OSI Request in FDA Submissions

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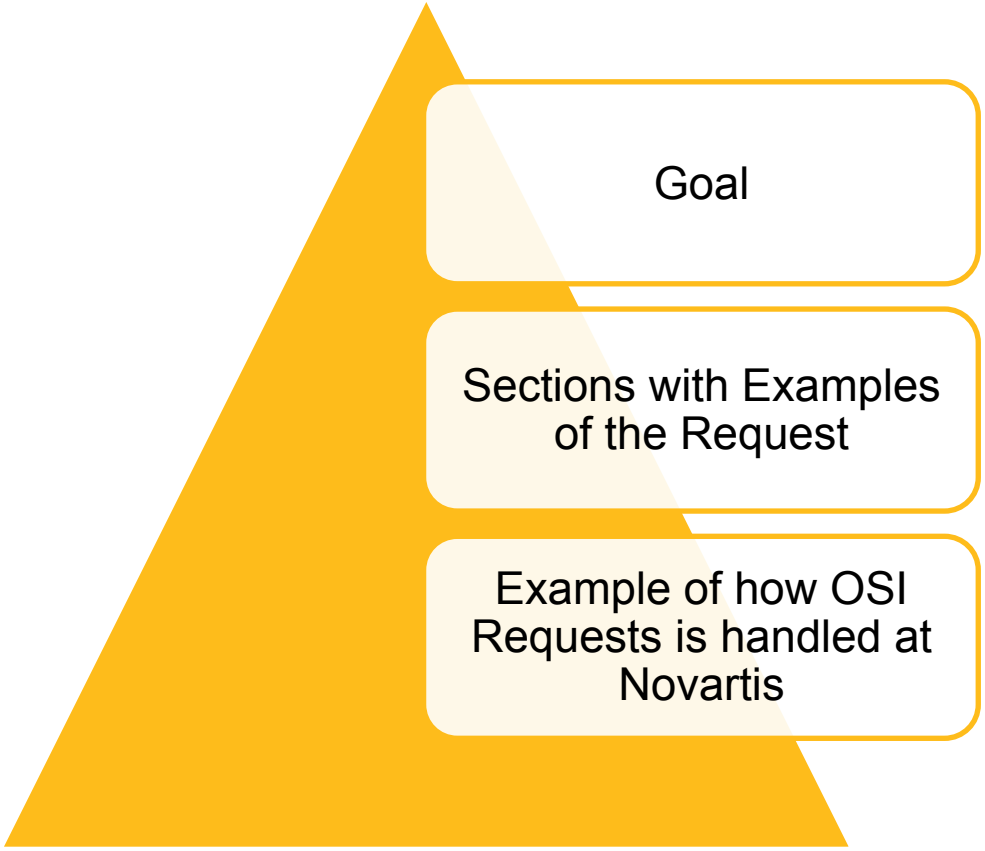
Agenda

OSI – **Office of Scientific Investigations**



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Goal

The **Center for Drug Evaluation and Research** (CDER) is part of the U.S. Food and Drug Administration (FDA) responsible for regulation of over-the-counter and prescription drugs, including biological therapeutics and generic drugs.

Office of Scientific Investigations (OSI) is a part of CDER Office of Compliance, which protects public health. The main goals of OSI are

- To verify the integrity of efficacy and safety data submitted to the FDA in support of new drug applications
- To assure that the rights and welfare of human research subjects are protected.

How OSI achieves the Goal?

- Auditing and verifying submitted data for
  - Safety
  - Efficacy
  - Bioequivalence of drugs for human use
- Directing inspections of IRB's for compliance.
- Ensuring GCP and GLP is followed during the conduct of Clinical Trial.

BIMO Clinical Data

Bioresearch Monitoring (BIMO) Clinical Data

BIMO Clinical Data

- Facilitate timely selection of clinical sites for potential FDA inspection as part of the NDA/BLA and/or supplementary review processes
- Used in the site inspection Audit

Requested for every NDA/BLA by FDA OSI

- included in Module 5 of eCTD

Similar requests from EMA and other HA

BIMO Clinical Data - Requests

An example...

- Part I : General and Clinical Investigator information(.pdf)
- Part II : Individual Site Level Listings (.pdf)
- Part III (optional) : Site Level Dataset (.xpt)

Part I : General and Clinical Investigator information

For each of the completed Phase 3 trials provide

- Section 1 :
  - Site number
  - Principal investigator
  - Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - Current Location of Principal Investigator (if no longer at Site).

- Section 2: By Site
  - Number of subjects screened for each site
  - Number of subjects randomized for each site
  - Number of subjects treated who prematurely discontinued for each site.

