Summary Level Information and Data for CDER's Inspection Planning

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Agenda

- Summary of OSI Requests
- CDER Clinical Investigator Inspection Site Selection Tool
- eData XPT Dataset eCTD Location
- Shift towards Data Standards

Goals of Bioresearch Monitoring

- Protect the rights, safety and welfare of research participants

- Help ensure reliable data are submitted in marketing applications.
  - For regulatory decision making (Approval)
  - As evidence base for clinical use of drug (Label)
  - Evaluating compliance with FDA regulations through inspections of Sponsors, CROs, CIs, IRBs, non-clinical research firms (GLP), and bioanalytical labs (BE/BA).

Clinical Trial Inspection Process

- FDA's GCP application inspection program.
- Joint effort across multiple functions
  - Office of Compliance (OC)
  - Office of New Drugs (OND)
  - Office of the Center Director (OCD)
  - Office of Planning and Informatics (OPI)
  - Office of Biostatistics (OB)
  - FDA's Office of Regulatory Affairs (ORA)

Challenges to Current Inspection System

- PDUFA timelines require high level of efficiency
- Complexity of the clinical trial enterprise
- Increasing number of sites per clinical trial
- Increasing number of foreign clinical trial sites
- Delays in analysis due to lack of data standards in submissions
- Finite inspectional resources limit the number of inspections

OSI's Pre-Approval Inspection Planning

- NDA/BLA submissions frequently do not contain all information needed to support OSI's pre-approval inspection planning
  - Selecting sites for inspection in collaboration with OND
  - Generating inspectional assignments
  - Generating background packages that Office of Regulatory Affairs (ORA) investigators need to conduct inspections.

- OSI historically requested information directly from sponsors or through OND Regulatory Project Managers (RPMs) once applications had been submitted (i.e. on the "clock").

Pre-NDA/Pre-BLA Meetings Request

- In 2010, OSI developed information requests for items to be provided in the original NDA/BLA

  Goals

  - Reduce on the clock information requests to obtain necessary information
  - Simplify process and expedite inspection conduct

- Information request provided to sponsors during Pre-NDA/Pre-BLA meetings/process
  - Discussed in OSI Webinar (October 2012)
  - http://www.fdanews.com/ext/files/Conference/FIS11Presentations/MeekerOConnell-FDANews%20Inspection%20Summit%20version%2021sep2011.pdf

- Generally has not been a need for additional information requests when Applicants provide responses consistent in content and format with OSI information requests.

eSubmissions and BIMO Inspections

PART I — Tabular Listings of Site Information

- Tabular data for all sites in the study (pdf)
- Protocols and Annotated CRFs for each study (pdf)

PART II — Line Listing by Site

- Subject data listings organized by site for each study (pdf)

PART III — Site-Level Data Set

- Voluntary site level summary data for site selection tool across all pivotal studies (xpt)

Part III: Site Level Dataset

- Information Requested
  - Site Level Dataset for CDER Inspection Site Selection Tool.
- Reason for Request for Voluntary Submission
  - The CDER Inspection Site Selection Tool is being developed by CDER to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
- Comment
  - This is a voluntary submission for a single clinical site dataset (SAS transport file).

Part III – Draft Guidance Published

- Providing Submissions in Electronic Format — Summary Level Clinical Site Data for CDER's Inspection Planning
- Industry concerns with guidance referencing "submissions in electronic format"
  - Plan to change in final version
- Publication Date: Wednesday, December 19, 2012
- Comment Period Closed: Feb 19, 2013 11:59 PM ET
  - Comments Received
  - Received multiple direct inquiries
- Next Step: Comments review and re-drafting

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CDER Inspection Site Selection Tool

Objectives:

- Develop a tool to support prioritization of clinical trial sites for inspection.
- Define a multi-decision approach to score clinical site/investigator based on risk-based multi-attribute algorithm.

