AstraZeneca

OSI/BIMO Overview and Lessons Learned

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Scenario

- FDA inspector

- Study-100 sites participating in clinical trial
  - Total deaths=10
  - Site 1: 6 deaths recorded from one single site (60%)
  - Site 2: 50 subjects enrolled in one site; no AE observed during the study

Why do you need to know about BIMO?

- Part of submission package for NDA or BLA.
- Office of Scientific Investigations (OSI) manages the Bioresearch Monitoring (BIMO) program
- Verify Integrity of efficacy and safety data
- OSI/BIMO identify sites to be inspected and prepare the inspection package for inspectors
- Pivotal studies

Agenda

- Components of BIMO package
  - Part I
  - Part II
  - Part III
- Lessons learned

Components of BIMO package – Part I

- Clinical study-level information
- List of all Clinical sites (PDF)
- Investigator = Primary investigator
- One investigator per site
- Time consuming- request at an early stage
- QA the formats

* Responsibility: Clinical operations

Table A: Format for Clinical Site Lists

Protocol Number: Protocol Title			
Site Identifier	**Investigator Name (Prior Clinical Investigator(s))**	**Site Address at Time of Clinical Study (Updated Site Address when exists and available)**	**Site Contact Information at Time of Clinical Study (Updated Contact Information when exists and available)**
SITEID	**LASTNAME, FRSTNAME, MINITIAL**	**FACILITY NAME STREET CITY, STATE, POSTAL COUNTRY**	**PHONE FAX EMAIL**
0001*	Doe, John M.	Doe University Department of Medicine 1 Main St., Suite 100 Silver Spring, MD 20850 USA	Phone: 1-555-555-5555 Fax: 1-555-555-5555 Email: john.doe@mail.com
0002	Doe, Jean (Smith, John)	Doe University Department of Medicine 1 Main St., Suite 100 Silver Spring, MD 20850 USA	Phone: 1-555-555-5555 Fax: 1-555-555-5555 Email: john.smith@mail.com (Phone: 1-555-555-5554 Email: jean.doe@mail.com)
003	Dietric-Fischer, Inge	Hartmannstrasse 7 5300 Bonn 1 Germany	Phone:49-555-555-5555 Fax: 49-555-555-5555 Email: Dietric.Fischer@web.de
* Site terminated, or clinical investigator changed, at request of sponsor before study completion.			