Contd.

- Section 3
  - Location where documents are maintained and would be available for inspection.
  - Name/address and contact information of all CROs used in the conduct of the clinical trials
  - Location where all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
  - Location of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

- Provide annotated Case Report Forms (CRF) and Protocols with all amendments for each pivotal trial.

Part II : Individual Site Level Listings

This section would provide subject data listings organized by site for each pivotal study .

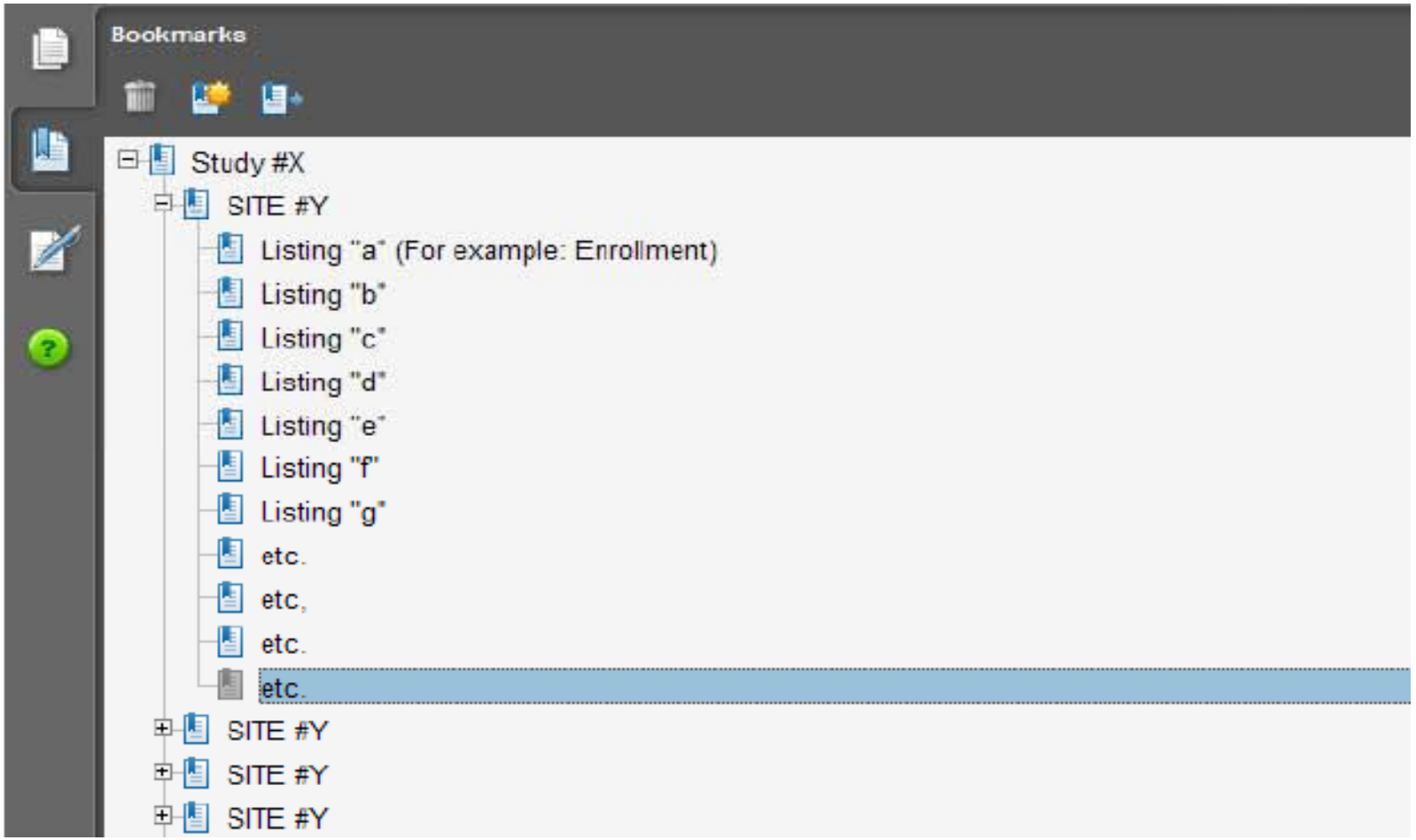
1. Listing for each subject/number screened and reason for screen-failure subjects
2. Subject listing for treatment assignment (randomization)
3. Subject listing of drop-outs and discontinued with date and reason
4. Subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
5. Subject listing of AEs, SAEs, deaths and dates
6. Subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation

Contd.

7. Subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
8. Subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
9. Subject listing, of laboratory tests performed for safety monitoring.

We create one **PDF** file with **Bookmarks** for each Pivotal trial and present all the requested listings for each site.(See example in next slide.)

Example for PDF with Bookmarks



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Example of how OSI Requests is handled in Novartis

One program

Re-use of existing listing programs that were NOT done by site subgroup

Re-use of tracking sheet to get footnotes

Automatic bookmark reordering, no matter how many sites and how many or what listings you have.

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Programming Techniques used to create bookmarked PDF...

- Re-use CSR listings programs
- **Perl Regular expressions** and RETAIN statement:
  - Identify sections in the programs and call them sequentially to apply consistent updates in program.
- **Call Execute** to Execute CSR programs with updates
- **ODS PDF** to create bookmarked PDFs
- **Proc document** to Re-arrange by site and Listing

```
ods pdf file="&genpgm./export/pgm_saf/&FINALOUTPUT..pdf";

proc document name=neworder ;
    replay;
run;

ods pdf close;
run;
```

Create bookmarked PDF using ODS and Proc Document

compile all listings by site subgroup into one temporary pdf file using ODS RTF

bookmarks are the automatic ones : Listing1>Site1,2,3,…,n ; Listing2>Site 1,2,3,…,n, plus some some additional for procedures.

Export into a txt file the list of bookmarks with theirs levels and paths.

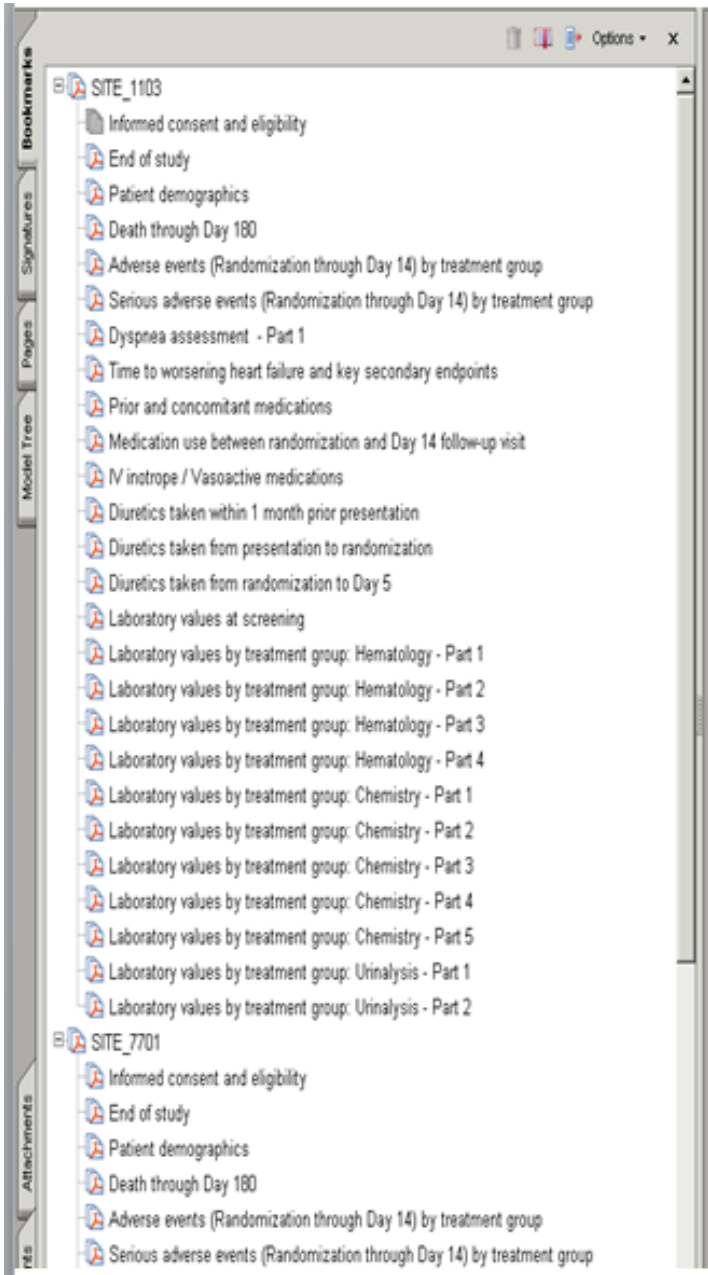
Create a new pdf file with custom folders and custom hierarchy

Based on the original list of bookmarks

PROC DOCUMENT to rearrange and replay the outputs.

bookmarks renamed automatically with the site number or the title of the listing depending on the level.

bookmarks are now: Site1>Listing1,2,3,…,n ; Site2>Listing 1,2,3,…,n.



