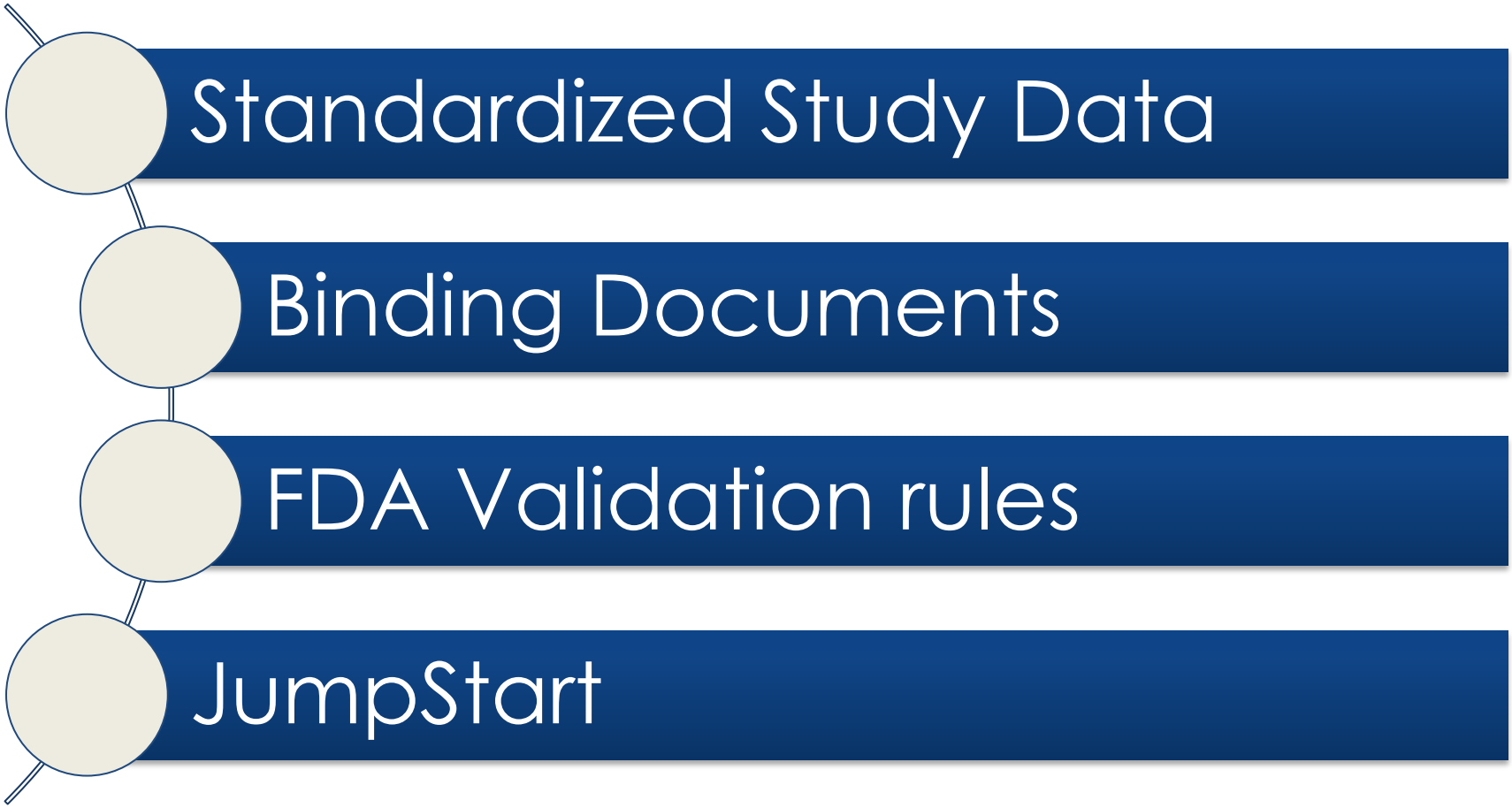
Business & Decision Life Sciences

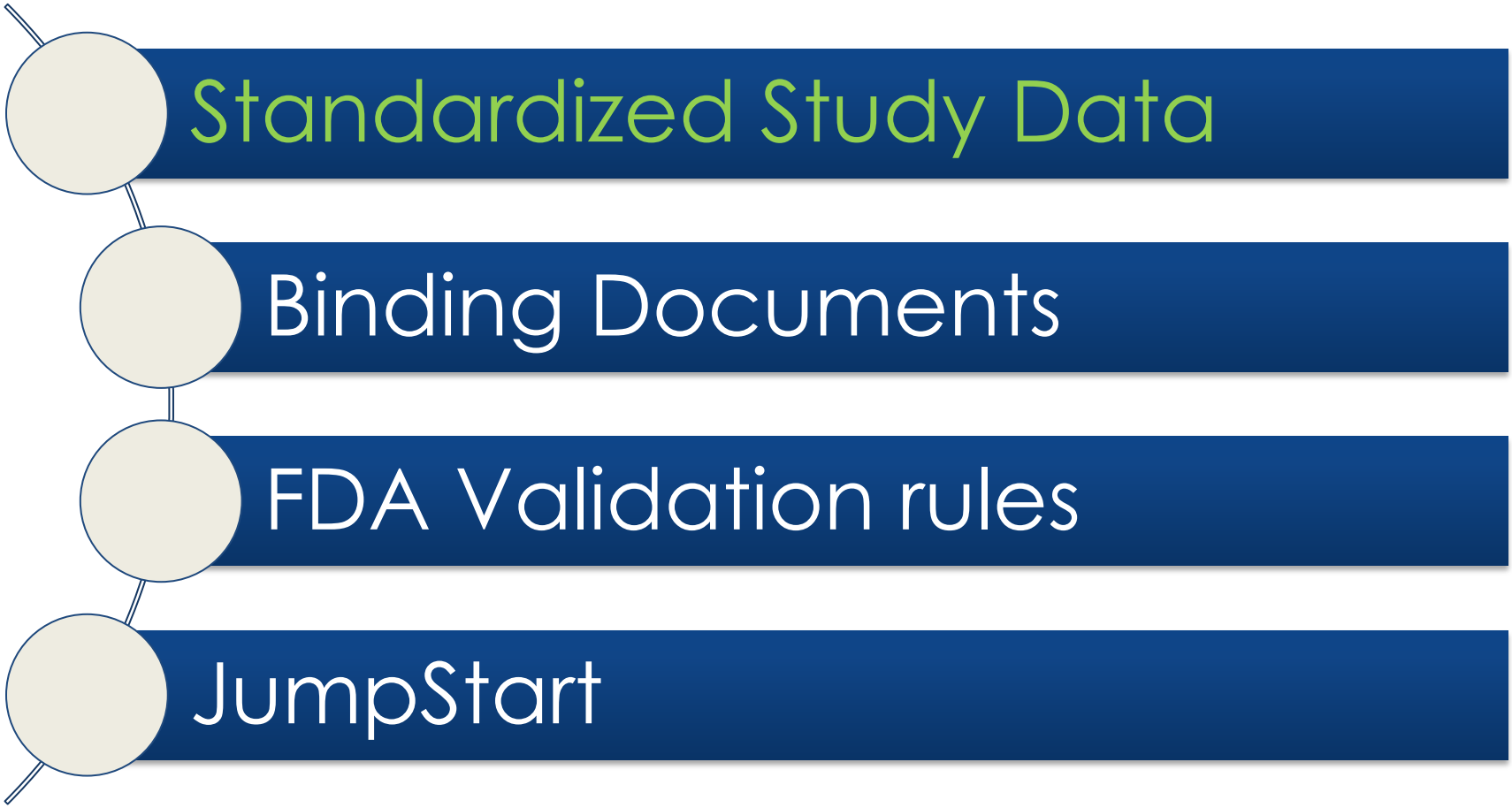
FDA Guidance on Standardized Study Data

Peter Van Reusel / 19 MAY 2015

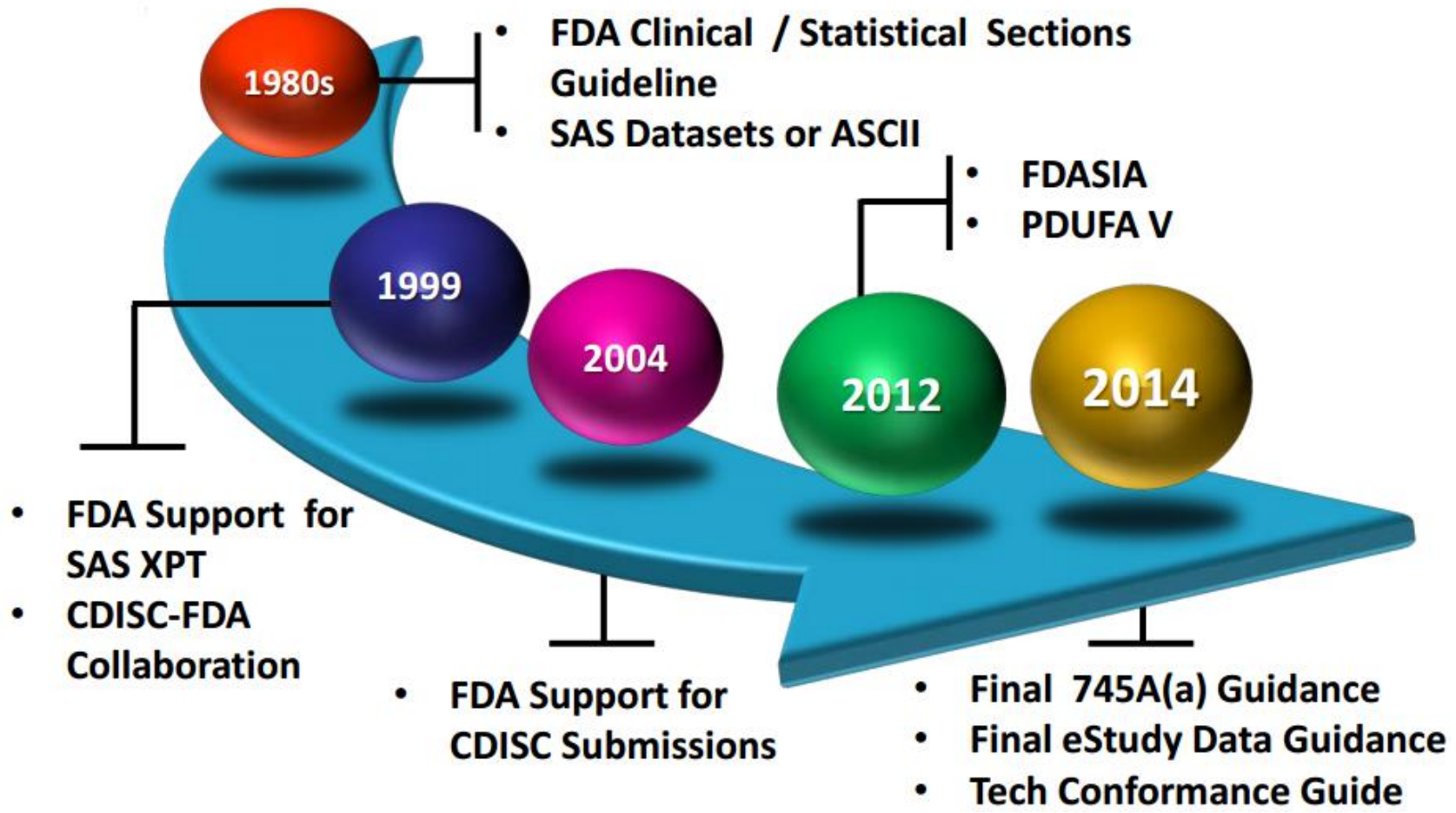
Agenda



Agenda



Path to Electronic Standardized Study data



Source: FDA CDER Webinar – Ron Fitzmartin (FDA)

Value Proposition of Study Data Standards

Source: FDA CDER Webinar – Ron Fitzmartin (FDA)

