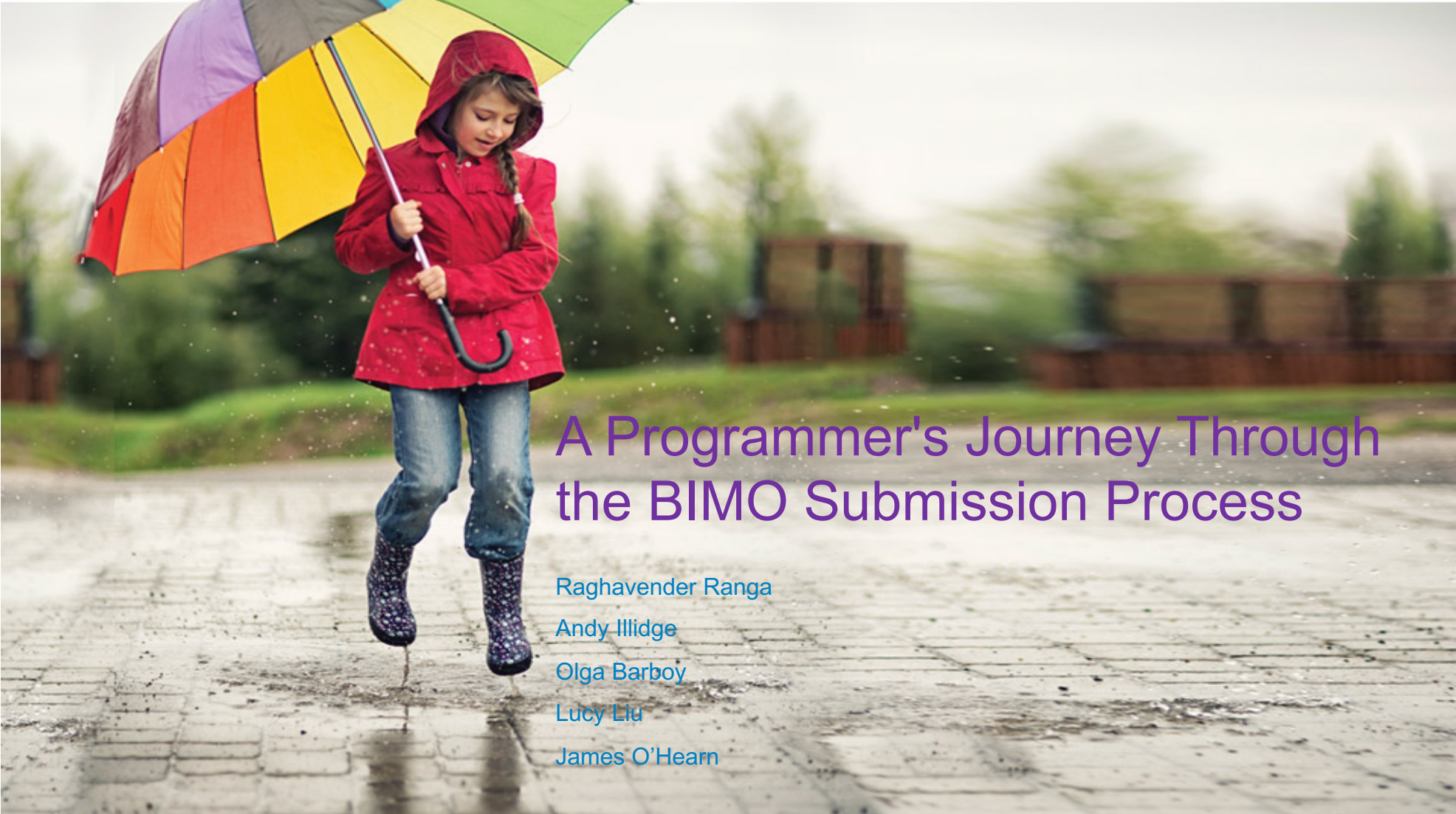




THE SCIENCE *of* POSSIBILITY



A Programmer's Journey Through the BIMO Submission Process

Raghavender Ranga

Andy Illidge

Olga Barboy

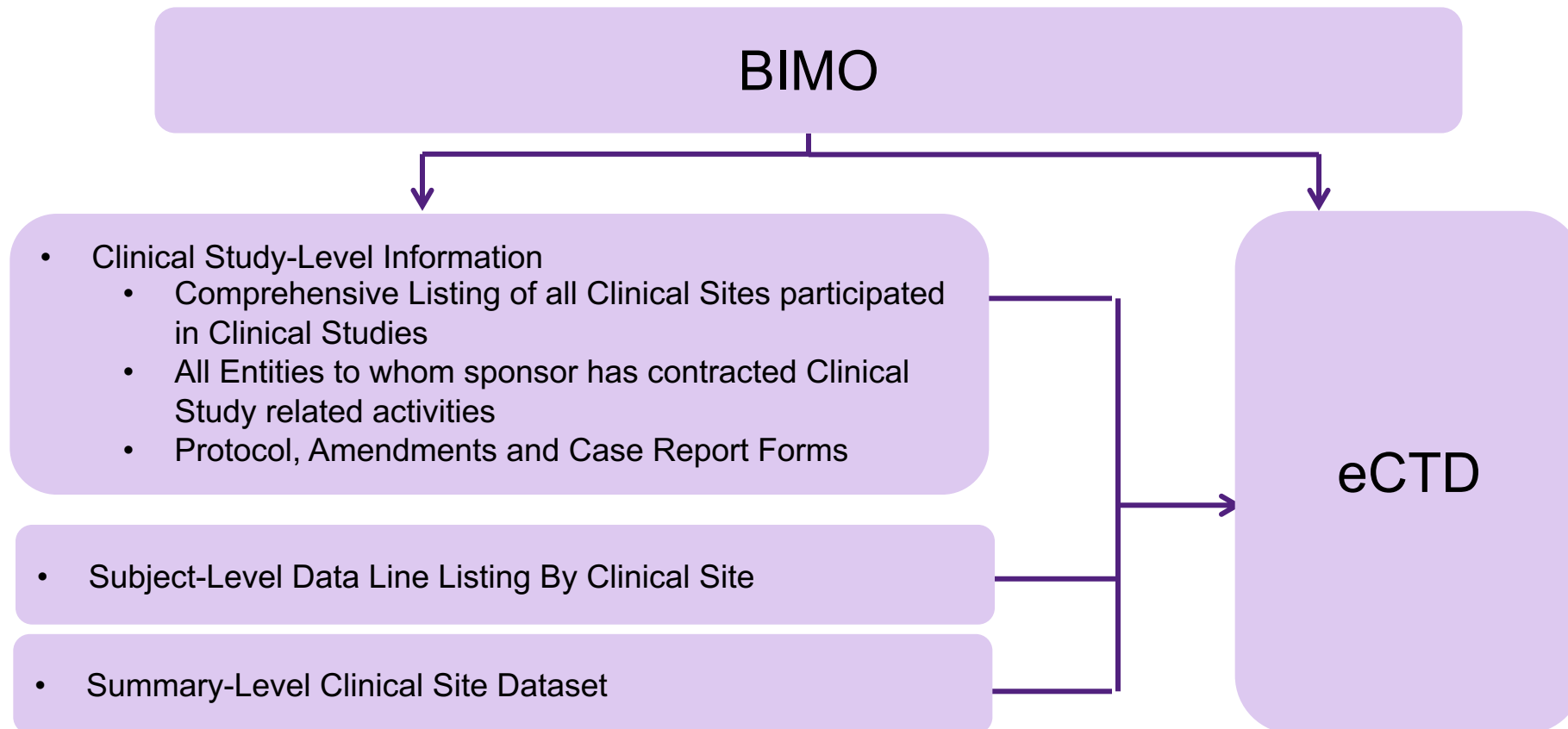
Lucy Liu

James O'Hearn



Background - BIMO

- CDER's OSI responsible for verifying integrity of data
- CDER's inspection planning for FDA's BIMO inspection includes
 - Selection of sites/regulated entities
 - Preparation of memos and packages provided to ORA
- ORA conduct site inspections of clinical investigators, sponsors, CRO, and IRB
- BIMO draft guidance published in 2018
 - Consistent format for submitting data for BIMO inspection
 - Critical to meet PDUFA timeline goals