Site : 1103 - Listing 1
Informed consent and eligibility

			Presentation		Admission		Consent			Criteria not met		
Treatment Group	Patient Number	Age/ Sex	Date	Time	Date	Time	Date	Time	Eligible?	Inclusion	Exclusion	Waiver obtained?
Placebo	008	79/M	30JAN08	09:53	30JAN08	12:50	30JAN08	10:40	No	7		No
	011	82/F	04MAR08	11:00	04MAR08	14:30	04MAR08	11:00	Yes			
	012	70/M	11MAR08	10:20	11MAR08	12:30	11MAR08	10:20	Yes			
	015	82/F	08APR08	16:55	08APR08	22:30	09APR08	08:30	Yes			
	016	69/M	11MAY08	09:48	11MAY08	15:00	11MAY08	13:15	Yes			
10mcg/kg/day	007	81/F	26JAN08	23:09	27JAN08	02:00	27JAN08	08:40	Yes			
	010	71/M	21FEB08	00:10	21FEB08	01:30	21FEB08	09:00	Yes			
	017	80/M	18MAY08	10:45	18MAY08	12:40	18MAY08	11:40	Yes			
	019	82/F	29JUN08	04:29	29JUN08	08:09	29JUN08	08:15	Yes			
30mcg/kg/day	001	67/F	11DEC07	09:25	11DEC07	13:20	11DEC07	10:00	Yes			
	003	58/M	17DEC07	10:15	17DEC07	14:00	17DEC07	10:20	No		14	No
	014	49/M	03APR08	09:16	03APR08	12:40	03APR08	09:30	Yes			
	018	74/F	01JUN08	08:39	01JUN08	12:30	01JUN08	10:00	Yes			
100mcg/kg/day	002	80/M	12DEC07	09:45	12DEC07	11:30	12DEC07	10:00	No		6	No
	005	76/F	07JAN08	11:00	07JAN08	13:05	07JAN08	11:20	Yes			

Part III (Optional): Site Level Datasets

A **voluntary** submission of BIMO electronic dataset in a form of single clinical site dataset (.xpt) **might** be requested for CDER Inspection Site Selection Tool, developed by CDER for selection of appropriate clinical sites for FDA inspection.

This dataset contains

- Administrative Information of the sites
- Summary Statistics by site and Treatment arm
- Patient Disposition
- Protocol Deviations
- Efficacy Endpoints
- Deaths and SAE.

Note : This may be requested as part of or after the submission.
The teams can challenge FDA on the need of providing this dataset

Format of Site Level Dataset

Site-Specific Efficacy Results

The final electronic datasets must be in XPT format and follow specific pre-defined FDA format

- The SAS transport file (SAS XPORT V.5) is called “clinsite.xpt”
- The Dataset structure is one record per **study** per **site** per **treatment arm**
- It has 39 pre-defined variables with specific names, labels, definitions and formats.

Note: *This dataset is independent of CDISC structure.*

Adobe Acrobat Document

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Specification For Site Level Dataset

Appendix 1: Clinical Site Data Elements Summary Listing

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1."	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFE	Treatment Efficacy Endpoint	Num	Floating Point	Summary statistic for each primary efficacy endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Endpoint Standard Deviation	Num	Floating Point	Standard deviation of the summary statistic (TRTEFFE) for each primary efficacy endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Treatment Effect	Num	Floating Point	Site-specific treatment effect reported using the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Treatment Effect Standard Deviation	Num	Floating Point	Standard deviation of the site-specific treatment effect (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount ($USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00