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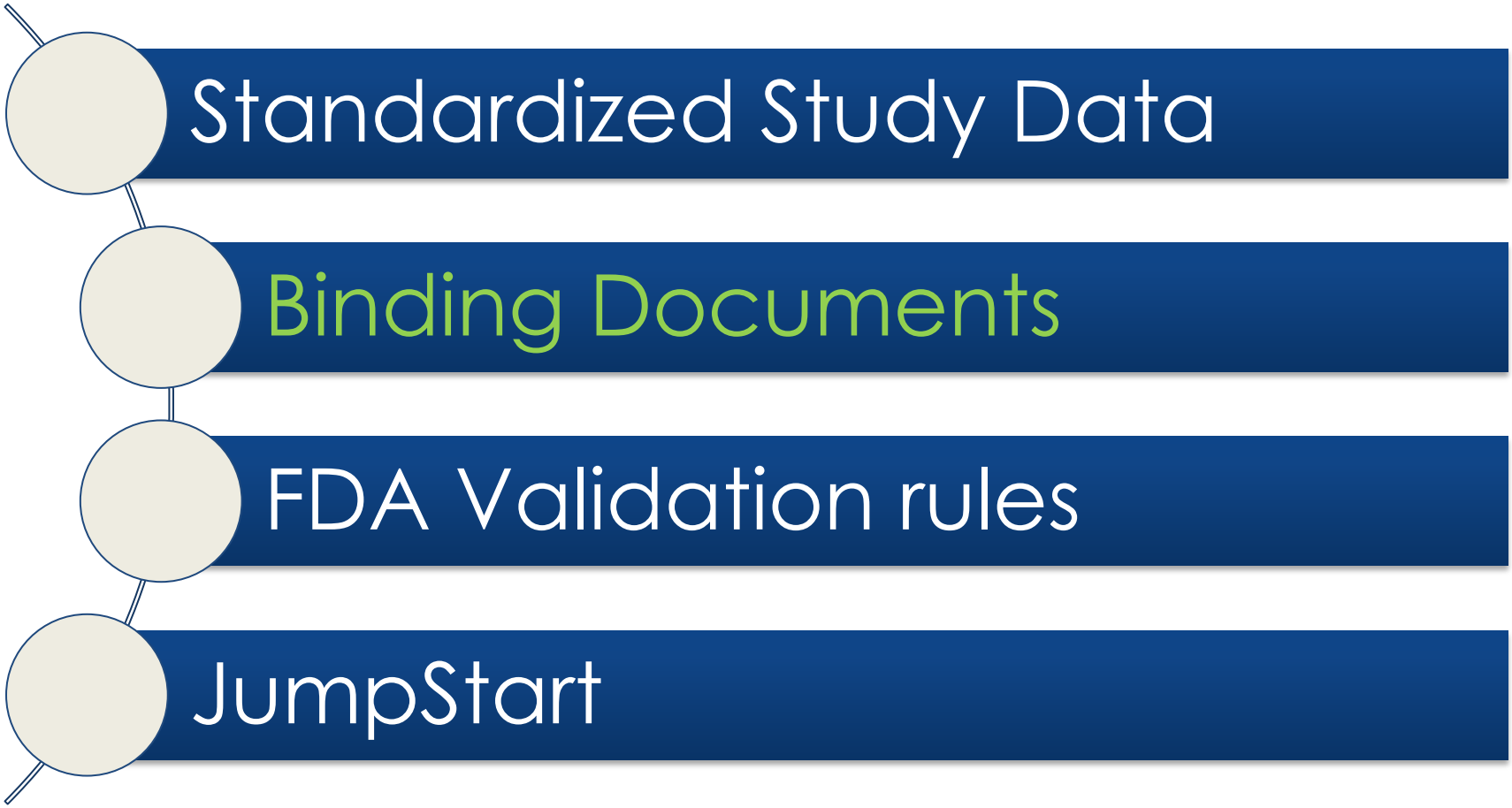
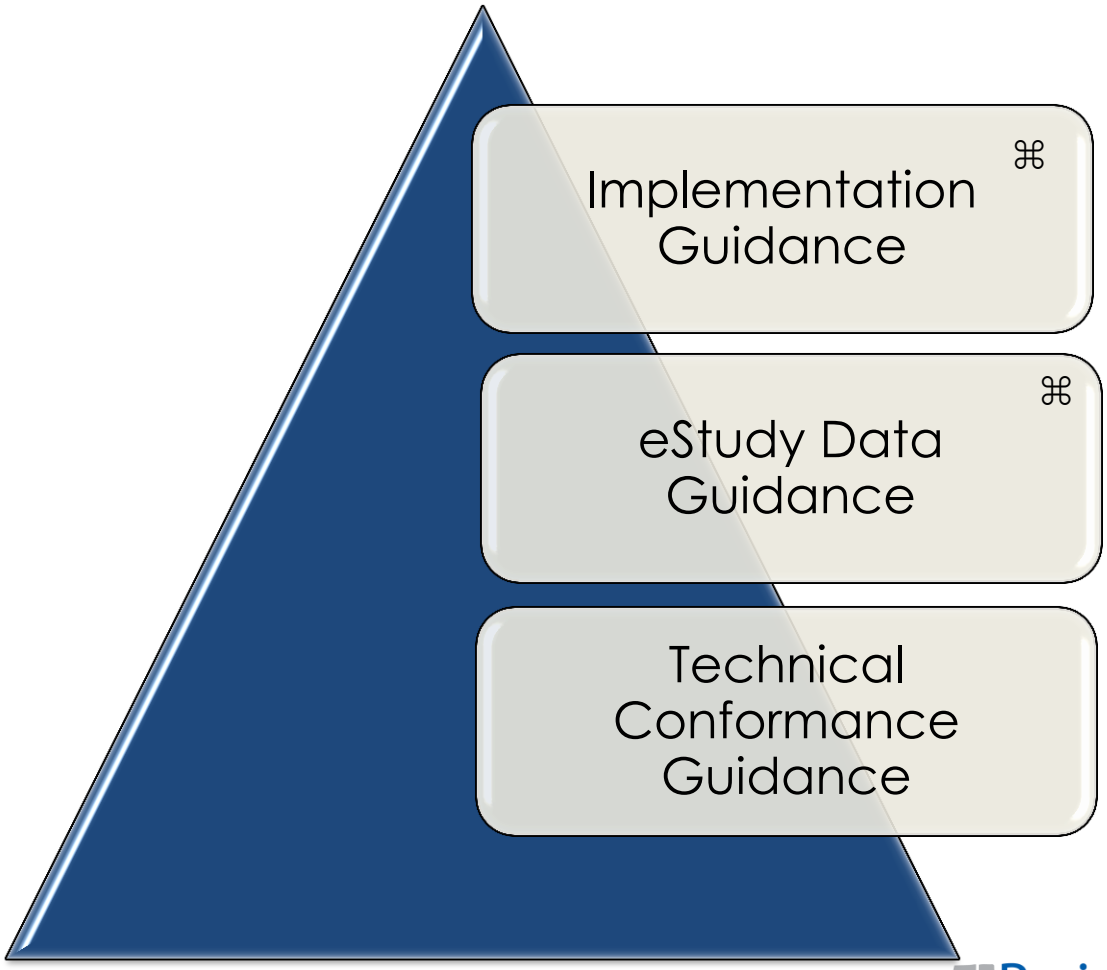


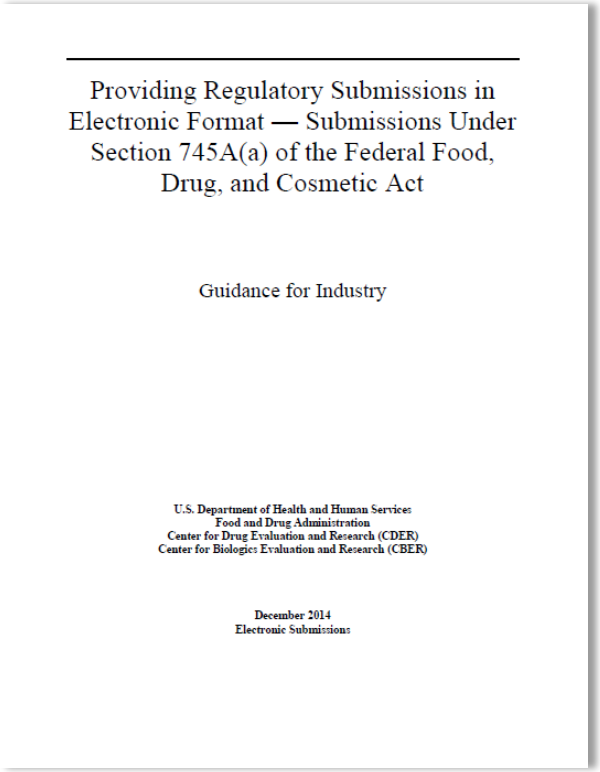
Relationship between documents

Food and Drug Administration Safety and Innovation Act (FDASIA)



⌘: Binding Document

The documents



Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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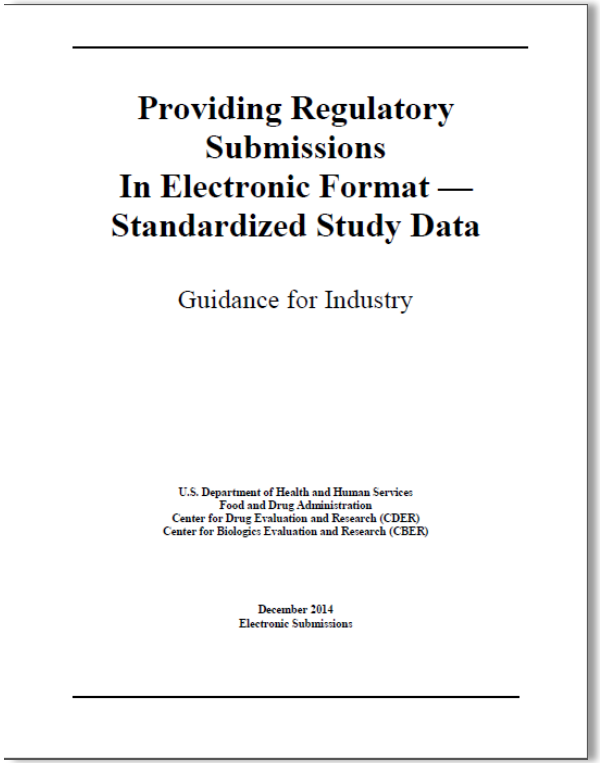
December 2014
Electronic Submissions