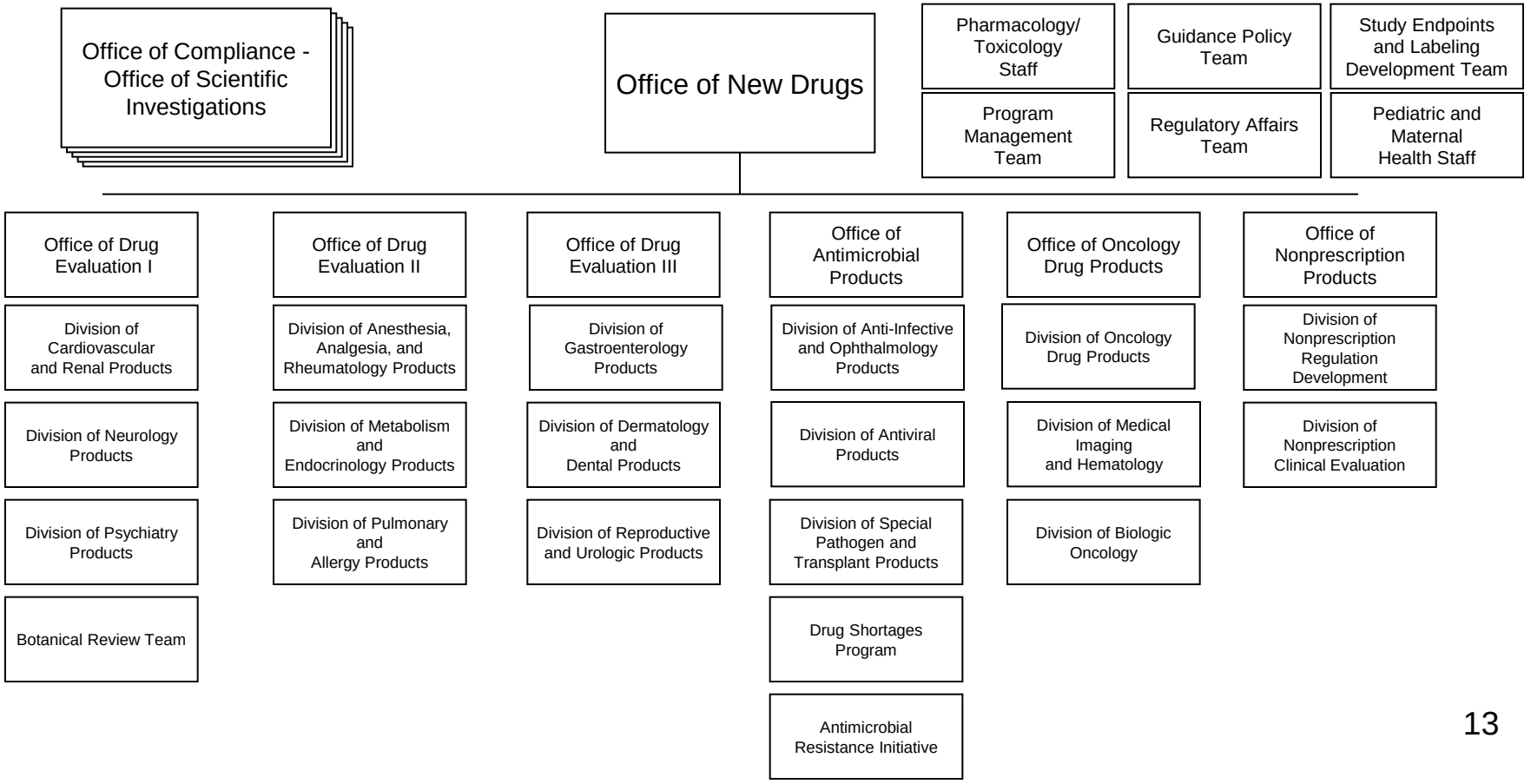
Goals:

- Develop a more consistent, science-based approach to selection of clinical sites for inspection.
- Enable deployment of limited resources towards sites that pose the potentially greatest risk to public health
- Significantly reduce time and effort required to select sites