Implementation

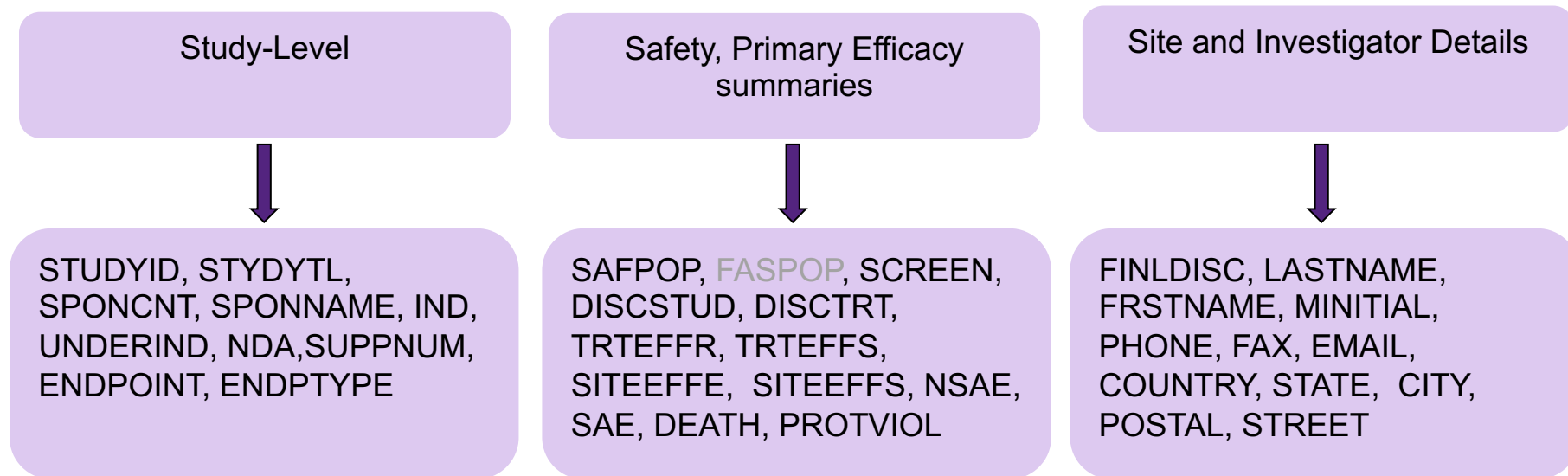
- Identify the BIMO components that are already available
 - Existing CSR listings to be converted into Subject-Level Data Line listings
 - Clinical Study Level Components
 - Clinical Site information
 - Protocol, SAP, CRF
- Development of new components
 - Summary-Level Clinical Site data set
 - Define File
 - BIMO Reviewer Guide
- Collaboration with Clinical Operations and Regulatory Operations

Clinical Study-Level Information

- Listing of Sites participated in Clinical Studies (Appendix in Module 5.3.5.1 of CSR)
 - Site identification number
 - Site address and contact information
 - Name of the clinical investigator
- Sponsor contracted entities (Section 6 of CSR)
- Protocol and all Amendments (Section 16.1.1 of Module 5)
- Case Report Forms (eCTD data package)

Site-Level Dataset

- Data from all pivotal studies
- One record per Pivotal Study per Clinical Site per Treatment arm
- Three category of variables



Programming Considerations

Clinical Sites

- » Subjects transfer between sites
- » Satellite sites
- » Sites with only screen failures
- » Site Investigator changes

Treatment Arm

- » Planned Treatment Arm – Efficacy and Disposition
- » Actual Treatment Arm – Safety