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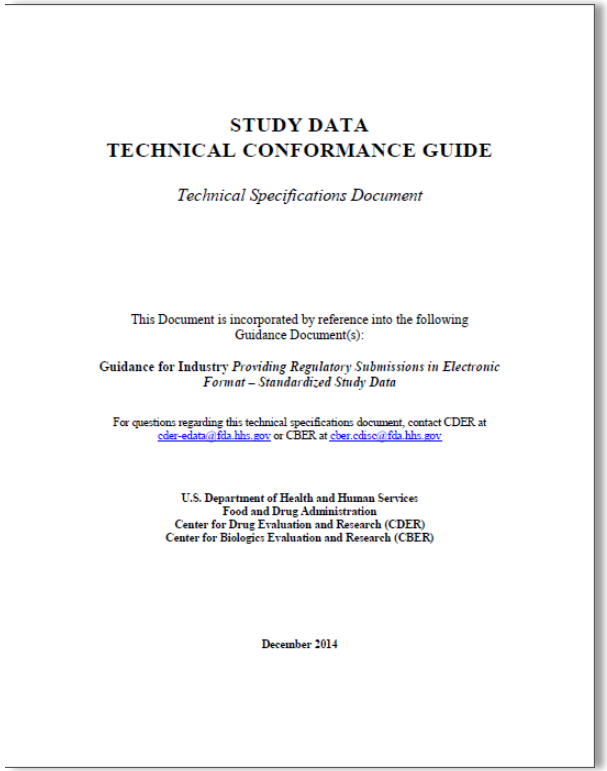

STUDY DATA TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

This Document is incorporated by reference into the following Guidance Document(s):

Guidance for Industry *Providing Regulatory Submissions in Electronic Format – Standardized Study Data*

For questions regarding this technical specifications document, contact CDER at cder-edata@fda.hhs.gov or CBER at cber.edise@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
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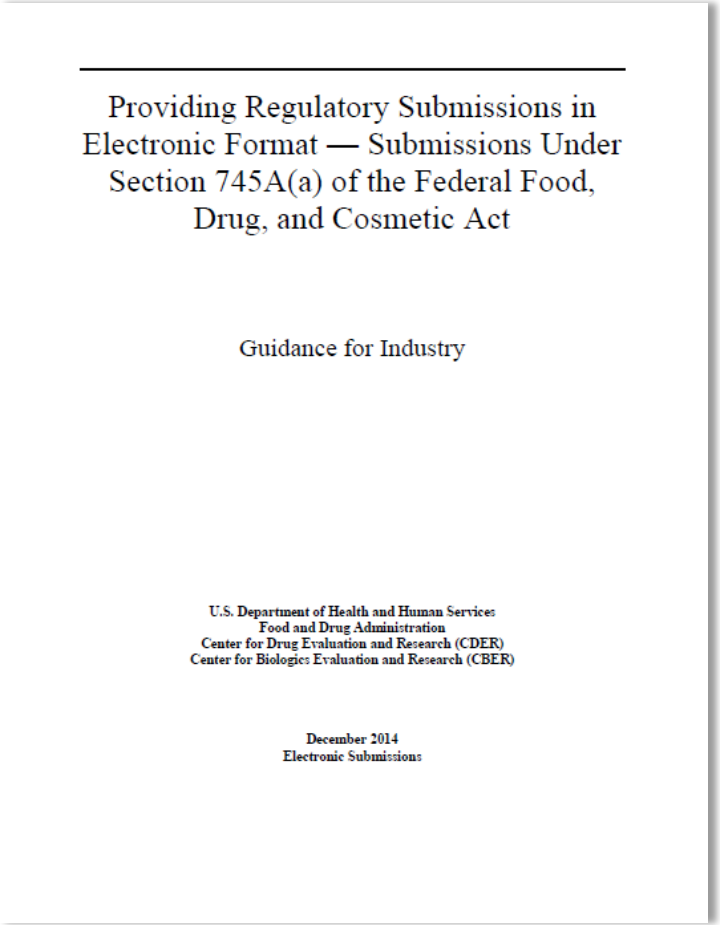
December 2014

BINDING DOCUMENTS

eSubmissions: How?

- Final published December 2014
- Framework for submissions on electronic format
- Applicable to INDs, NDAs, ANDAs, BLAs
- Exemptions can be obtained



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December 2014
Electronic Submissions

Study Data Standards: When?

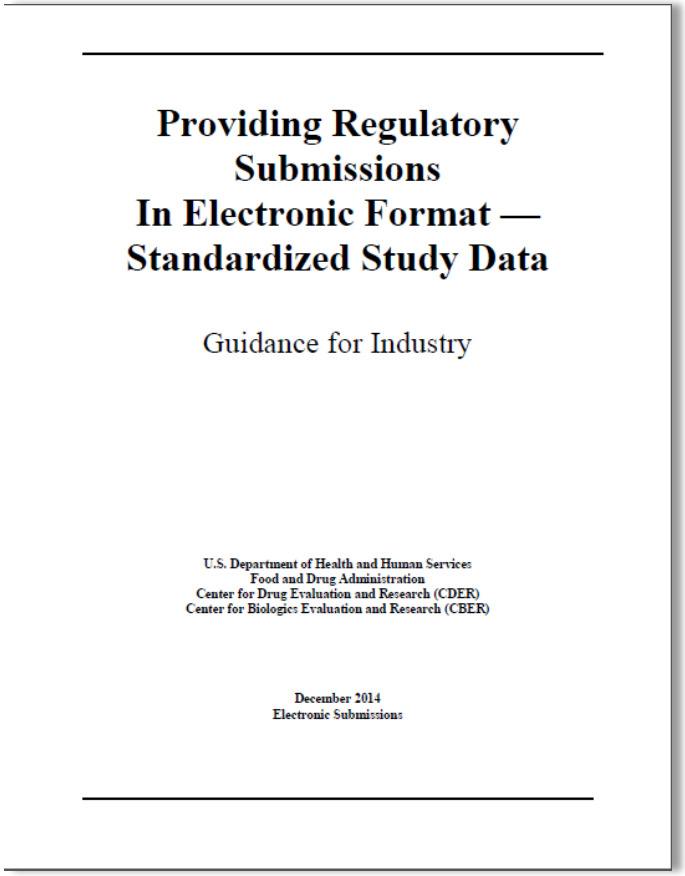
- Final published December 2014

NDAs, ANDAs and certain BLAs

Must follow details in the Data Standards Catalogue for all studies with earliest informed consent date **24 months** after Federal Register notice of final guidance availability

Certain INDs

Must use specified formats in studies with earliest informed consent date **36 months** after Federal Register notice of availability



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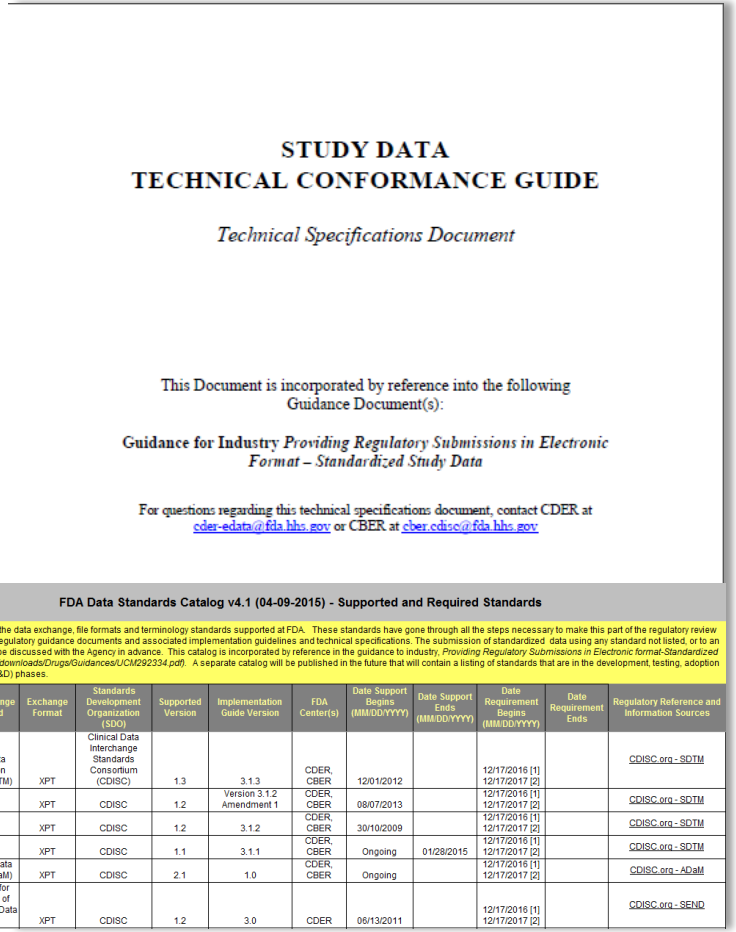
Data Standards Technical Specifications: How?