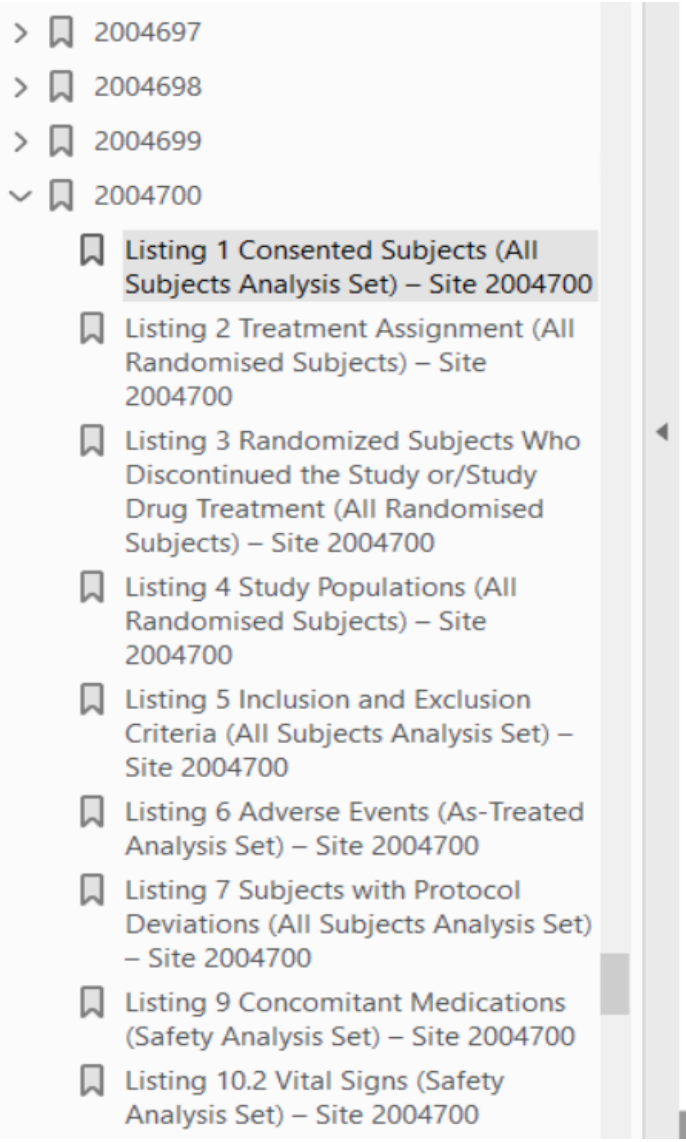
Components of BIMO package – Part II