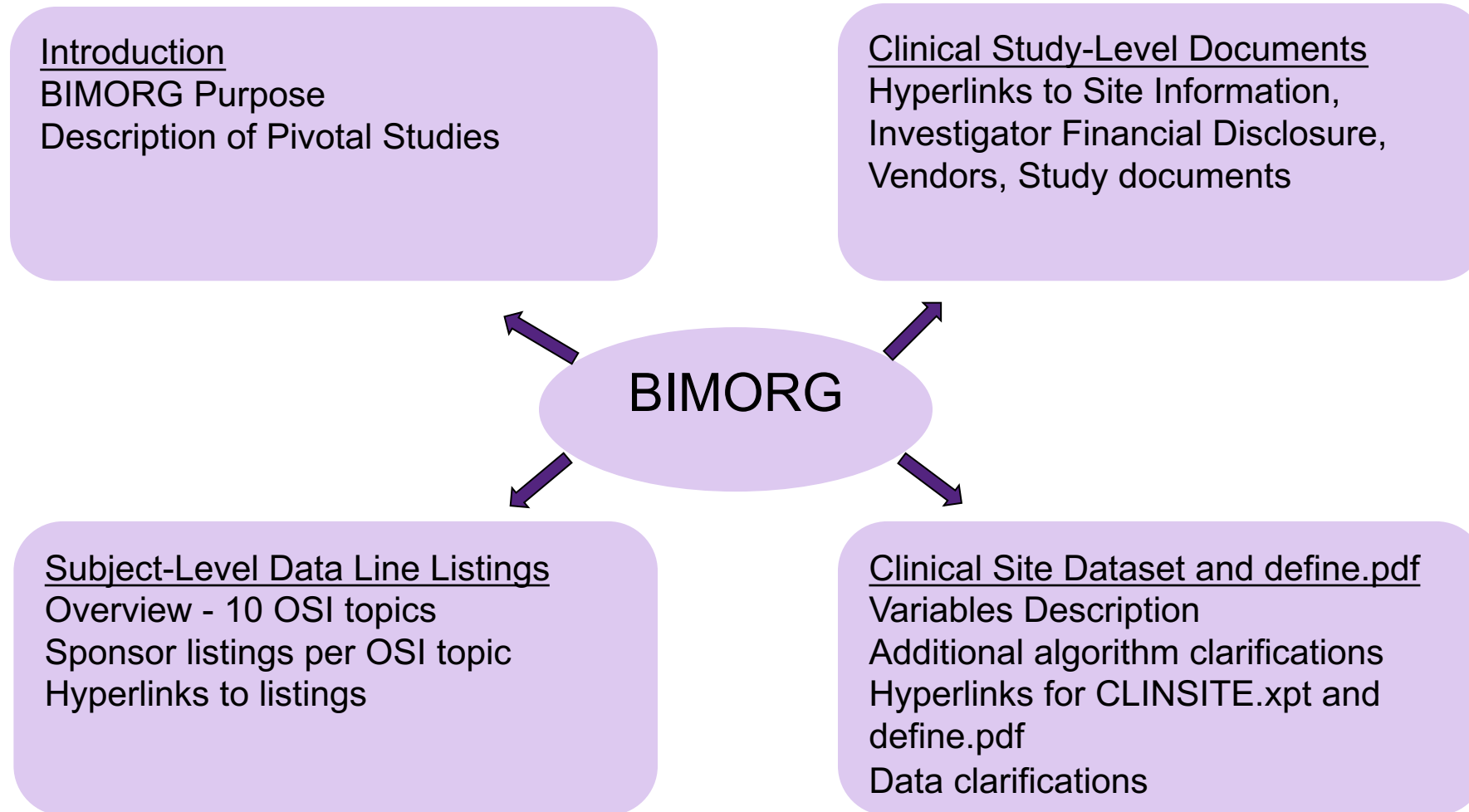
Metadata

- » Variable labels exceeded 40 characters
 - » DISCTR, TRTEFFS, and SITEEFFS
- » Custom variable (FASPOP) was added

Define.pdf and BIMORG

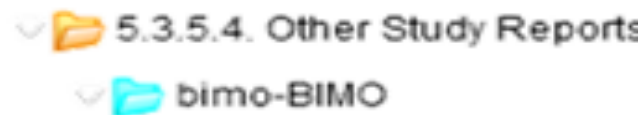
- Define.pdf
 - Created using define.xml and converted to define.pdf
 - Links to CLINSITE.xpt dataset and bimorg.pdf
- Bioresearch Monitoring Reviewer's Guide (BIMORG)
 - Recommended but not required
 - Overview of all the components of BIMO
 - Includes links to other components in eCTD
 - Explains/clarifies issues associated with CLINSITE dataset
 - Custom template

Bioresearch Monitoring Reviewer's Guide (BIMORG)