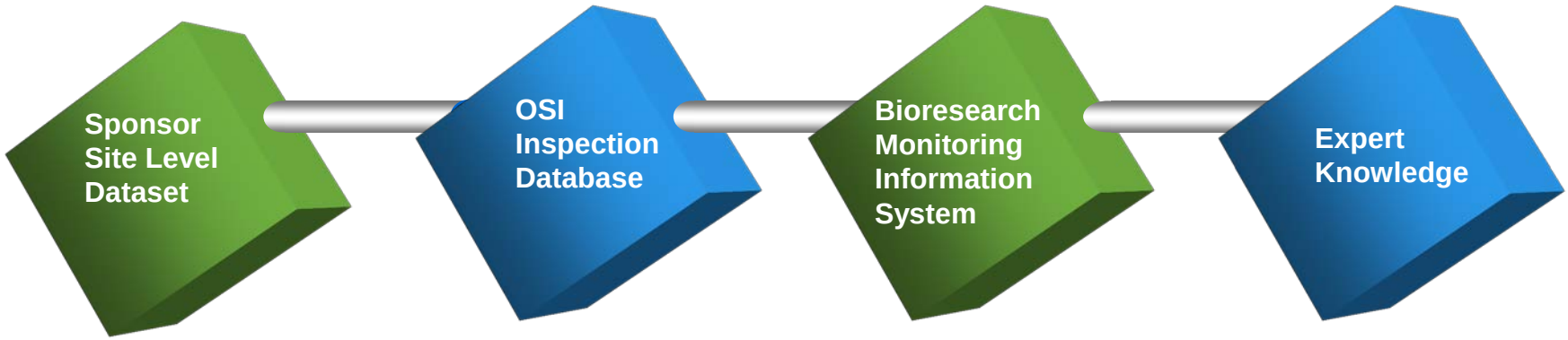
Collaborative Effort within CDER's

Office of Compliance, Office of New Drugs, and Office of Biostatistics

Office of New Drugs Organization Chart



CDER Inspection Site Selection Tool Data Sources



- Tool uses voluntarily submitted site-level summary dataset
- Dataset is formatted to run in the tool.
- Draft industry guidance is under development.

- CDER/OC/OSI Internal Database

Example Data
- Inspection Classification
- BIMO Program
- Inspection Start/End Day
- Time Since Last Inspection

- Historical Information identifying CI's participation in the conduct of FDA regulated research.

Example Data
- # of INDs

- OND, OSI, Biostats Reviewers (etc) expert input and judgment.

Example Data
- Evaluation of data quality concerns
- Evaluation of data consistency

Model Attributes

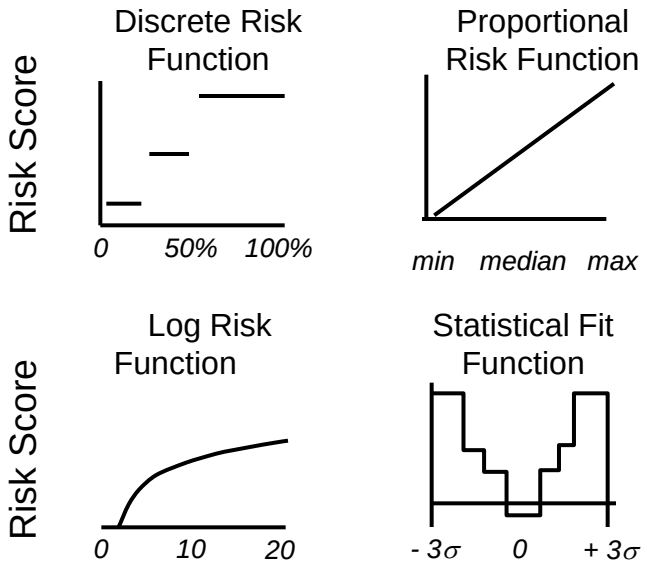
Three levels of risk attributes

- Application level
  - Submission type, Population Vulnerability, Severity of disease, Target population size, Impact of Indication
- Study level
  - Pivotal Status, Trial Design Type, Geography of Trial
- Clinical Site level
  - Enrollment, Site Specific Efficacy, Protocol Deviations, AEs, SAEs, Percentage of Subject Deaths, Enroll/Screen Percentage, Subject Discontinuations, Financial Disclosure (FD).
  - Clinical Investigator Complaints, Inspection History