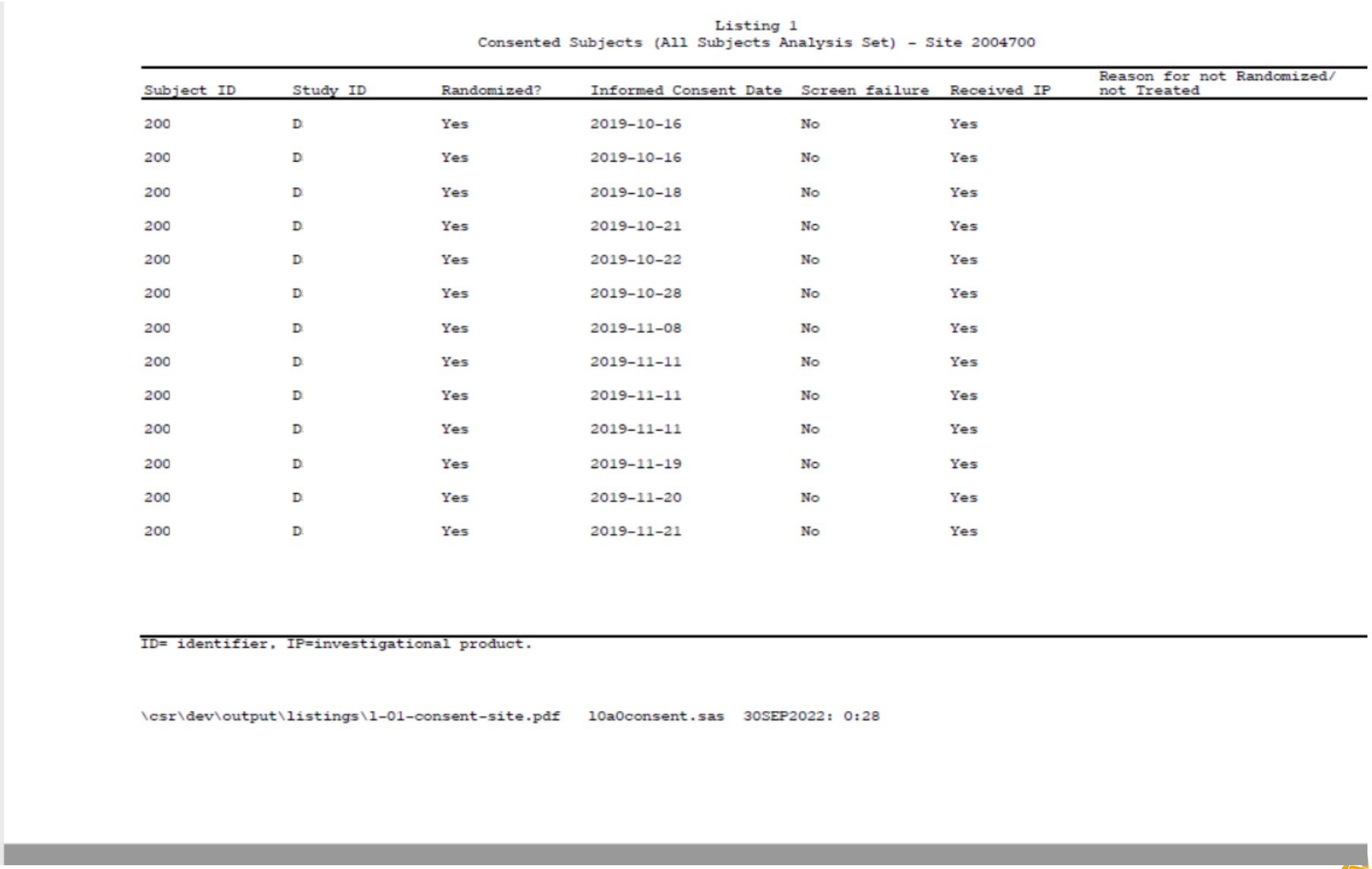
Subject level data line listings by clinical site