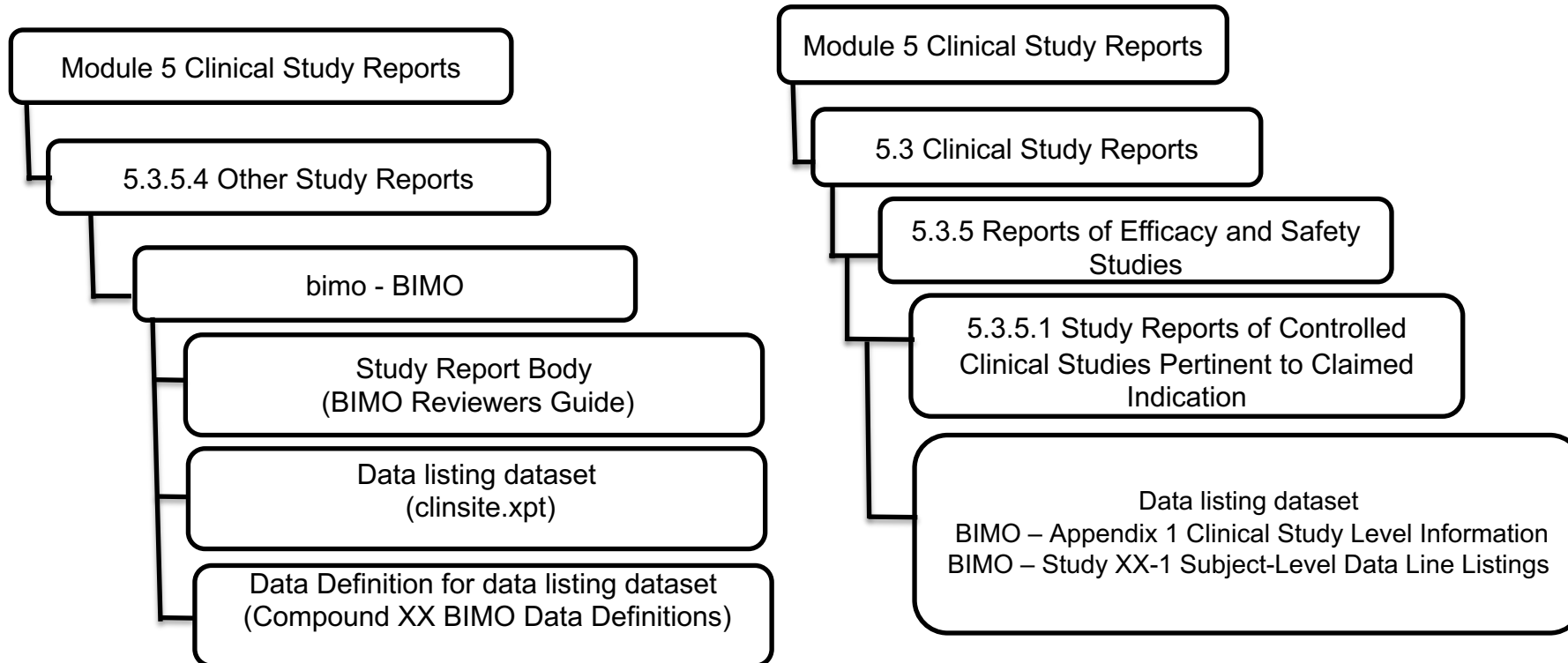
eCTD for BIMO

- Construct a BIMO study tagging file (STF) and place it in eCTD Module 5.3.5.4
- Other Study Reports. Study ID is BIMO
- For the site-level dataset, filename clinsite.xpt
- Link the site-level dataset files into this BIMO STF using file tags



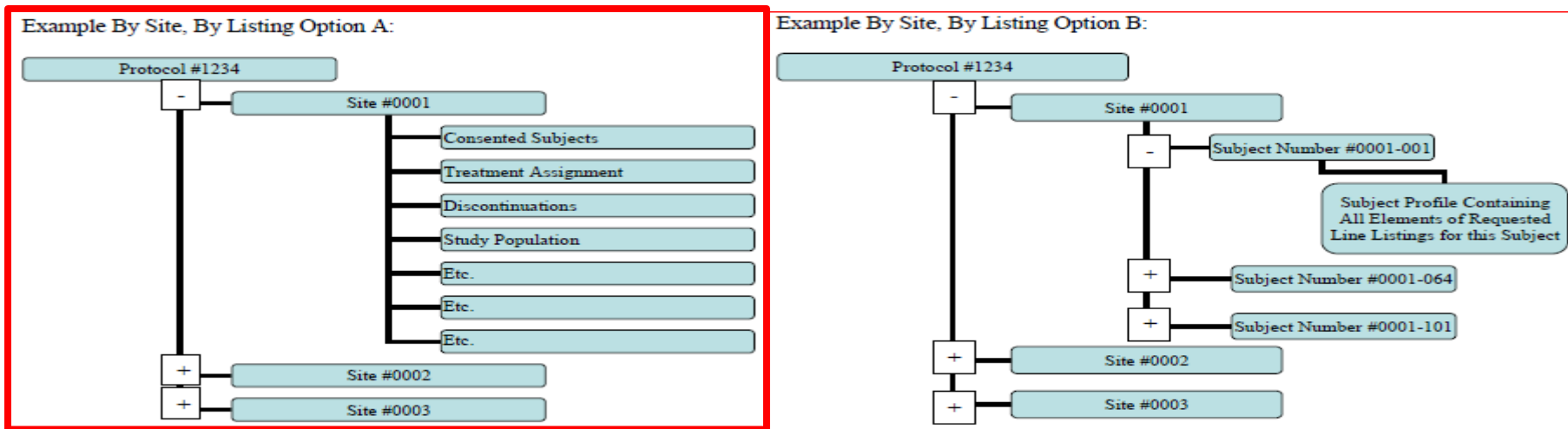
STF File Tag	Used For	Allowable File Formats
data-listing-dataset	Site-level datasets, across studies	.xpt
data-listing-data-definition	Define file	.pdf