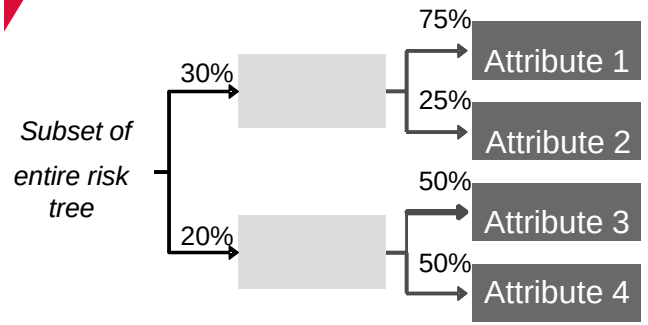
Input data is processed with a decision analysis algorithm

1 Attribute Raw Values

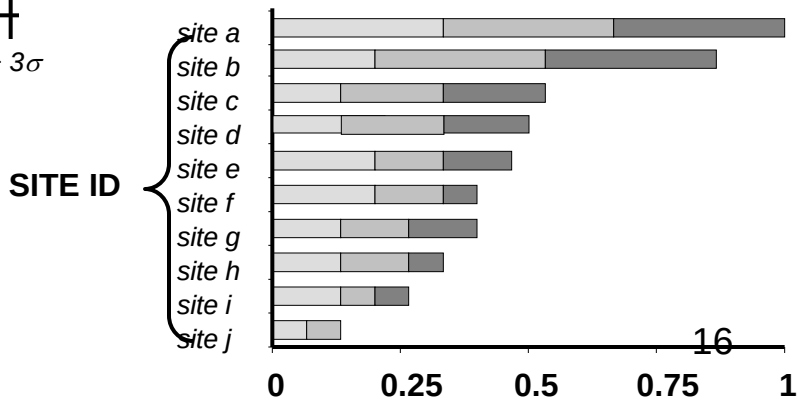
2 Risk Functions applied to Attribute Values



3 Hierarchical Weighting Schema applied



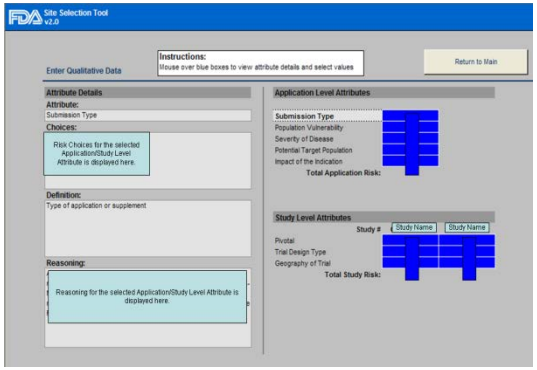
4 Final Risk Score for each site



*** Information shown on this slide are example of the risk function methodologies utilized but does not represent the actual algorithm values**

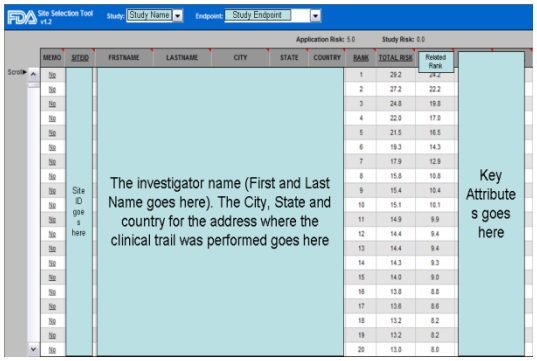
The CDER Inspection Site Selection Tool supports site selection through a series of dashboards and automated generation of forms