- Version 2.0 published December 2014
- Specifications on submitting standardized study data
- The document is a mix between the CDER common data issues and new information (e.g. TA standards)
- New release always on 15 March 20xx



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FDA Data Standards Catalog v4.1 (04-09-2015) - Supported and Required Standards

This table contains a listing of the data exchange, file formats and terminology standards supported at FDA. These standards have gone through all the steps necessary to make this part of the regulatory review process, including posting of regulatory guidance documents and associated implementation guidelines and technical specifications. The submission of standardized data using any standard not listed, or to an FDA Center not listed, should be discussed with the Agency in advance. This catalog is incorporated by reference in the guidance to industry, *Providing Regulatory Submissions in Electronic format-Standardized Study Data (http://www.fda.gov/downloads/Drugs/Guidances/UCM292334.pdf)*. A separate catalog will be published in the future that will contain a listing of standards that are in the development, testing, adoption or research & development (R&D) phases.

Use	Data Exchange Standard	Exchange Format	Standards Development Organization (SDO)	Supported Version	Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY)	Date Requirement Ends	Regulatory Reference and Information Sources
Clinical study datasets	Study Data Tabulation Model (SDTM)	XPT	Clinical Data Interchange Standards Consortium (CDISC)	1.3	3.1.3	CDER, CBER	12/01/2012		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.2	Version 3.1.2 Amendment 1	CDER, CBER	08/07/2013		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.2	3.1.2	CDER, CBER	30/10/2009		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.1	3.1.1	CDER, CBER	Ongoing	01/28/2015	12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	Analysis Data Model (ADaM)	XPT	CDISC	2.1	1.0	CDER, CBER	Ongoing		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - ADaM
Animal study datasets	Standard for Exchange of Nonclinical Data (SEND)	XPT	CDISC	1.2	3.0	CDER	06/13/2011		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SEND

What Study Data Standards will be Required? (2)

- FDA Data Standards Catalogue v4.1
  - http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

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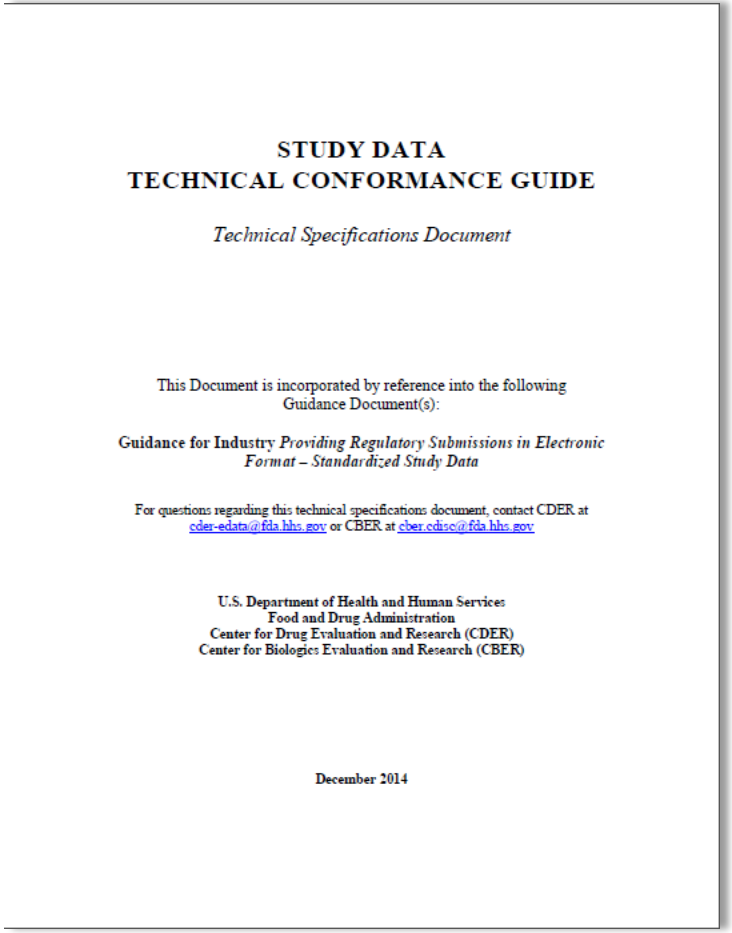
Data Standards Technical Specifications: Content

- Sections 1 to 8 provide an overview of the following:
  - Introduction
  - Planning and Providing Standardized Study Data
  - Exchange Format – Electronic Submissions
  - Study Data Submission Format: Clinical and Nonclinical
  - Therapeutic Area Standards
  - Terminology
  - Electronic Submission Format
  - Data Validation and Traceability



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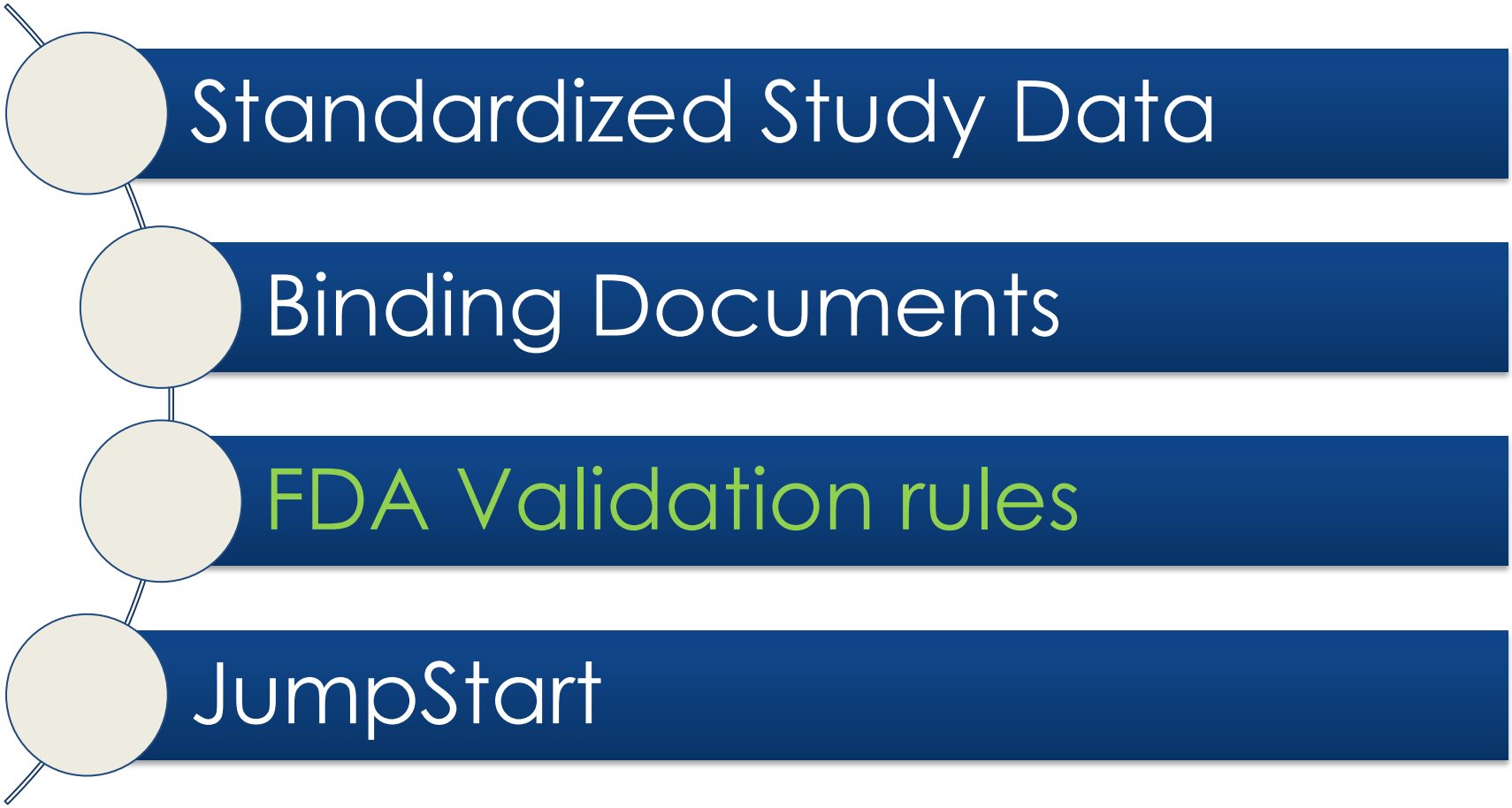