BIMO Package in eCTD Viewer



Subject-Level Data Line Listing By Clinical Site

- Subject-level data line listings provided for each major pivotal study
- For clinical investigator sites involved in multiple studies, subject listings should be provided independently for each study
- Details about the listings are provided in Bioresearch Monitoring Technical Conformance Guide



Subject-Level Data Listings

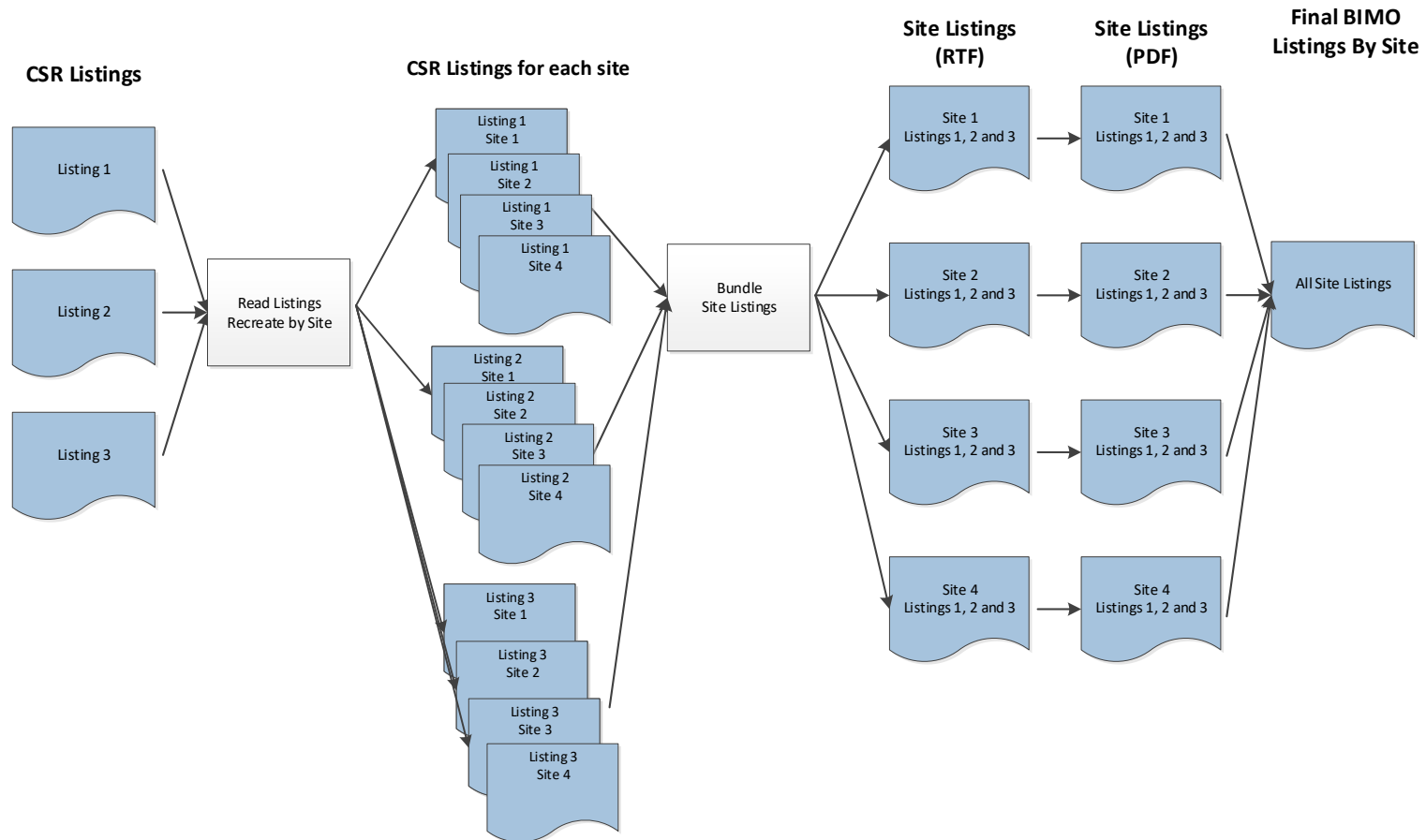
	Topic
1	Consented Subjects
2	Treatment Assignment
3	Discontinuations
4	Study Population
5	Inclusion and Exclusion Criteria
6	Adverse Events
7	Important Protocol Deviations
8	Efficacy Endpoints
9	Concomitant Medications
10	Safety Monitoring

May include multiple listings

Goals

- Utilize existing CSR listings
- Automate the process
- Re-Usability for other studies

