

Automating SDTM Annotated CRF (aCRF) Creation

Leveraging Upstream Metadata

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DISCLAIMER

This presentation is for education purposes only and should not be construed as an endorsed standard of operation for every company. We will discuss the tool, several factors and operating procedures that we follow that have enabled the processes to be effective in generating quality deliverables.

Overview

1. Brief Background and Context
2. Development of the SDTM aCRF Annotator Tool
3. Pilot to Pressure Test
4. Further Enhancing the Tool
5. Walk-through

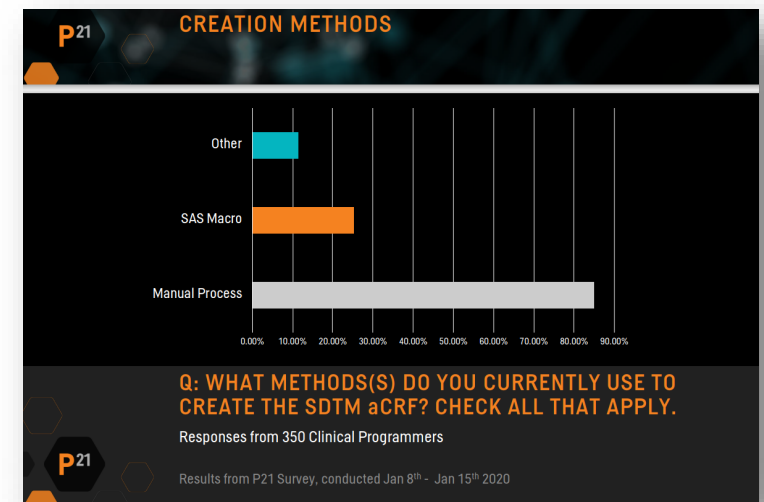
Background and Context

Brief explanation of purpose and expectations of an aCRF

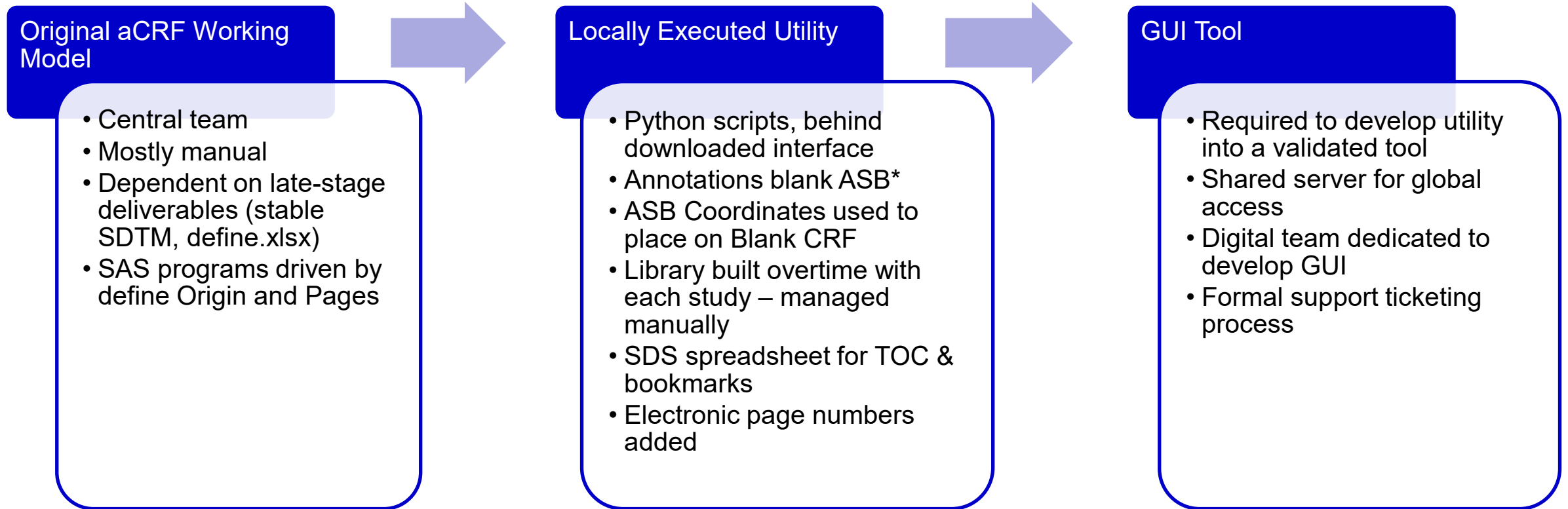
- **Is an industry-wide expectation** when submitting data to some regulatory agencies, e.g., FDA, PMDA, or NMPA.
- Enables the user to **understand how the study data were collected and to trace back from study analysis results to the origin** where it was collected.*
- Should be submitted **preferably at the time a protocol is submitted**.**
- Practices:
 - Pinnacle 21 2020 survey asking how aCRFs are being created
 - **Majority (>80%) respondents are manually annotating Blank CRFs**
 - Time consuming and tedious
 - Ideal opportunity for automation