FDA Validation Rules (1)

- Purpose = **Communicate** FDA requirements to the industry and **help** the industry to implement high quality data
- Based on OpenCDISC checks
- Additional rules
- Changes in Severity message

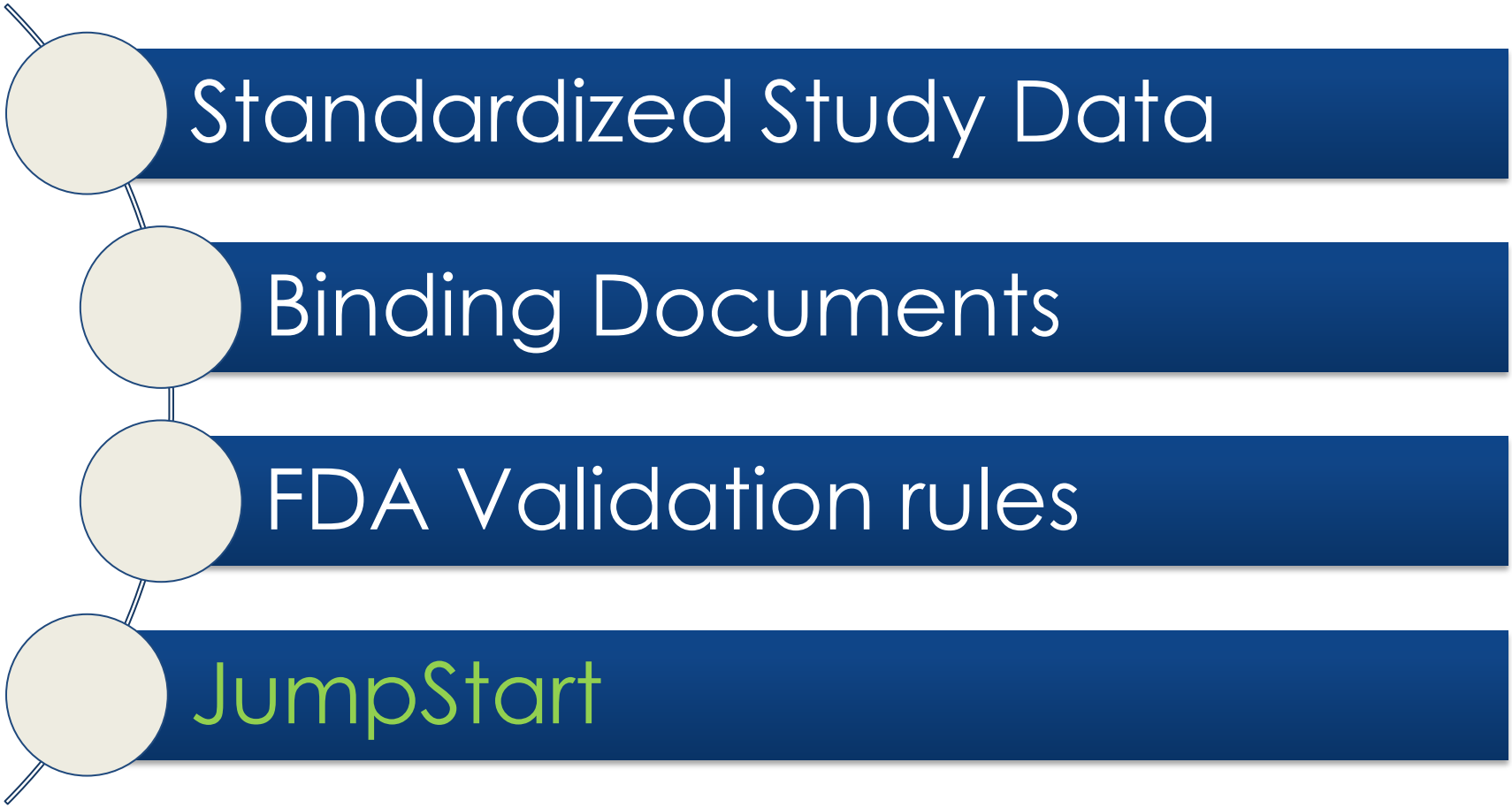
FDA Validation Rules (2)

FDA Rule ID	MESSAGE	DESCRIPTION	DOMAINS	SEVERITY	3.1.1	3.1.2	3.1.3 (3.1.2 A1
FDAC001	Missing DM dataset	Demographics (DM) dataset must be included in every submission	DM	Error	X	X	X
FDAC002	Missing TS dataset	Trial Summary (TS) dataset must be included in every submission	TS	Error	X	X	X
FDAC003	Missing DS dataset	Disposition (DS) dataset should be included in every submission	DS	Warning	X	X	X
FDAC004	Missing EX dataset	Exposure (EX) dataset should be included in every submission	EX	Warning	X	X	X
FDAC005	Missing AE dataset	Adverse Events (AE) dataset should be included in every submission	AE	Warning	X	X	X
FDAC006	Missing LB dataset	Lab Test Results (LB) dataset should be included in every submission	LB	Warning	X	X	X
FDAC007	Missing VS dataset	Vital Signs (VS) dataset should be included in every submission	VS	Warning	X	X	X
FDAC008	Missing SE dataset	Subject Elements (SE) dataset should be included in every submission	SE	Warning	X	X	X
FDAC009	Missing TA dataset	Trial Arms (TA) dataset should be included in every submission	TA	Warning	X	X	X
FDAC010	Missing TE dataset	Trial Elements (TE) dataset should be included in every submission	TE	Warning	X	X	X
FDAC012	Missing MB dataset, when MS dataset is present	Microbiology Specimen (MB) dataset should be included, when a Microbiology Susceptibility Test (MS) dataset is present	MB	Warning	X	X	X
FDAC013	Incompatible data source	Domain table must have a valid format (e.g., SAS transport (XPORT) v.5 or text-delimited)	ALL	Error	X	X	X
FDAC014	No records in data source	Domain table should have at least one record	ALL	Error	X	X	X
FDAC016	Dataset is greater than 1 GB in size	Large datasets should be split into smaller datasets no larger than 1 GB in size.	ALL	Warning	X	X	X
FDAC017	SDTM Required variable not found	Variables described in SDTM as Required must be included in the dataset	ALL	Error	X	X	X
FDAC018	NULL value in variable marked as Required	Required variables (where Core attribute is 'Req') cannot be NULL for any records	ALL	Error	X	X	X
FDAC020	SDTM Expected variable not found	Variables described in SDTM as Expected should be included in the dataset	ALL	Warning	X	X	X
FDAC021	FDA Expected variable not found	Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH and ELEMENT	ALL	Warning	X	X	X
FDAC022	No Treatment Emergent info for Adverse Event	According to FDA expectations, a treatment-emergent flag should be included in SUPPAE according to SDTM IG v3.1.2 #8.4.3	SUPPAE	Warning	X	X	X
FDAC023	Dataset is not present in define.xml	Datasets included in study data must be described in the data definition document (define.xml)	ALL	Error	X	X	X
FDAC024	Domain referenced in define.xml but dataset is missing	Domains referenced in data definition document (define.xml) should be included in the submission	ALL	Warning	X	X	X