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

*Responsibility: Stats for shells and review

Components of BIMO package – Part II





Listing 1
Consented Subjects (All Subjects Analysis Set) - Site 2004700

Subject ID	Study ID	Randomized?	Informed Consent Date	Screen failure	Received IP	Reason for not Randomized/ not Treated
200	D	Yes	2019-10-16	No	Yes	
200	D	Yes	2019-10-16	No	Yes	
200	D	Yes	2019-10-18	No	Yes	
200	D	Yes	2019-10-21	No	Yes	
200	D	Yes	2019-10-22	No	Yes	
200	D	Yes	2019-10-28	No	Yes	
200	D	Yes	2019-11-08	No	Yes	
200	D	Yes	2019-11-11	No	Yes	
200	D	Yes	2019-11-11	No	Yes	
200	D	Yes	2019-11-11	No	Yes	
200	D	Yes	2019-11-19	No	Yes	
200	D	Yes	2019-11-20	No	Yes	
200	D	Yes	2019-11-21	No	Yes	

ID= identifier, IP=investigational product.

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Components of BIMO package – Part III

Clinical Site Data Summary (Clinsite dataset) & define.xml

Refer to Appendix 3: BIMO Technical conformance guide for details

APPENDIX 3: CLINICAL SITE DATA ELEMENTS SUMMARY LISTING

Table B: Clinical Site Data Elements Summary Listing

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDYID	Study Identifier	Char	String	Study or trial identification number.	ABC-123
2	TITLE	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters). If the title exceeds 200 characters, provide shortened title and define (e.g., use the abbreviated title from clinicaltrial.gov).	Double blind, randomized, placebo-controlled clinical study on the influence of drug X on indication Y
3	SPONCNT	Sponsor Count	Num	Integer	Total count of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, with sponsors as defined in § 312.3 (21 CFR 312.3), enter an integer indicating the total count of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1."	1
4	SPONSOR	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as sponsor is defined in § 312.3. If the sponsor name exceeds 200 characters, provide short-form sponsor name and define.	DrugCo, Inc.
5	IND	IND Number	Num	6 digit identifier	IND number. If study not performed under IND, leave blank.	010010
6	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND (i.e., a Form FDA 1572 was signed by the investigator) and "N" if study was not conducted under an IND at the site (i.e., a Form FDA 1572 was not signed by the investigator).	Y
7	NDA	NDA Number	Num	6 digit identifier	FDA NDA number, if available/applicable. If not applicable, leave blank.	021212
8	BLA	BLA Number	Num	6 digit identifier	FDA identification number for BLA, if available/applicable. If not applicable, leave blank.	123456
9	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If no infomation is available, leave blank.	4
10	SITEID	Study Site Identifier	Char	String	Investigator site identifier assigned by the sponsor.	50
11	ARM	Description of Planned Treatment Arm	Char	String	Plain-text label for the name given to an arm or treatment group as referenced in the clinical study report (limit 200 characters). When no arm or treatment group is available due to only screen failure subjects at site, use label "Screen Failure."	Active name and dose (e.g., "Active 25mg"), Comparator product name (e.g., "Drug x"), Placebo, Screen Failure
12	COHORT	Description of Planned Cohort	Char	String	For cohort studies, the plain-text label given to a cohort as referenced in the clinical study report (limit 200 characters). When not a cohort study, leave blank.	A
13	SAFPOP	Number of Subjects in Safety Population	Num	Integer	Total number of subjects in safety population at a given site by treatment arm. When a subject has transferred from one site to another, the applicant should handle reporting of such subjects consistently across sites and include in the define file the reporting convention used. The applicant may opt to further explain the reasons subjects transferred between sites in the BIMO Reviewer's Guide, if a guide will be provided.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened (and consented) at a given site (overall number per site as subjects have not yet been assigned to treatment arm). When a subject has transferred from one site to another, the applicant should handle reporting of such subjects consistently across sites and include the reporting convention used in the define file or the BIMO Reviewer's Guide (if provided). The applicant may opt to further explain the reasons subjects transferred between sites in the BIMO Reviewer's Guide, if provided.	100
15	DISCSTUD	Number Subjects Discont. Study	Num	Integer	Number of subjects in the safety population who discontinued from the study by treatment arm at a given site.	5
16	DISCTRT	Number Subjects Discont. Study Treatment	Num	Integer	Number of subjects in the safety population who discontinued from the study treatment by treatment arm at a given site.	10
17	ENDPOINT	Primary 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
18	ENDPTYPE	Primary Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., "continuous," "discrete," "time to event," or "other").	Continuous
19	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Summary statistic for each primary efficacy endpoint by treatment arm at a given site for subjects in SAFPOP.	1.00
20	TRTEFFS	Treatment Efficacy Result STD	Num	Floating Point	Standard deviation (STD) of the efficacy result (TRTEFFR) for each primary efficacy endpoint by treatment arm at a given site for subjects in SAFPOP. If N=1, set to "0."	0.065
21	CENSOR	Number of Censored Observations	Num	Integer	Total number of censored observations at a given site by treatment arm for primary endpoint (e.g., applicable to time-to-event). If not applicable, leave blank.	5
22	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of nonserious adverse events at a given site by treatment arm for subjects in the SAFPOP. 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 that are treatment emergent events). When events with the same preferred term have occurred on different dates for a subject, each event should be counted separately in event count.	10

Components of BIMO package – Part III

View

STUDYID	TITLE	SPONCNT	SPONSOR	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	COHORT	SAFPOP	SCREEN	DISCSTUD	DISCTRT	ENDPOINT	ENDPTYPE
	A Phase 3 Rand...	1	AstraZeneca		Y				20040...	MEDI8...		76	102	18	0	Incidence of med...	Continuous
	A Phase 3 Rand...	1	AstraZeneca		Y				20040...	Placebo		26	102	8	0	Incidence of med...	Continuous

