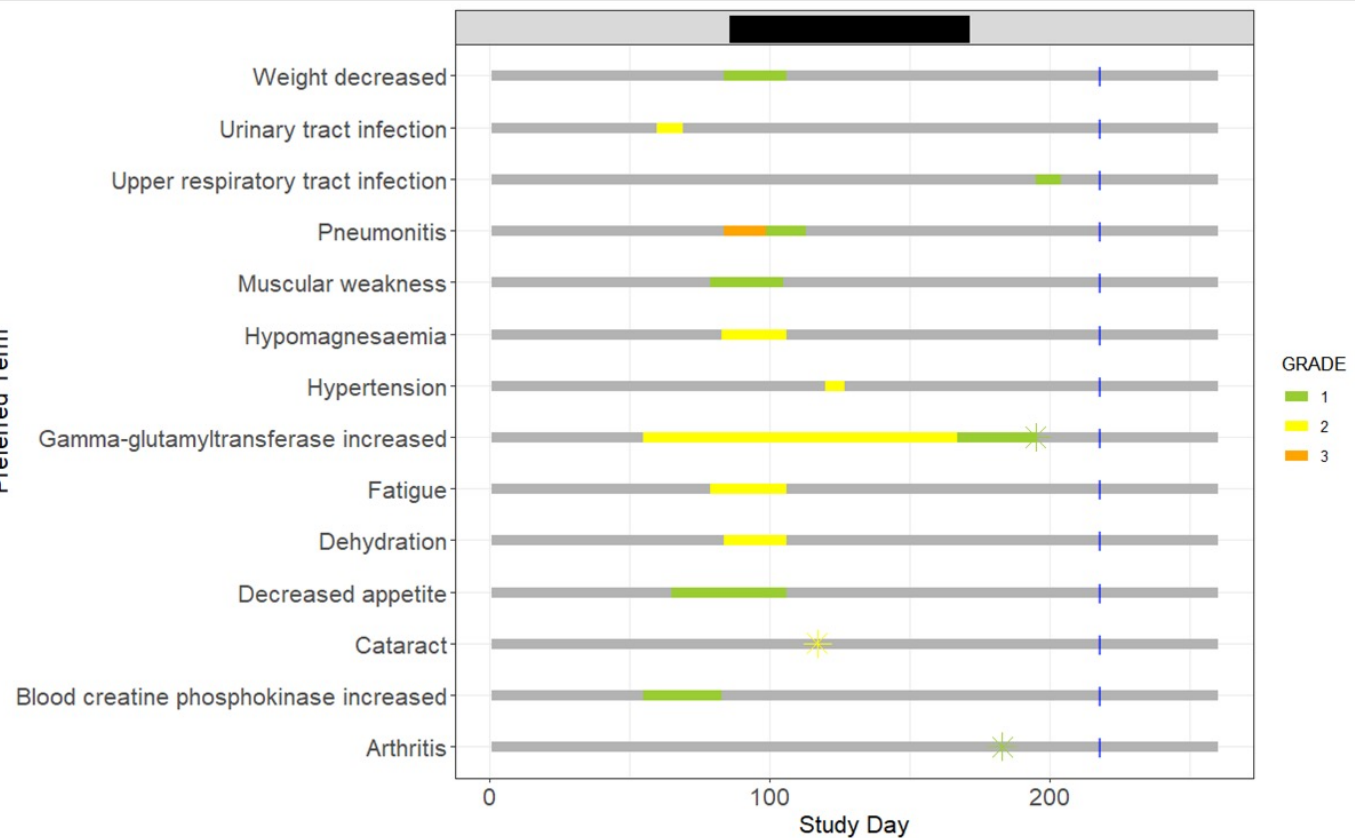
LAB

CON MED

- ☐ Serious adverse event
- ☐ Adverse events leading to discontinuation
- ☐ Adverse events leading to death
- ☐ Drug-related adverse events
- ☐ All adverse events

Unique Subject Identifier

Preferred Term



* indicates AE end date is missing.
Grey bar represents the reporting period.
Blue line indicates the last drug administration date.