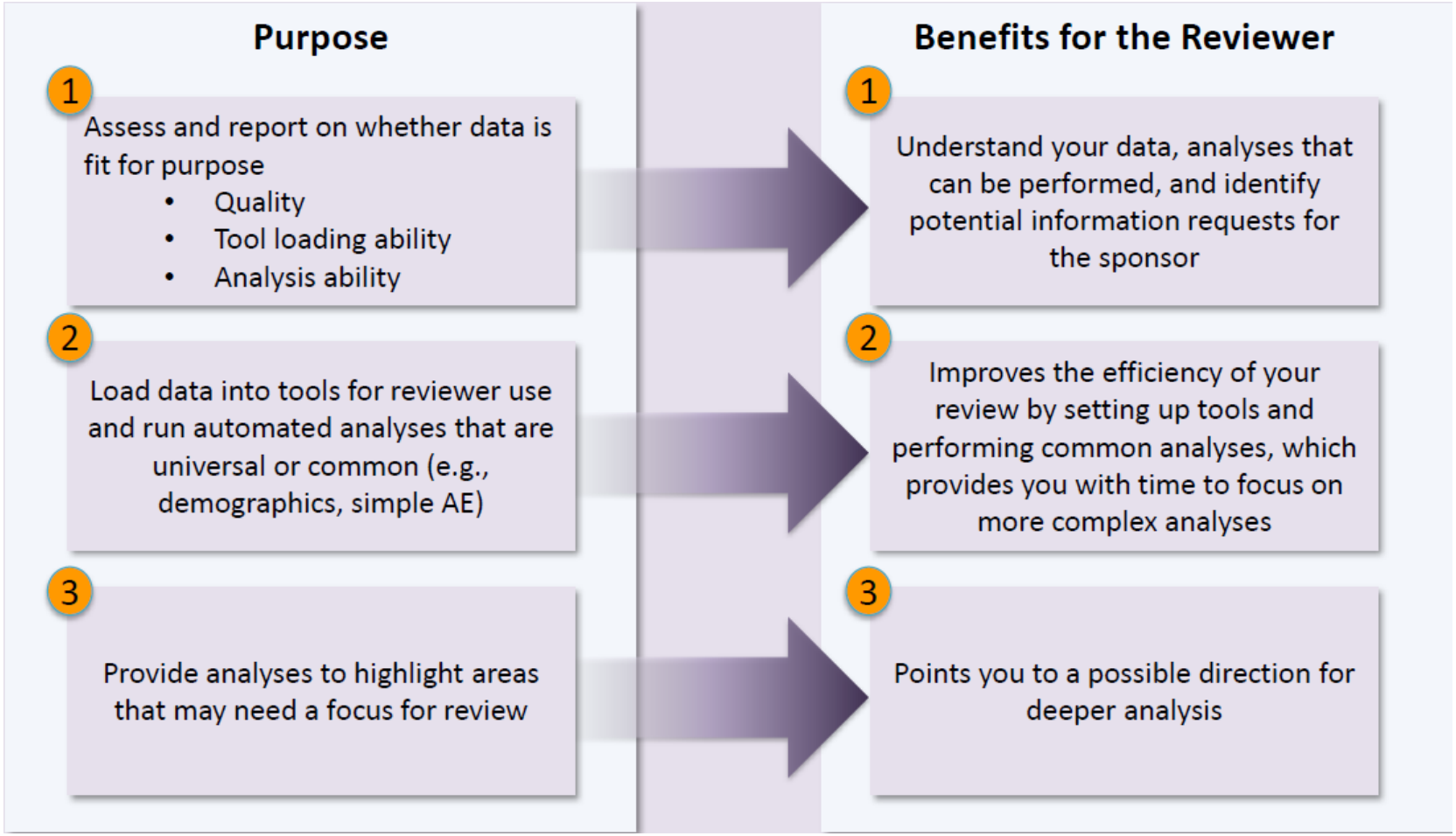
Additional rules

- Checks against MedDRA dictionary
- Validation rules for FDA specific requests
  - Presence of standard domains
  - Presence of permissible variables
  - Dataset size checks
  - Domain TS specific checks (39)

Agenda

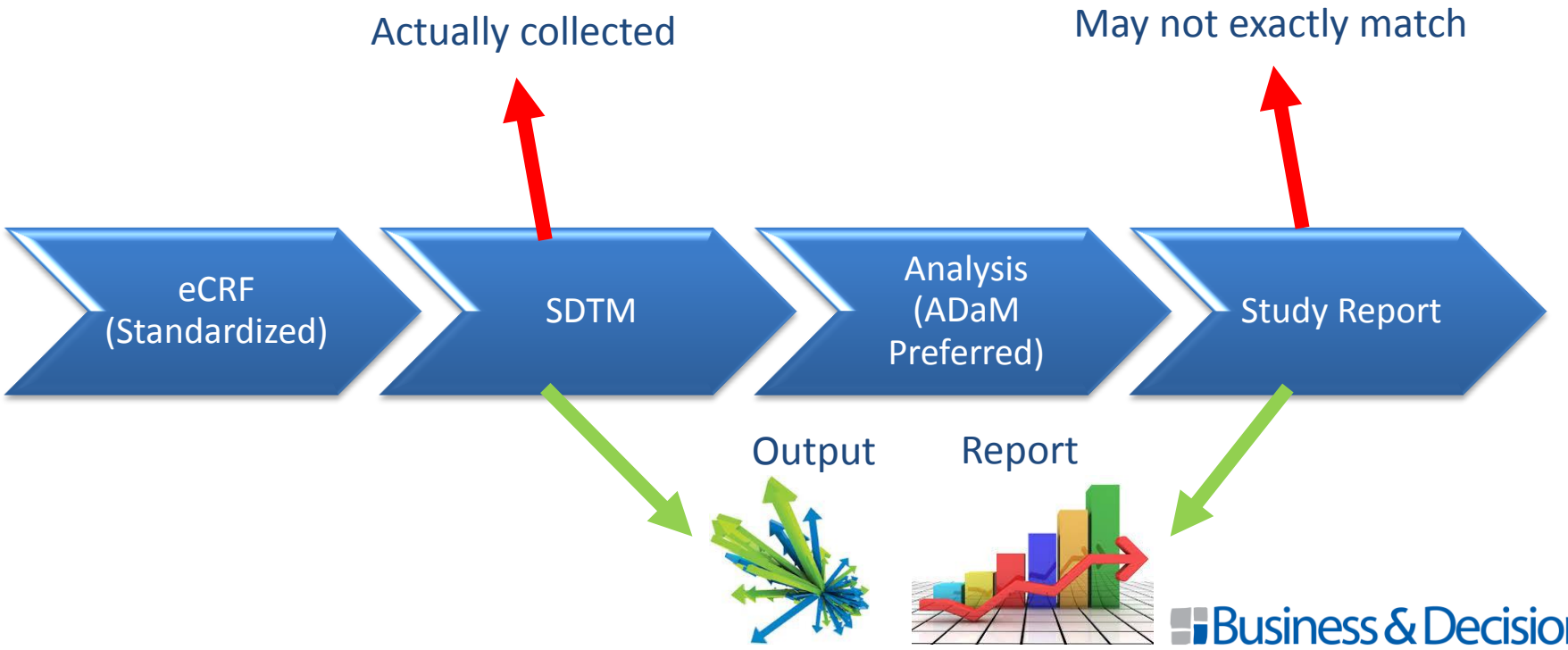


Benefits of JumpStart



JumpStart uses SDTM Tabulations

- JumpStart uses the following domains:
  - Data Fitness → all datasets submitted for a trial
  - Safety Analysis → DM, DS, EX, AE, LB and VS