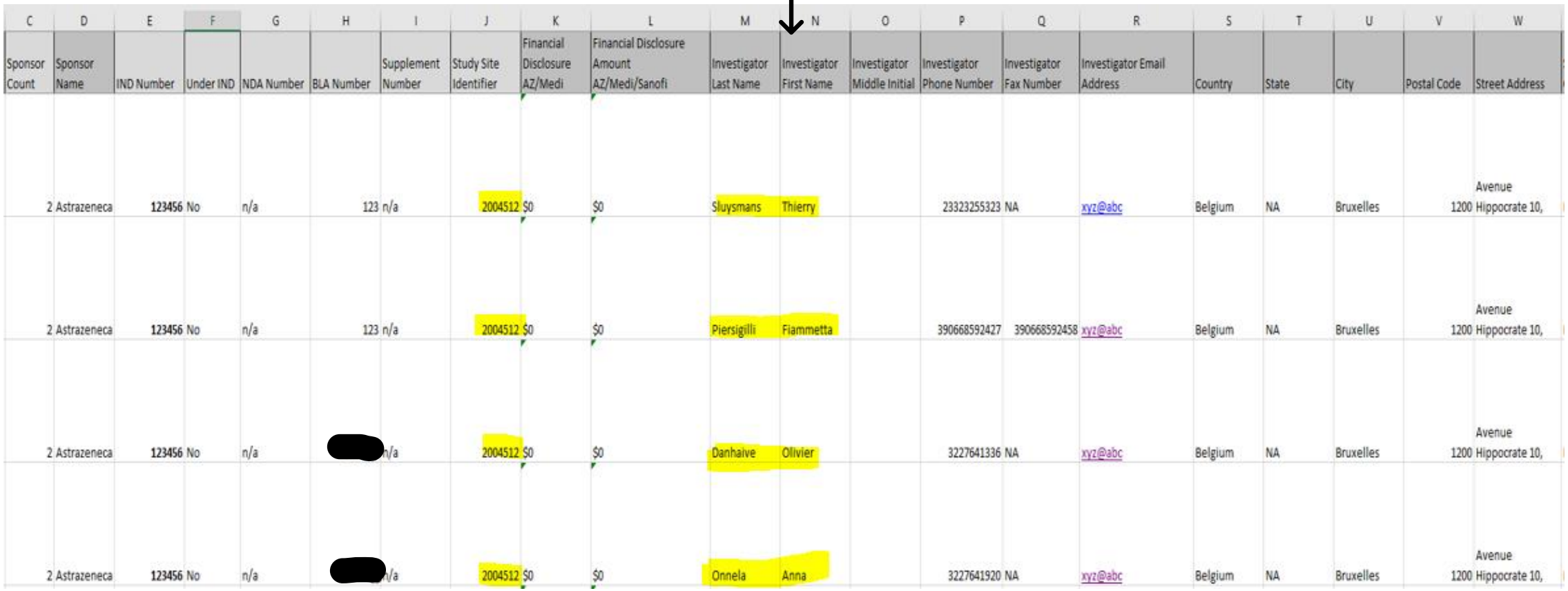
TRTEFFR	TRTEFFS	CENSOR	NSAE	SAE	DEATH	IMPDEV	NOIMPDEV	FINLDISC	LASTNAME	FRSTNAME	MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET	STREET1	STREET2
0	0		388	7	0	1	253	$0		Heather			NA	heathe...	South Af...	NA	Cape Town	7700	Red Cro...	NA	
0	0		137	2	0	1	73	$0		Heather			NA	heathe...	South Af...	NA	Cape Town	7700	Red Cro...	NA	

- Clinsite is unique by SITEID and ARM
- Primary Objective vs Primary endpoint
- Define.xml, Reviewer's guide, external document
- Reviewer's guide : Current and previous protocol versions, aCRFs

Lessons Learned

Lessons Learned

1. Excel files from Clinical operations for one study



C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W
Sponsor Count	Sponsor Name	IND Number	Under IND	NDA Number	BLA Number	Supplement Number	Study Site Identifier	Financial Disclosure AZ/Medi	Financial Disclosure Amount AZ/Medi/Sanofi	Investigator Last Name	Investigator First Name	Investigator Middle Initial	Investigator Phone Number	Investigator Fax Number	Investigator Email Address	Country	State	City	Postal Code	Street Address
2	Astrazeneca	123456	No	n/a	123	n/a	2004512	$0	$0	Sluysmans	Thierry		23323255323	NA	xyz@abc	Belgium	NA	Bruxelles	1200	Avenue Hippocrate 10,
2	Astrazeneca	123456	No	n/a	123	n/a	2004512	$0	$0	Piersigilli	Fiammetta		390668592427	390668592458	xyz@abc	Belgium	NA	Bruxelles	1200	Avenue Hippocrate 10,
2	Astrazeneca	123456	No	n/a	[redacted]	n/a	2004512	$0	$0	Danhaive	Olivier		3227641336	NA	xyz@abc	Belgium	NA	Bruxelles	1200	Avenue Hippocrate 10,
2	Astrazeneca	123456	No	n/a	[redacted]	n/a	2004512	$0	$0	Onnela	Anna		3227641920	NA	xyz@abc	Belgium	NA	Bruxelles	1200	Avenue Hippocrate 10,

Q: Do you notice any problem with the excel file in highlighted part?