Data monitoring: more details

Additional Variables

Nothing selected

Search:

Unique subject identifier	AE onset date	AE end date	AE duration in days	Common terminology criteria grade	AE action taken	MedDRA PT description
All	All	All	All	All	All	All
	2013-10-04	2013-10-15	12	3	1	Anaemia
	2013-08-30	2013-10-28	60	1	1	Bladder spasm
	2013-08-25	2013-08-25	1	1	1	Blood urine present
	2013-09-02	2013-09-06	5	1	1	Diarrhoea

DEMO

AE

LAB

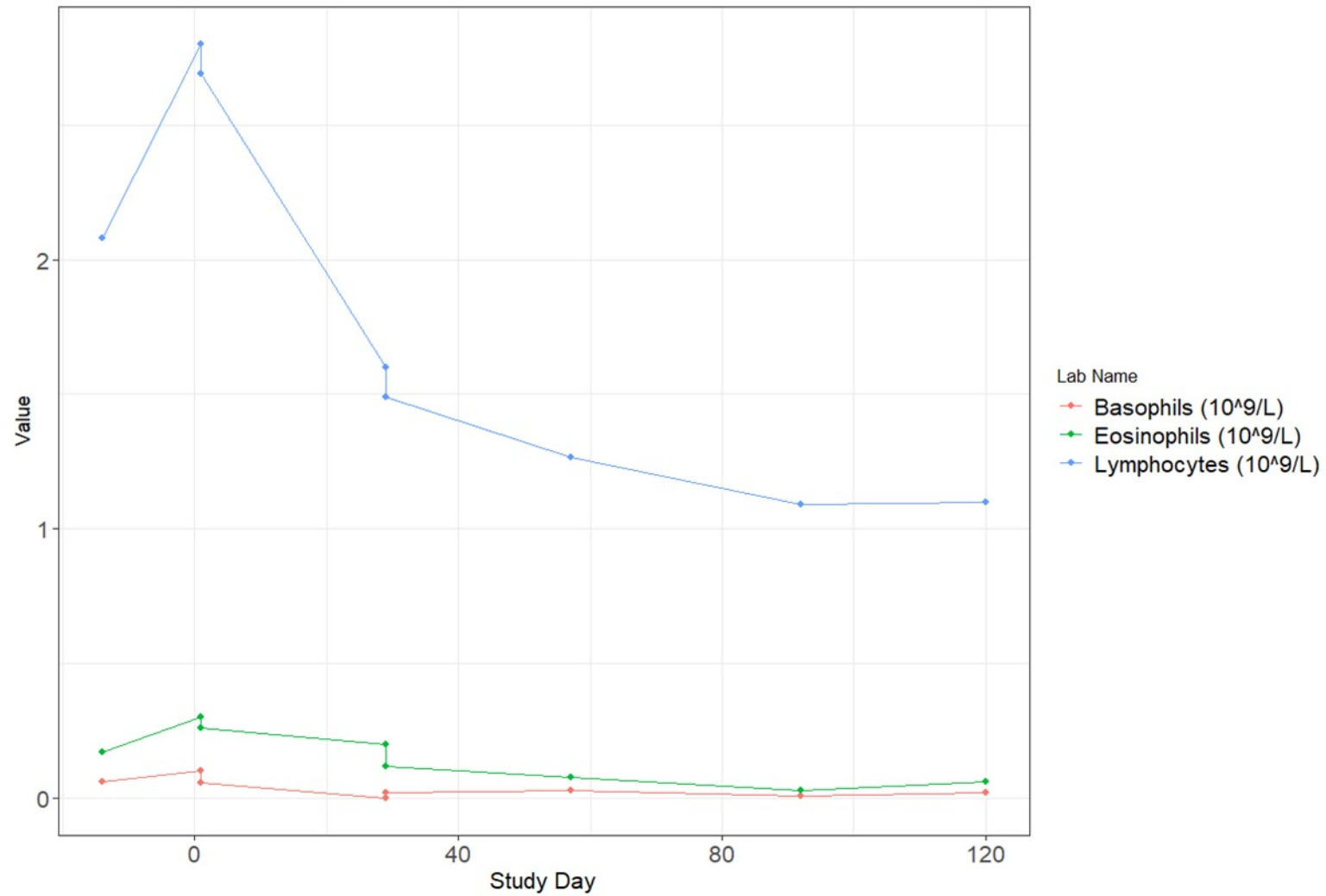
CON MED

Unique Subject Identifier

Select All

☐ Clearance☐ Coagulation☒ Differentials☐ Differentials, Manual☐ Electrolytes

Lab Name

☒ Basophils ($10^9/L$)☒ Eosinophils ($10^9/L$)☒ Lymphocytes ($10^9/L$)☐ Monocytes ($10^9/L$)☐ Neutrophils ($10^9/L$)