Data Fitness Findings Flow

Review Questions (1)

- SDRG
  - Were the SDTM datasets used as sources for the analysis datasets?
  - If there are issues with the data, why did the sponsor choose not to fix them?
  - What version of MedDRA/WHODRUG did the sponsor use?
  - Where is the efficacy data located?

SDRG/Define File

- Define File
  - How does the information in the annotated CRFs map to the datasets?
  - Does the sponsor provide an explanation of the codes used?

SDRG/Define File

Review Questions (2)

Supplemental Information

- Supplemental Information
  - What information is available in the supplemental domains?
  - How does the information contained in these domains map to the parent domains?
  - What information from the supplemental domains could be useful for analysis?

Controlled Terminology

- Controlled Terminology
  - How does the sponsor's terminology map to the controlled terminology?
  - Which domains do not use controlled terminology?
  - Did a lack of controlled terminology cause ambiguity in the data?

Review Questions (3)

- Deaths
  - How many deaths occurred during the study?
  - Where is information about deaths located?
  - Was the death information represented consistently across domains?
- Missing Data
  - What data is missing?
  - How will the missing data impact analyses?
  - Are there other variables that can be used in lieu of the missing data?

Deaths

Missing Data

Review Questions (4)

- CDER Common Issues
  - Does the DM domain include start and end dates, an actual arm variable, a death flag, and a date of death variable?
  - Are the domains missing the EPOCH variable?
  - Did the sponsor include the trial summary domains?
  - Does the AE domain include a treatment emergent flag?
- Duplicates
  - Do any of the datasets contain potential duplicate records?
  - How will these duplicates impact analyses?

Review Questions (5)

- Term Matching
  - How can you efficiently review coding quality?
  - Was an adverse event mapped to the appropriate dictionary term?
  - Was the disposition term reported using the appropriate dictionary term?
  - Did the sponsor use the term "Other" appropriately?
- Standard Units
  - Did the sponsor use standard units?
  - Did the sponsor use the same units for each type of test?
  - Did the list of stand units submitted by the sponsor match the data?

Term Matching

Standard Units

Review Questions (6)

- Safety Population

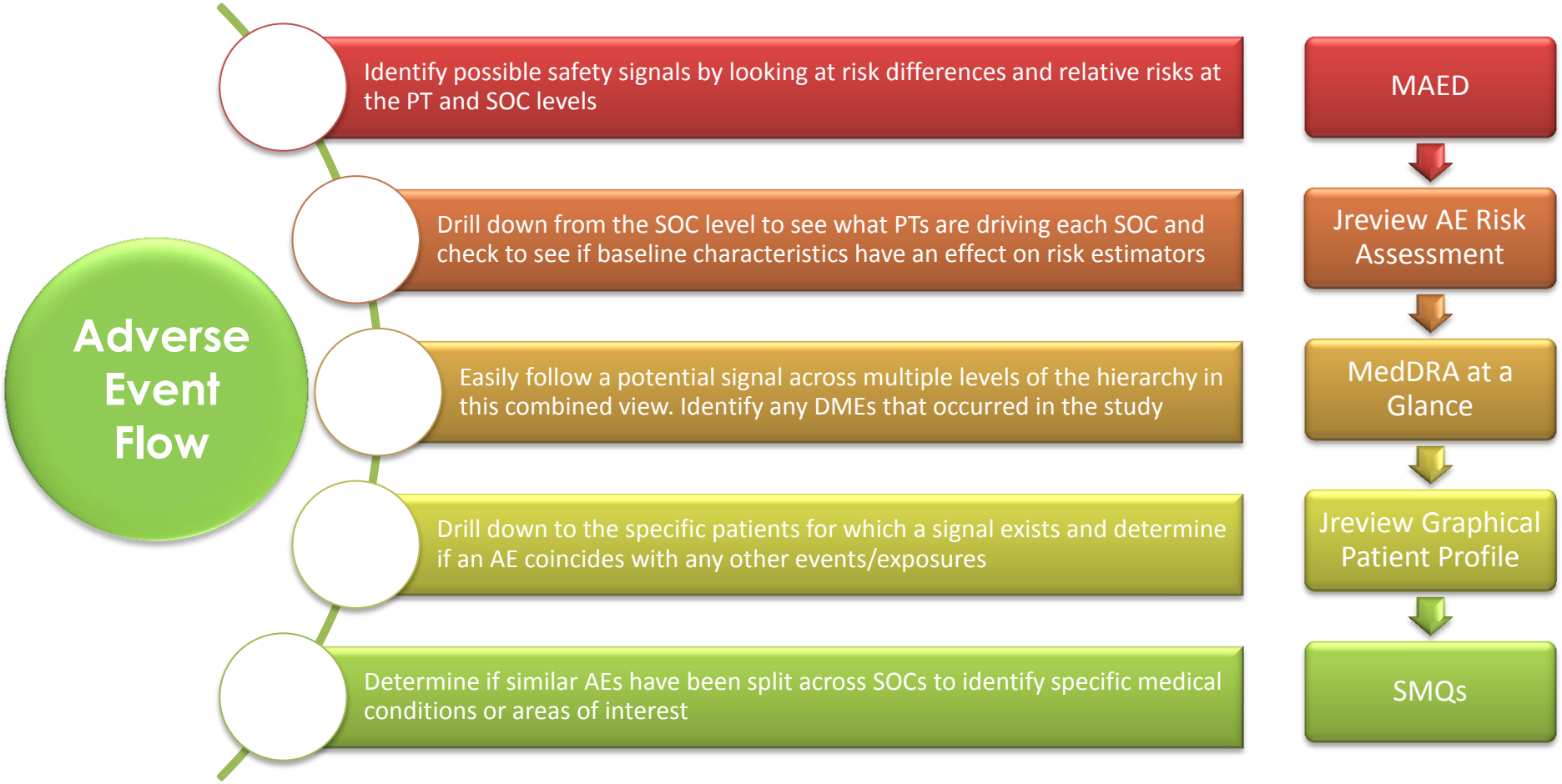
Safety Population

  - Are there population inconsistencies between the SDTM data and the study report?
  - Are there any subjects who were randomized but not treated?
  - Are there any subjects who received a treatment that was different from their planned treatment?
- Race and Ethnicity

Race and Ethnicity

  - How does the sponsor indicate race/ethnicity?
  - Where is the detailed information about race/ethnicity located?
  - Are there any subjects who are missing race or ethnicity data?

Review of the Complementary Capabilities of each AE Analysis



Thank you

London, UK, 19 MAY 2015

Business & Decision
Life Sciences

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