Workflow



Reading CSR Listings: Titles and Footnotes

Titles

Footnotes

RTF

My Pharmaceutical Company
BIMO Listings

Listing 1
Randomization Scheme and Codes
All Subjects Set

Page 1 of 1

- ¹: F- Female, M- Male.
- ²: W- White, B- Black or African American, A- Asian, AA- American Indian or Alaska Native, HP- Native Hawaiian or other Pacific Islander,
NC- Not collected per local regulations, and O- Other.
Program: Draft MyStudy\1-rand.sas

Creation: 01JAN2019 09:00

SAS Data Set

tf_id	type	count	value
1	TITLE	1	My Phamaceutical Company
1	TITLE	2	BIMO Listings
1	TITLE	3	Listing 1
1	TITLE	4	Randomization Scheme and Codes
1	TITLE	5	All Subjects Set
1	FOOTNOTE	1	- ¹ : F- Female, M- Male.
1	FOOTNOTE	2	- ² : W- White, B- Black or African American, A- Asian, AA- American Indian or Alaska Native, HP- Native Hawaiian or other Pacific Islander, NC- Not collected per local regulations, and O- Other.



Reading CSR Listings

Column Headers	Column Values
----------------	---------------

RTF

Subject/Sex ¹ /Age/Race ²	Randomized Treatment	Actual Treatment	Randomization Date	Stratum		Region	Country	Site
				Age	Sex			
123456789/M/45 /W	Placebo	--	2019-01-01	≥40 Years	Male	North America	United States	(001) Site 001

SAS Data Set

Metadata

h1	h2	h3	h4	h5	h6	h7	h8	h9
Subject/Sex_super1_line_/Age/Race_super2_	Randomized_line_Treatment	Actual_line_Treatment	Randomization_line_Date	Stratum Age	Stratum Sex	Region	Country	Site

Widths	hw1	hw2	hw3	hw4	hw5	hw6	hw7	hw8	hw9	Justification	hj1	hj2	hj3	hj4	hj5	hj6	hj7	hj8	hj9
	1623	1776	1481	1481	1185	1185	1185	1481	1776		c	c	c	c	c	c	c	c	c

Justification	cj1	cj2	cj3	cj4	cj5	cj6	cj7	cj8	cj9	Identifiers	tf_id	hd_id	page
	c	c	c	c	c	c	c	c	c		1	1	1

Data

c1	c2	c3	c4	c5	c6	c7	c8	c9
123456789/M/45/W	Placebo	--	2019-01-01	>=40 Years	Male	North America	United States	(001) Site 001



Generate Listings By Site

```
ods rtf file = "%sysfunc(getoption(work))/site-001-002-I-randomization.rtf" style = odsrtf nogtitle nogfootnote
keepn notoc_data;
proc report data = rtf1_2 nowd headskip missing split = "~" headline;
compute after c1 / style = [just = l]; line ' '; endcomp;
```

tf_id	type	count	value
1	TITLE	1	My Pharmaceutical Company
1	TITLE	2	BIMO Listings
1	TITLE	3	Listing 1
1	TITLE	4	Randomization Scheme and Codes
1	TITLE	5	All Subjects Set
1	FOOTNOTE	1	- _super1_: F- Female, M- Male.
1	FOOTNOTE	2	- _super2_: W- White, B- Black or African American, A- Asian, AA- American Indian or Alaska Native, HP- Native Hawaiian or other Pacific Islander, NC- Not collected per local regulations, and O- Other.

```
title3 j = c "Listing 2(*ESC*){\line}Randomization Scheme and Codes(*ESC*){\line}All Subjects Set";
```

```
title4 j = l "Site: (001) Site 001";
```

Additional Generated Title

```
footnote1 j = l "- (*ESC*){\super 1}: F- Female, M- Male.(*ESC*){\line}- (*ESC*){\super 2}: W- White, B- Black or African American, A- Asian, AA- American Indian or Alaska Native, HP- Native Hawaiian or other Pacific Islander, NC- Not collected per local regulations, and O- Other";
```

Generate Listings By Site

```
ods rtf file = "%sysfunc(getoption(work))/site-001-002-l-randomization.rtf" style = odsrtf nogtitle nogfootnote
keepn notoc_data;
proc report data = rtf1_2 nowd headskip missing split = "~" headline;
compute after c1 / style = {just = l}; line ' '; endcomp;
```

			Widths			Header Justification			Value Justification		
h1	h5	h6	hw1	hw5	hw6	hj1	hj5	hj6	cj1	cj5	cj6
Subject/Sex_super1__line_/Age/Race_super2_	Stratum Age	Stratum Sex	1623	1185	1185	c	c	c	c	c	c

```
title3 j = c "Listing 2(*ESC*){\line}Randomization Scheme and Codes(*ESC*){\line}All Subjects Set";
```

```
title4 j = l "Site: (001) Site 001";
```