Lab: more details

Unique subject identifier	Functional group	Date of First Exposure	TRTSTM	Visit name	Lab Date	PARAM	Lab value - std	Range low - std	Range high - std	CTCAE grade
All	All	All	A	All	A	All	A	A	A	A
0010000	Haematology	2013-08-23	13:26:00	SCREENING	2013-08-22	Haemoglobin (g/dL)	98	130	175	2
0010000	Haematology	2013-08-23	13:26:00	C1_V1	2013-08-23	Haemoglobin (g/dL)	106	130	175	1
0010000	Haematology	2013-08-23	13:26:00	C1_V2	2013-08-30	Haemoglobin (g/dL)	87	130	175	2
0010000	Haematology	2013-08-23	13:26:00	C1_V3	2013-09-09	Haemoglobin (g/dL)	97	130	175	2
0010000	Haematology	2013-08-23	13:26:00	C1_V5	2013-09-20	Haemoglobin (g/dL)	93	130	175	2
0010000	Haematology	2013-08-23	13:26:00	C2_V1	2013-09-23	Haemoglobin (g/dL)	102	130	175	1
0010000	Haematology	2013-08-23	13:26:00	C2_V2	2013-09-30	Haemoglobin (g/dL)	96	130	175	2

After triggering:

- sample **unblinded** outputs produced by iSAT

Section	Type	Output title
General information	table	Historical background rate table
	table	Demographic table
Outputs for anticipated SAE	table	Summary of comparison of active vs. placebo for anticipated SAE
	figure	KM curve for anticipated SAE
	figure	Smoothed KM curve for anticipated SAE
	table	AE overall summary table for anticipated SAE
	table	Frequency of patients with anticipated SAE
	listing	Listing of patients with anticipated SAE
Other	Lab, narratives, etc.	

iSAT- what is more

- ▶ Since the fire wall system is setup for IND safety reporting, iSAT can also handle various other unblinding related activities:
- ▶ Act as internal independent analysis team for Interim Analysis for decision making; for DMC/SMC in non-pivotal double blind or open label trial (e. g. support adaptive design in PHASE II).
- ▶ For DMC, iSAT statistician can also function as DMC statistician.
- ▶ Programming support for Randomization Specialist Group
 - ▶ Create R-Shiny App
 - ▶ Create program for some special complicated randomization case
- ▶ Other unblinded activities – for example Monitoring aggregated unblinded PFS analysis for triggering IA

iSAT- what is more in supporting DMC/SMC/IA

- ▶ iSAT takes *unblinding* responsibility
 - ▶ Trial team prepares Blinded ADaM/TFLs
 - ▶ iSAT unblinds ADaM datasets, and generates unblinded TFLs
- ▶ iSAT takes *full programming* responsibilities
 - ▶ Trial team only needs to copy source data (collected data instead of SDTM)
 - ▶ Operation is easier
 - ▶ More frequent DMCs (every month on average)
 - ▶ More data collected in short time and fresher data for DMC to review
 - ▶ Support phase II/III open label trial which is hard to prepare in blinded fashion based on the nature of the trial design.

iSAT- Advantages

- ▶ Internal programmers/statisticians know company system, standards and process well.
- ▶ Much more flexible to adapt and fit trial team's needs.
- ▶ Reliable on both timeline and quality.
- ▶ Update key outputs based on the most current data before DMC.
- ▶ Be accountable and have ownership as part of the team.
- ▶ Flexible to provide additional analysis based on DMC request for closed sessions

Thank you!