*SDTM aCRF Guideline, Guideline for SDTM annotation in Case Report Forms, Summary and Recommendations for Best Practice, v10 2020-11-20

**FDA Study Data Technical Conformance Guide, Technical Specifications Document, v5.7, March 2024



aCRF Tool Development



*Annotated Study Book
** Study Design Specifications

Pilot to Prepare for Rollout to Study Teams

Pressure testing

Scope: Low priority studies, in-house programming teams. Early in study conduct but completed studies acceptable.



Requirement: Studies using current database system (InForm) only.



Time commitment: estimated 20% time over two weeks



Execution: Teams will work on their own to create an aCRF, with the SME team available for questions. Any gaps will be incorporated into the materials for rollout.



Duration: Two weeks

Pilot Readout

Feedback and metrics

Metrics

Number of Participants	TAs Represented	Average Total Time to Complete First aCRF	Breakdown of aCRF Complexity
7	I&I, Onco, Rare Disease, Vaccines	12.3 days	57% HIGH 29% MED 14% LOW

Pros

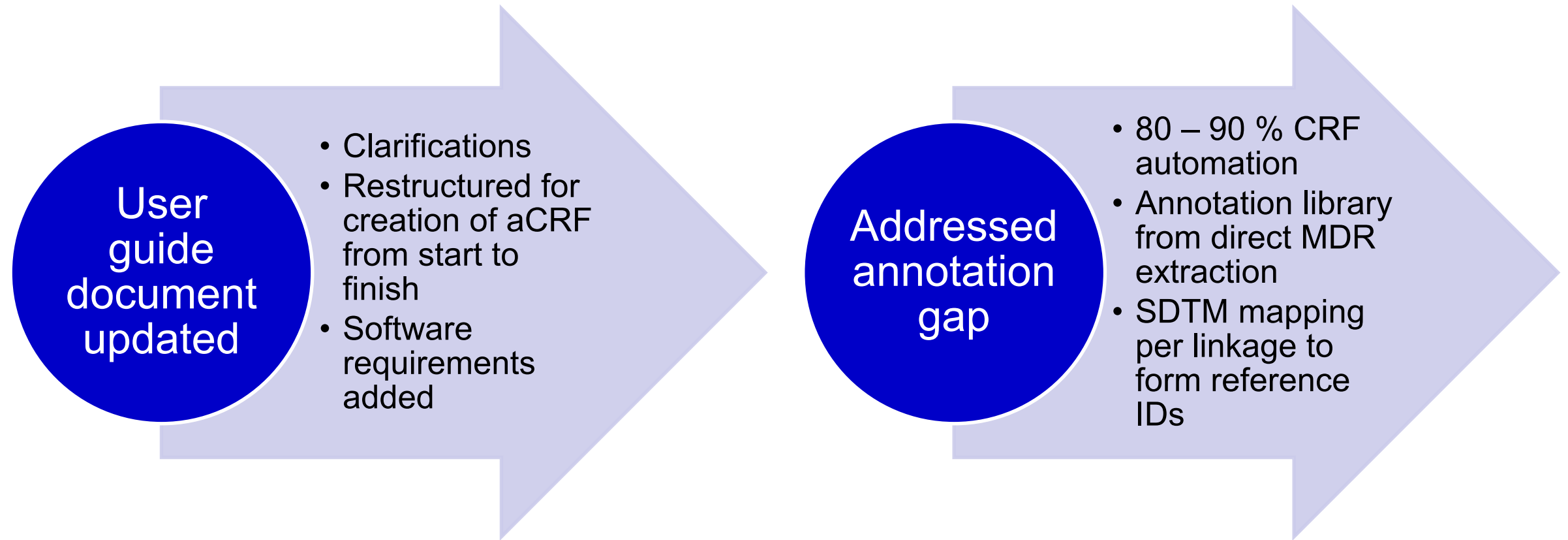
- Easy to use
- Better than current process
- Fast processing time