Additional Generated Title

```
footnote1 j = l "- (*ESC*){\super 1}: F- Female, M- Male.(*ESC*){\line}- (*ESC*){\super 2}: W- White, B- Black or African American, A- Asian, AA- American Indian or Alaska Native, HP- Native Hawaiian or other Pacific Islander, NC- Not collected per local regulations, and O- Other";
```

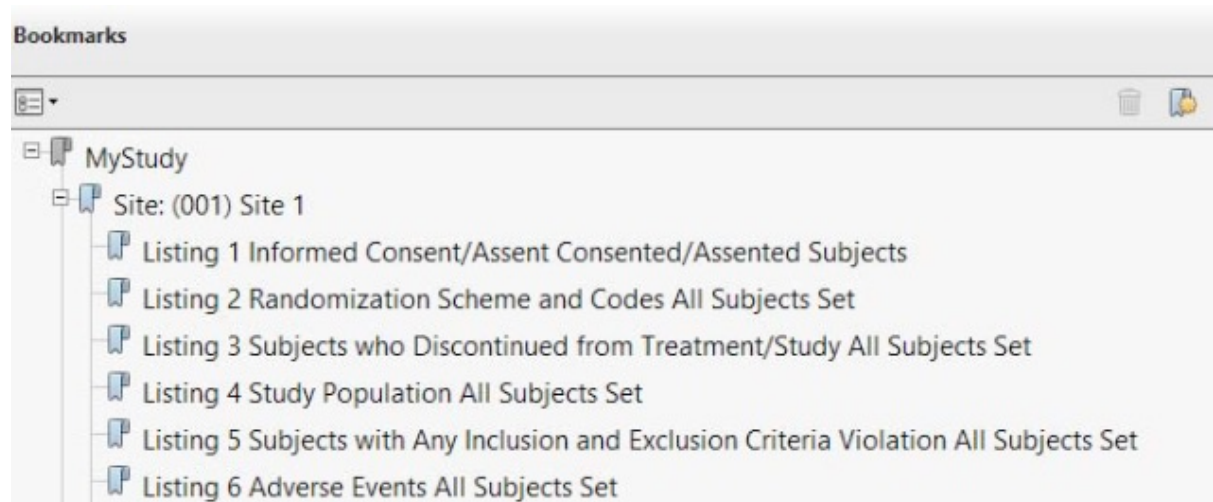
```
column c1 c2 c3 c4 ("Stratum" c5 c6) c7 c8 c9;
```

```
define c1 / order order = data "Subject/Sex(*ESC*){\super 1}{*ESC*){\line}/Age/Race(*ESC*){\super 2}"
```

```
style(header) = {just = c cellwidth = 81.9pt} style(column) = {just = c};
```

Listings by Site (RTF) to Study Level PDF

- Programmatically bundled all listings for each site together
- Bundled Listings QCed by independently reading CSR Listings and bundled listing into SAS and comparing
- Individual PDF files generated programmatically using VBS
- PDF files manually combined using Adobe “Combines files into a single PDF ...”
- PDF Bookmarks generated programmatically by reading RTF and creating text file with 3-level bookmarks
- Bookmarks loaded using Adobe Plug-In



Challenges

- Some listings had no data for some sites
 - Add an empty observation to data set
 - Add additional code to proc report

```
compute before / style(lines) = [just = c cellwidth = 8in];  
  line " ";  
  line " No data met the criteria for this listing.";  
  line " ";  
endcomp;
```

Subject/Sex ¹ /Age/Race ²	Randomized Treatment	Randomized	Dosed	Inclusion Criteria		Exclusion Criteria	
				Criteria Number		Criteria Number	
				Not Met	Explanation/Reason	Met	Explanation/Reason

No data met the criteria for this listing.

Challenges

- Spanning column headers

h1	h2	h3	h4	h5	h6	h7	h8	h9
Subject/Sex_super1__line_/Age/Race_super2_	Randomized_line_Treatment	Actual_line_Treatment	Randomization_line_Date	Stratum Age	Stratum Sex	Region	Country	Site

- Pipe-delimited column headers parsed to generate spanning headers in column statement

column c1 c2 c3 c4 ("Stratum" c5 c6) c7 c8 c9;

Conclusion

- Multiple sources of data to prepare BIMO package
- Need for additional variables for proper interpretation of the CLINSITE dataset
- Took advantage of the existing CSR listing and created site-level listings
- Information summarized in this BIMORG should assist the agency

Questions