Lessons Learned

1. Excel files from Clinical operations: There are multiple investigators listed

C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W
Sponsor Count	Sponsor Name	IND Number	Under IND	NDA Number	BLA Number	Supplement Number	Study Site Identifier	Financial Disclosure AZ/Medi	Financial Disclosure Amount AZ/Medi/Sanofi	Investigator Last Name	Investigator First Name	Investigator Middle Initial	Investigator Phone Number	Investigator Fax Number	Investigator Email Address	Country	State	City	Postal Code	Street Address
2	Astrazeneca	123456	No	n/a	123	n/a	2004512	$0	$0	Sluysmans	Thierry		23323255323	NA	xyz@abc	Belgium	NA	Bruxelles	1200	Avenue Hippocrate 10,
2	Astrazeneca	123456	No	n/a	123	n/a	2004512	$0	$0	Piersigilli	Fiammetta		390668592427	390668592458	xyz@abc	Belgium	NA	Bruxelles	1200	Avenue Hippocrate 10,
2	Astrazeneca	123456	No	n/a	[redacted]	n/a	2004512	$0	$0	Danhaive	Olivier		3227641336	NA	xyz@abc	Belgium	NA	Bruxelles	1200	Avenue Hippocrate 10,
2	Astrazeneca	123456	No	n/a	[redacted]	n/a	2004512	$0	$0	Onnela	Anna		3227641920	NA	xyz@abc	Belgium	NA	Bruxelles	1200	Avenue Hippocrate 10,

*File should have Principal investigator only

Lessons Learned

1. Excel files from Clinical operations

Eg: Death count at the following site? 2 or 26?

	STUDYID	SPONSOR	SITEID	ARM	SAFPOP	SCREEN	DISCSTUD	DEATH	LASTNAME	FRSTNAME
1742		AstraZeneca	2004109		104	190	15	2	Tamblyn	Amy
1743		AstraZeneca	2004109		104	190	15	2	Koen	Anthonet
1744		AstraZeneca	2004109		104	190	15	2	Thombrayil	Asha
1745		AstraZeneca	2004109		104	190	15	2	Oommen Jose	Aylin
1746		AstraZeneca	2004109		104	190	15	2	Ikulinda	Benit
1747		AstraZeneca	2004109		104	190	15	2	GrefFranceth	Johann Christiaan
1748		AstraZeneca	2004109		104	190	15	2	Jones	Stephanie
1749		AstraZeneca	2004109		104	190	15	2	Jose	Lisa
1750		AstraZeneca	2004109		104	190	15	2	Madhi	Shabir
1751		AstraZeneca	2004109		104	190	15	2	Matlala Ntoagae	Jane
1752		AstraZeneca	2004109		104	190	15	2	Khan	Muneerah
1753		AstraZeneca	2004109		104	190	15	2	Bhikha	Sutika
1754		AstraZeneca	2004109		104	190	15	2	Thombrayil	Ashini