Cons

- < 5 to <20 % CRF automated annotations
- Time consuming to review and adjust annotations
- Still considerable manual work involved
- No time savings for new annotations

Updating SDTM aCRF Annotator Tool

Incorporating pilot feedback to ensure enhance experience for users



SDTM aCRF Annotator Tool – Current State

Final version – a validated, globally accessible tool leveraging the MDR

- Python scripts, **behind a globally accessible GUI tool**
- Attaches SDTM variable annotations to database source variable fields to a blank Annotated Study Book (ASB)
- Uses coordinates from field reference IDs on ASB to place SDTM variables on to corresponding Blank CRF pages
- **Uses a library of annotations repository from MDR extracted file**
 - **80 – 90 % annotation automated**
 - **User review of all annotations still required**
 - **Minimizes manual effort**
- Utilizes Study Design Specifications (SDS), with sheet for time & events schedule, to create hyperlinked TOC, bookmarks by Visit and Domain
- Creates footer for page numbers to reflect new electronic file page

SDTM aCRF Annotator Tool Benefits

Overview of the value added using the tool

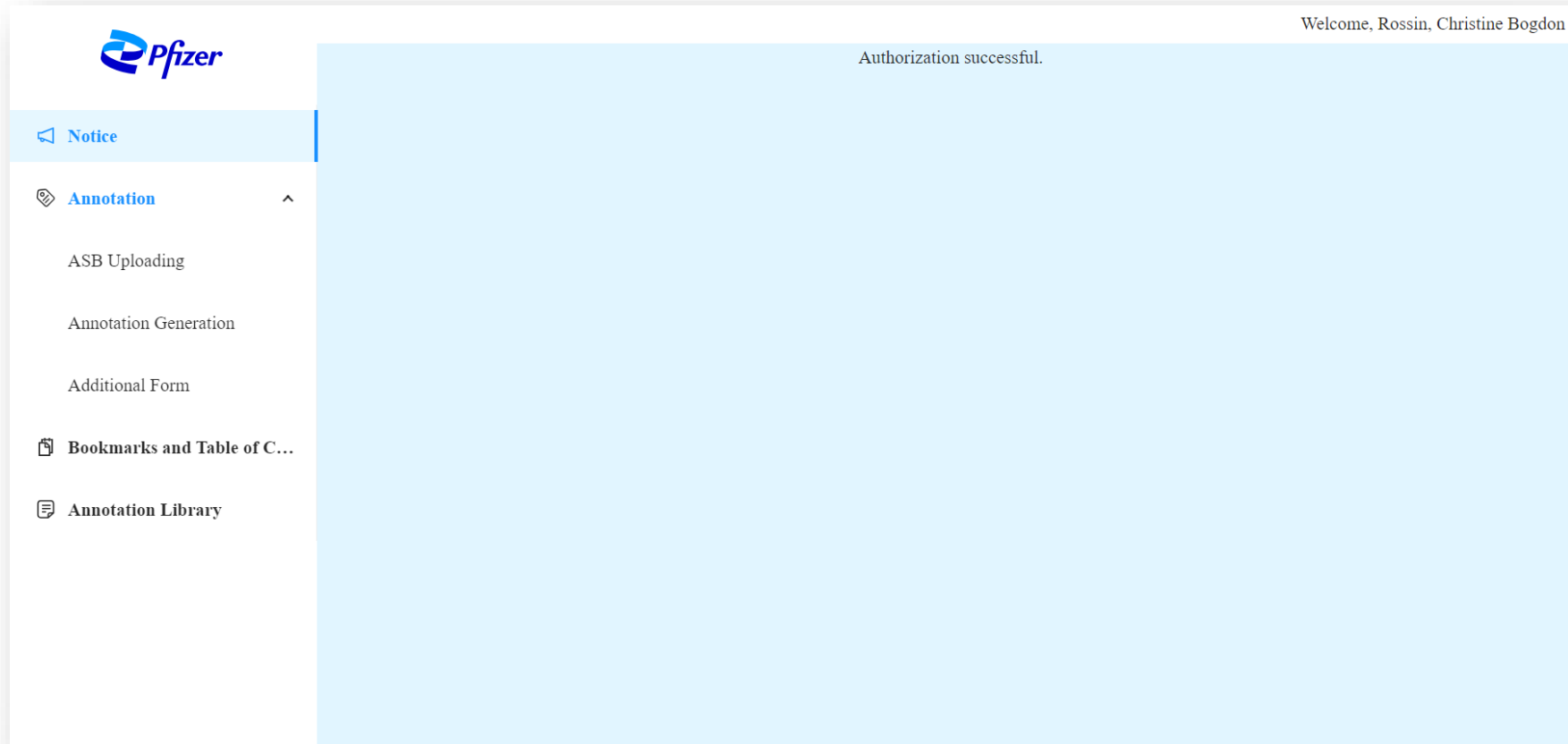
- Leveraging upstream deliverables and metadata
- Significantly reduced manual work: Shift from manual/partial automation -> Full Automation
- Increased quality and consistency
- Full traceability back to collection & SDTM standards
- Timing: aCRF creation can start as early as database activation
 - No enrollment or data is required to start
 - As soon as ASB, SDS and Blank CRF are available
 - Can be submitted with protocol to FDA
- Front loading (submission to Regulatory agency)
- Early identification of any mapping concerns



Navigating the Tool

A Walk Through

Landing Page



Generate an aCRF

Documents needed for annotations

Annotated Study Book (ASB)