Method: Comparison to historical rates

Availability of information from Historical Data					Blinded monitoring	
Number of patients	Number of patient years	Number of patients with SAE	Rate: Events / 100 PY ¹	Risk: Events / Patients	Analysis type	Section ²
					Rate	<u>PRRH</u>
					Risk	<u>ChiSqH</u>
					Risk	<u>BH</u>
					Number of events	<u>WCSA (no information)</u>

■ information available
 ■ either one or both information are available
 ■ information not available

¹ Normalized Rate – per 100 patient years provided as example. Refer to Section 4.2.1 for more information on how different formats are handled in the analysis.

² **PRRH**: Poisson Rate Ratio vs Historical / **ChiSqH**: Chi-Square vs. Historical / **BH**: Binomial Test vs Historical **WCSA**: Worst Case Scenario Analysis

Background (1) – FDA Final Rule on IND Safety reporting

- ▶ In September 2010, FDA published Final Rule addressing the IND safety reporting requirements; effective on March 28, 2011

The sponsor

“[...] must report any suspected adverse reaction that is both serious and unexpected”

But

*“[...] the sponsor must report an adverse event as a suspected adverse reaction **only if there is evidence to suggest a causal relationship** between the drug and the adverse event.”*

Background(2) – Guidance on IND Safety reporting (2012)

- ▶ **In December 2012, FDA published a final Guidance describing the operationalization of this Final Rule**
 - ▶ defines terms used for safety reporting,
 - ▶ makes recommendations on when and how to submit a safety report,
 - ▶ provides advice on other safety reporting issues that have arisen from sponsors and investigators;

Background(2) – Guidance on IND Safety reporting (2012)

- ▶ In December 2012, FDA published a final Guidance describing the operationalization of this Final Rule
 - ▶ Suspected **U**nexpected **S**erious **A**dverse **R**eaction (SUSAR)
 - ▶ **Suspected**: related with the drug
 - ▶ **Unexpected**: not listed in IB
 - ▶ **Serious**: i.e. life-threatening or required hospitalization
 - ▶ **Adverse Reaction**: undesired harmful effect

Background(2) – Guidance on IND Safety reporting (2012)

- ▶ In December 2012, FDA published a final Guidance describing the operationalization of this Final Rule
 - ▶ Suspected **U**nexpected **S**erious **A**dverse **R**eaction (SUSAR)
 - ▶ **Suspected**: related with the drug
 - ▶ **Unexpected**: not listed in IB
 - ▶ **Serious**: i.e. life-threatening or required hospitalization
 - ▶ **Adverse Reaction**: undesired harmful effect

Background(2) – Guidance on IND Safety reporting (2012)

Three types of evidence to suggest causal relationship:

- ✓ **Single Occurrence:** uncommon and known that is strongly associated with drug exposure (e.g. Hepatic injury, Stevens-Johnson Syndrome)
- ✓ **One or More Occurrences:** not commonly associated with drug exposure, but uncommon in the study population (e.g. tendon rupture)
- ✓ **Aggregate Analysis of Specific Events:** indicates anticipated events occur more frequently in drug group than (historical) control group

Anticipated:

- ▶ known consequences of underlying disease or condition under investigation;
- ▶ commonly occur in the study population independent of drug therapy

Background (3)– Safety Assessment for IND Safety Reporting Guidance(draft) (Dec. 2015)

- ▶ Guidance contains recommendations on the following:
 - ▶ Safety Assessment Committee (SAC),
 - ▶ Aggregate analyses for comparison of AE rates across treatment groups,
 - ▶ Planned **unblinding** of safety data,
 - ▶ Reporting thresholds for IND safety reporting,
 - ▶ Safety surveillance plan (SSP).
- ▶ **iSAT formed due to this new guidance!**
 - ▶ Anticipated Unexpected Serious Adverse Events

Background (4)– Sponsor Responsibilities— Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies(Jun. 2021)

- ▶ This guidance merges content from (the 2012 final guidance) and (the 2015 draft guidance).
- ▶ This guidance includes revised recommendations initially described in the 2015 draft guidance on the following topics:
 - ▶ (1) planned unblinding of safety data and implications for trial integrity;
 - ▶ (2) increased flexibility regarding the party reviewing aggregate safety information for IND safety reporting purposes;
 - ▶ (3) clarification regarding the scope and methodology of aggregate analyses;
 - ▶ (4) clarification regarding the plan for safety surveillance, including what elements should be included in the plan.
- ▶ The 2015 draft guidance has been withdrawn upon the publication of this guidance.