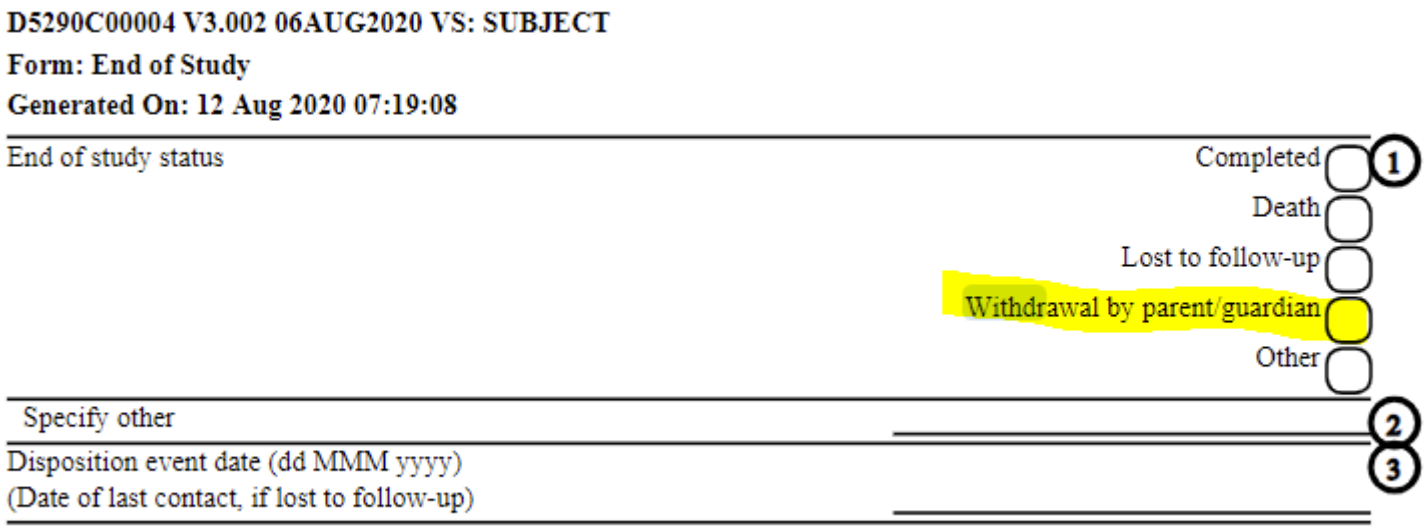
Lessons Learned

2. DISCSTUD, DISCTRT, NSAE, SAE, DEATH, IMPDEV, NOIMPDEV- Subset of Safety population

eg: DISCSTUD – Number of subjects discontinued study

Q: 5 randomized subjects with EOS status='Withdrawal by parents' and only 3 of them are SAFEPOP.

What is the count for DISCSTUD?



D5290C00004 V3.002 06AUG2020 VS: SUBJECT
Form: End of Study
Generated On: 12 Aug 2020 07:19:08

End of study status
Completed ☐ 1
Death ☐
Lost to follow-up ☐
Withdrawal by parent/guardian ☐
Other ☐

Specify other _____ 2

Disposition event date (dd MMM yyyy)
(Date of last contact, if lost to follow-up) _____ 3

Lessons Learned

2. DISCSTUD, DISCTRT, NSAE, SAE, DEATH, IMPDEV, NOIMPDEV- Subset of Safety population

eg: a. DISCSTUD: Only treated subject should be counted.

Q: 5 randomized subjects with EOS status='Withdrawal by parents' and only 3 of them are SAFEPOP.

What is the count for DISCSTUD? Answer: 3 (Only treated subject should be counted)

D5290C00004 V3.002 06AUG2020 VS: SUBJECT
Form: End of Study
Generated On: 12 Aug 2020 07:19:08

End of study status	Completed ☐	1
	Death ☐	
	Lost to follow-up ☐	
	Withdrawal by parent/guardian ☐	
	Other ☐	
Specify other	_____	2
Disposition event date (dd MMM yyyy) (Date of last contact, if lost to follow-up)	_____	3

Lessons Learned

3. DISCTRT: Treatment Discontinuation
   - Single dose study
   - Screened, Randomized, not treated because ‘Withdrawal by parents’ – Counted as DISCTRT- Not correct
   - Explained to FDA

Lessons Learned

4. IMPDEV/NONIMPDEV

- If no PDs/IPDs – Create empty listings
- Spot check few sites with PD/IPDs
- Legacy study – No DV, ADPRODEV available
- No derivation present in specs
- Zero count for IMPDEV/NONIMPDEV
- CSR (IPD section), IPD log in CSR, IPD listing
- Review the specs thoroughly
- Ensure all studies are covered

Lessons Learned

5. All sites present in ADSL should be present in CLINSITE and vice versa
   - SITEID present in ADSL but missing from excel files from clinops, following variables will be missing in clinsite

LASTNAME	FRSTNAME	MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET	STREET1	STREET2

   - SITEID present in excel files from clinops but missing in ADSL, all derived variables will be missing

   eg: DISCSTUD, DISCTRT, NSAE, SAE, DEATH, IMPDEV, NOIMPDEV

Lessons Learned

6. Double programming for all derived variables in clinsite
   - FDA guidance
   - AZ guidance
   - Request stats to review the specs

7. Include BIMO review during dry run

Useful resources

1. FDA guidance
2. BDRG package


QUESTIONS