1 Enter Qualitative Attributes



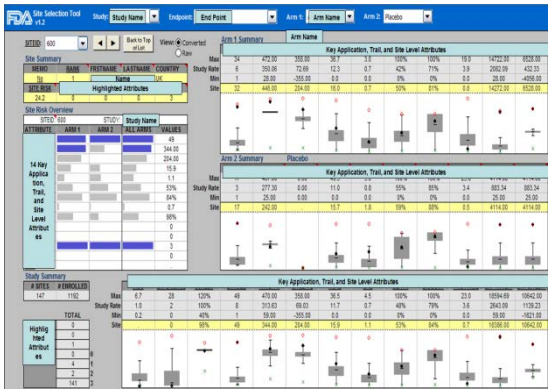
OND and OSI reviewers assign Study & Application level risk

2 View High-level Outputs



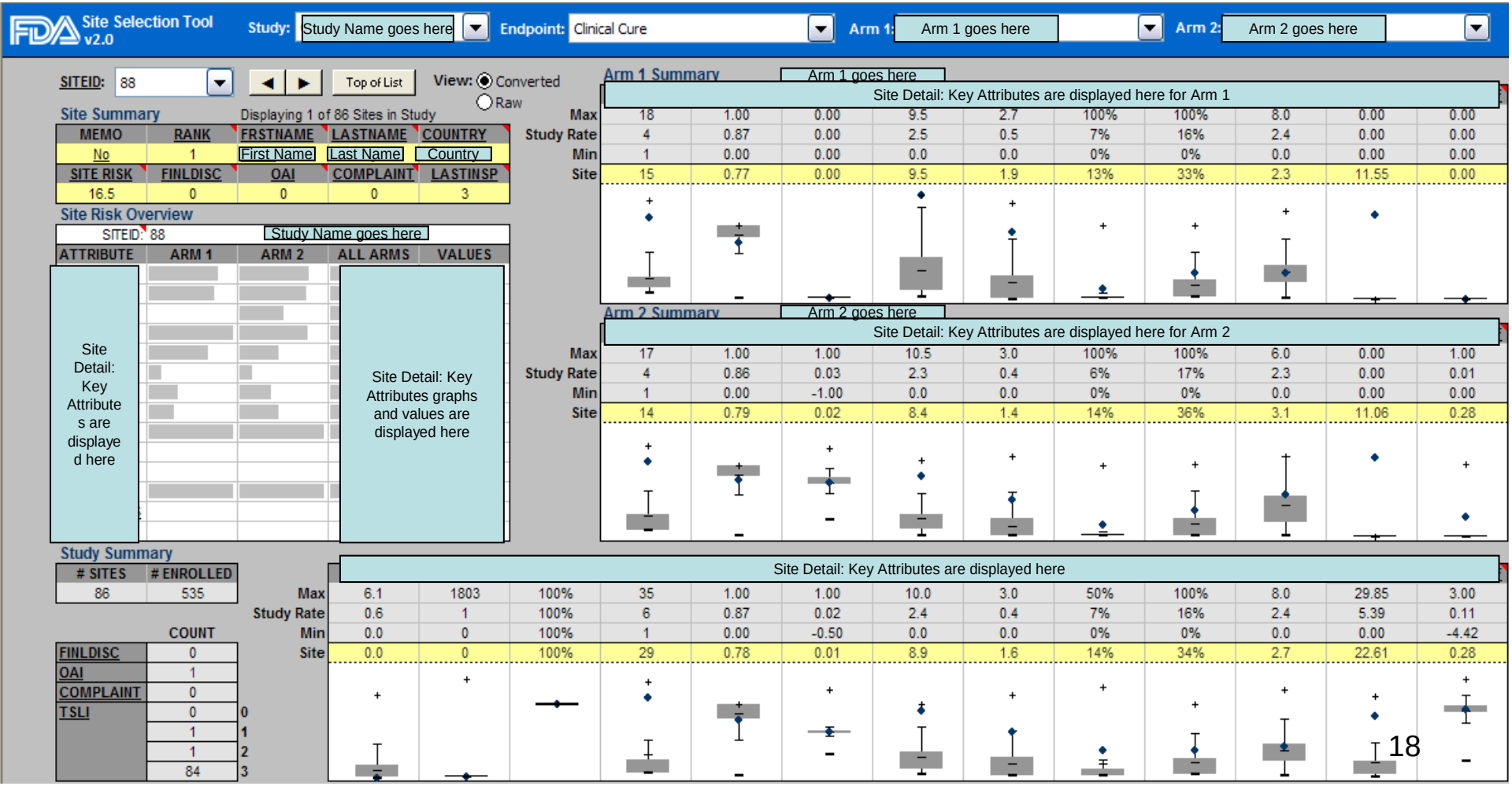
Risk-ranked output of site with ability to assign site for inspection & see further details