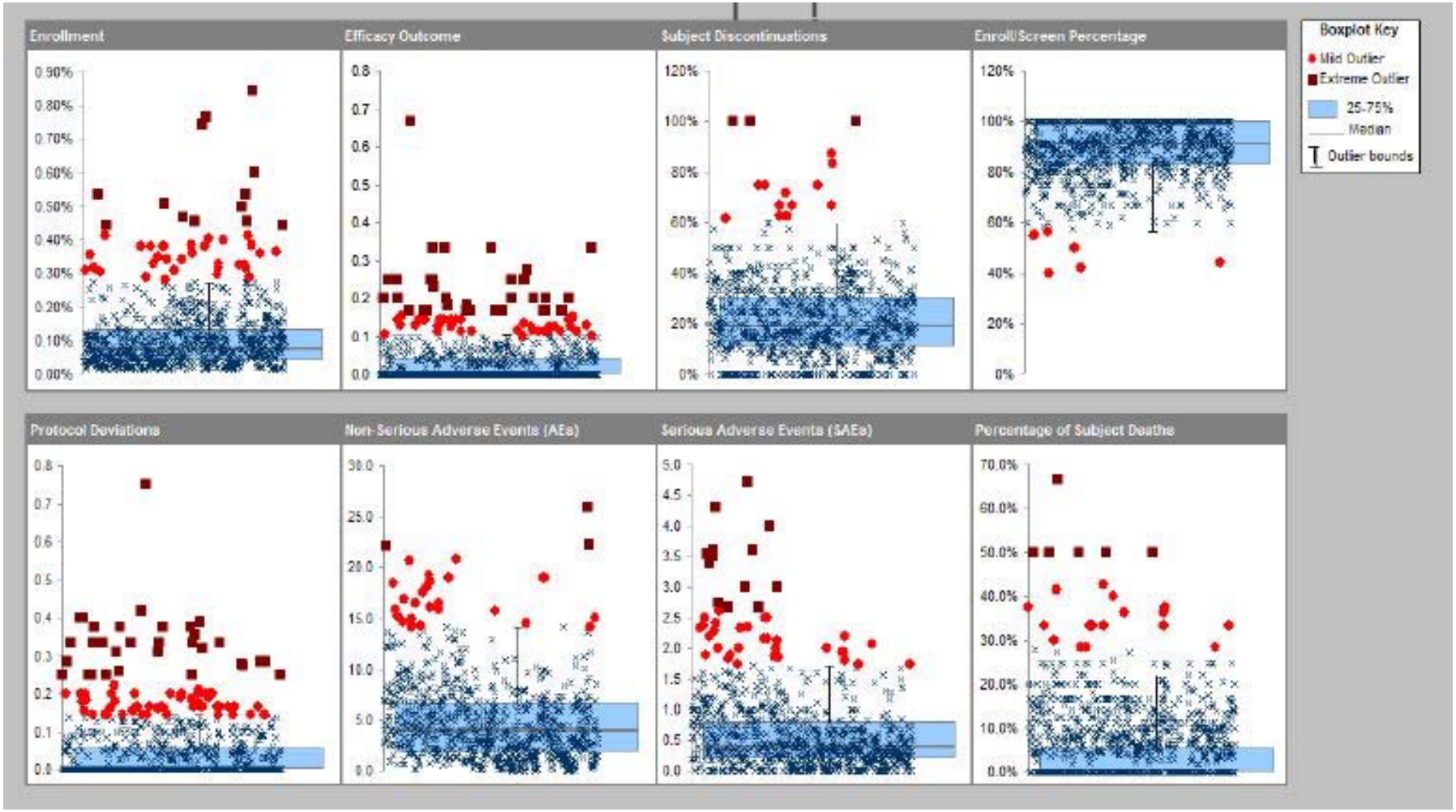
Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount ($USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parities. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-3	3 letter ISO 3166 country code in which the site is located.	USA
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

Analysis

The key derived variables and key risk indicators for systematic assessment in a clinical trial can be identified and categorized as **study conduct**, **safety perspective**, and **efficacy perspective**

Risk Category	Variable Name and Its Label in SLCS
Study Conduct	**ENROLL:** Total Number of Subjects Enrolled by Treatment Arm **SCREEN:** Total Number of Subjects Screened **DISCONT:** Number of Subjects Discontinuing from the Study by Treatment Arm **PROTVIOL:** Number of Protocol Violations
Safety Perspective	**DEATH:** Total Number of Deaths by Treatment Arm **NSAE:** Number of Non-Serious Adverse Events by Treatment Arm **SAE:** Number of Serious Adverse Events by Treatment Arm
Efficacy Perspective	**TRTEFFR:** The efficacy result for each primary endpoint by treatment arm **TRTEFFV:** The variance of the efficacy result for each primary endpoint by treatment arm **SITEEFFE:** Site-Specific Efficacy Effect Size **SITEEFFV:** Site-Specific Efficacy Effect Size Variance

Graphical Representation



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Being Pro-Active

- ✓ FDA/OSI communicates with pharmaceutical companies to provide BIMO Clinical Data for each NDA.
- ✓ The BIMO clinical data is now part of every submission. Can we act proactively and contact FDA well ahead of submission to discuss and clarify potential information that will be included in BIMO submission?

References

FDA website
OSI and the **overview of inspection process**
CDER
BIMO Program and its **objectives**
HSP/BIMO Initiative
BIMO clinical data:
information on FDA inspections (specific Novartis examples are presented in section **2** and Appendix **A**)
BIMO electronic dataset: **guidelines** and **specifications**