3 View Detailed Site Outputs

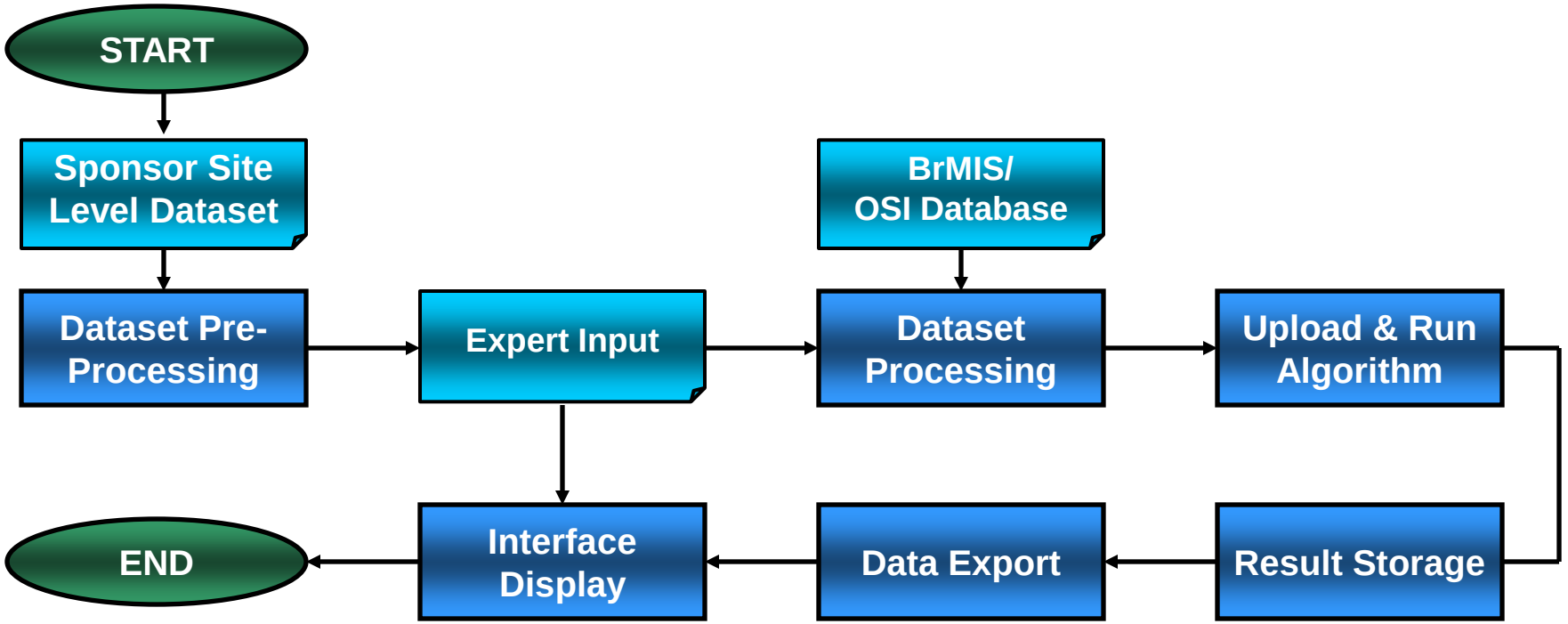


Site-level details w/ comparative analysis among treatment arms and other sites in study

Example - Site Detail Tab



Site-Level Dataset Review & Integration Process



FDA data review and integration process consist of:

- Automated process to ensure appropriate structure and quality of the data.
  - Data Processing Step
- Manual review to evaluate other data quality concerns.
  - Data Pre-Processing and Interface Display Steps

Advantages and Considerations

- Ranking of sites provides a framework for site selection
- Assembles site characteristics in one tool
- Provides standard data exploration methodology
- Improves data analysis time
- Automated documentation and form generation
- The tool gives the user the ability to choose sites based on risk scores and other considerations.
  - Data Irregularities
  - Outliers analysis with filters
  - Inspection history and Investigator experience
  - Clinical investigator cross-study analysis
  - Regional and country-specific summary
  - Site Level Details
  - Comparison of Treatment Arms
  - Raw data vs. converted data
  - Easy Navigation and functionalities
    - Study-to-study, endpoint-to-endpoint, data format, direct link of specific outlier to site detail, etc.

Common Questions

- Updating of Clinical Investigator's Information (e.g. address, phone, e-mail).
  - Use the most up-to-date information available to applicant.
  - Voluntary dataset can not be processed without the CI information
    - Needed for matching to other data sources.
- The Treatment and Site-Specific Efficacy Effect Size Standard Deviation appear to be variance.
  - The table is provided as an example and was not meant to represent actual standard deviation.
  - Use standard statistical software or technique to calculate the standard deviations
- Financial Disclosure and Maximum Financial Disclosure Amount
  - Include financial disclosure information when applicable and -1 when unable to obtain.

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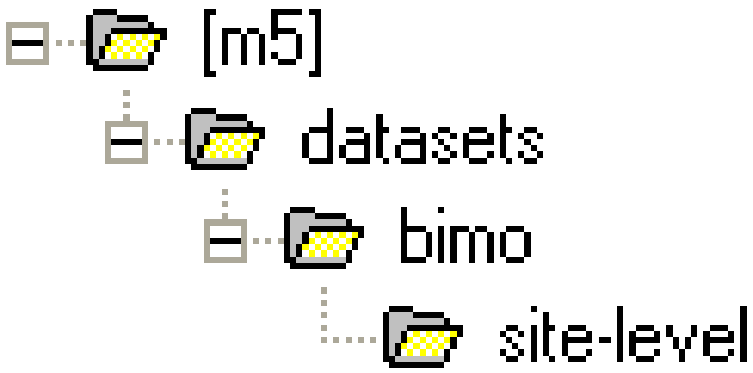
Data for OSI in Module 5 of eCTD

- Items I and II need a Study Tagging File (STF) for each study that data is being submitted for
  - Leaf titles for should be “BIMO [study ID].”
- Item III needs an STF for site-level data across studies and should be placed in Module 5.3.5.4, Other Study reports and related information.
  - The leaf title for the site-level dataset should be “bimo” and the filename should be “clinsite.xpt.”

OSI Pre-NDA Request Item	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line Listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

Location of OSI data in eSubmissions

- Items I and II files should be located in their study folders
- Item III site-level dataset should be located in the M5 folder as follows:



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Future Goals

- Request updates to CDISC to include variables not currently present in SDTM (PhUSE working group gap analysis/recommendations nearing completion)
- HLA7 Pilot – Potential in future for direct pull of CI address and contact information
- Begin to develop methods to pull site data for those variables available at patient level in SDTM format
- Enhanced statistical methods to detect data irregularities and outliers at the site-level
- Ongoing development of learning algorithm so risk attributes and weights will evolve over time with a greater understanding of risk based on actual inspection results

General Comments on OSI Requests

- OSI will continue to participate in pre-NDA/BLA meetings with Applicants to discuss and agree to information necessary for pre-approval inspection planning for GCP inspections.

- If there are questions related to the format or content of items contained in OSI's Pre-NDA/BLA information request:
  - Request clarification at Pre-NDA/BLA meeting.
  - Send requests for clarifications to the OND Regulatory Project Manager; they will be forwarded to OSI. Responses are generally turned around quickly in writing, or when needed a teleconference can be arranged.

Questions

Acknowledgements

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- Dr. Sean Kassim

- For more information, please contact:

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