- Contains field reference IDs and other metadata

#	Category	AE Identifier	Adjudication Event ID	Adverse Event	Start Date	Is the Adverse Event Still Ongoing	Severity	Serious	Is AE a Result of a Medication Error	Relationship to Study Treatment	Action Taken with Study Treatment	Concomitant Medication Given	Non-Drug Treatment Given	Outcome
1														
B7981031: ADVERSE EVENT REPORT (AE) - Repeating Form [AE01001]														
1.	Category: [read-only] [Category]	[AECAT_001] [A-1] ☐ ADVERSE EVENT												
2.	AE ID: [read-only] [AE Identifier]	[AESPID_001] A20*												
3.	PAC / Adjudication Event ID: [Adjudication Event ID]	[SUPPAE_AEPACID_001] A100*												
4.*	Adverse Event: (If possible specify diagnosis, not individual symptoms) [Adverse Event]	[AETERM_001] A100*												
5.*	Start Date: [Start Date]	[AESTDTC_001] (DD/MM/YYYY) Req ☒ / Req ☒ / Req ☒ (2022-2024)												
6.*	Is the adverse event still ongoing? [Is the Adverse Event Still Ongoing]	[X_AEONGO_001] [A-Y] ☐ YES [A-N] ☐ [AEENDTC_CMP_001] ☐ NO [AEENDTC_001] (DD/MM/YYYY) End Date: Req ☒ / Req ☒ / Req ☒ (2022-2024)												
7.*	Severity: [Severity]	[AESEV_001] [A-1] ☐ MILD [A-2] ☐ MODERATE [A-3] ☐ SEVERE												
8.*	Is the adverse event serious? If Yes, NOTIFY PFIZER IMMEDIATELY. Fatal; Life-threatening; Inpatient hospitalization or prolongation of existing hospitalization; Persistent or significant	[AESER_001] [A-Y] ☐ [AESCONG_CMP_001] ☐ YES [AESCONG_001] Is this serious event associated with congenital anomaly or birth defect? [A-Y] ☐ YES [A-N] ☐ NO [AESDTH_001] Did this serious event result in death? [A-Y] ☐ YES [A-N] ☐ NO												

Blank CRF

- Identical to ASB, without field reference IDs or metadata

#	Category	AE Identifier	Adjudication Event ID	Adverse Event	Start Date	Is the Adverse Event Still Ongoing	Severity	Serious	Is AE a Result of a Medication Error	Relationship to Study Treatment	Action Taken with Study Treatment	Concomitant Medication Given	Non-Drug Treatment Given	Outcome
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B7981031: ADVERSE EVENT REPORT (AE) - Repeating Form														
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1.	Category: [Category]	☐ ADVERSE EVENT												
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4.	Adverse Event: (If possible specify diagnosis, not individual symptoms) [Adverse Event]													
5.	Start Date: [Start Date]	☒ / ☒ / ☒												
6.	Is the adverse event still ongoing? [Is the Adverse Event Still Ongoing]	☐ YES ☐ NO End Date: ☒ / ☒ / ☒												
7.	Severity: [Severity]	☐ MILD ☐ MODERATE ☐ SEVERE												
8.	Is the adverse event serious? If Yes, NOTIFY PFIZER IMMEDIATELY. Fatal; Life-threatening; Inpatient hospitalization or prolongation of existing hospitalization; Persistent or significant	☐ YES Is this serious event associated with congenital anomaly or birth defect? ☐ YES ☐ NO Did this serious event result in death? ☐ YES ☐ NO Did this serious event require or prolong hospitalization? ☐ YES ☐ NO												

ASB Uploading Tab

Generate annotations

- Studies currently available will be listed
- New studies added using “Upload New File”
 - Will fetch annotations linked to study ASB fields using the library of annotations
- Review study annotations metadata file
 - May require manual updates

Welcome, Rossin, Christine Bogdon

Choose ASB File

Study Search Annotation Request Status

Study	Update Time	SPA Programmer	Locked By	Annotation Request Status	
A1281201	2022-04-11 10:12:01	PANCHS			View Lock
A5481092	2021-11-10 09:01:42	MOTUPG		Approved	View Lock
B1871061	2024-03-12 11:33:39	KINANA01		Approved	View Lock
B1931030	2023-08-02 01:35:22	KALYAS12		Approved	View Lock
B3461077	2024-01-24 03:47:28	RENQ13			View Lock
B5381012	2021-12-02 11:24:35	TOMB	TOMB	Approved	View Unlock
B7451015	2023-01-31 10:38:47	TOMB		Approved	View Lock
B7451092	2022-07-03 08:34:34	TOMB		Approved	View Lock
B7471012	2022-04-12 12:05:53	CHENGJ52		Pending	View Lock
B7841005	2023-06-13 18:06:43	TOMB		Approved	View Lock

< 1 2 3 4 5 ... 10 > 10 / page Go to

ASB Uploading Tab

Reviewing and updating annotations metadata

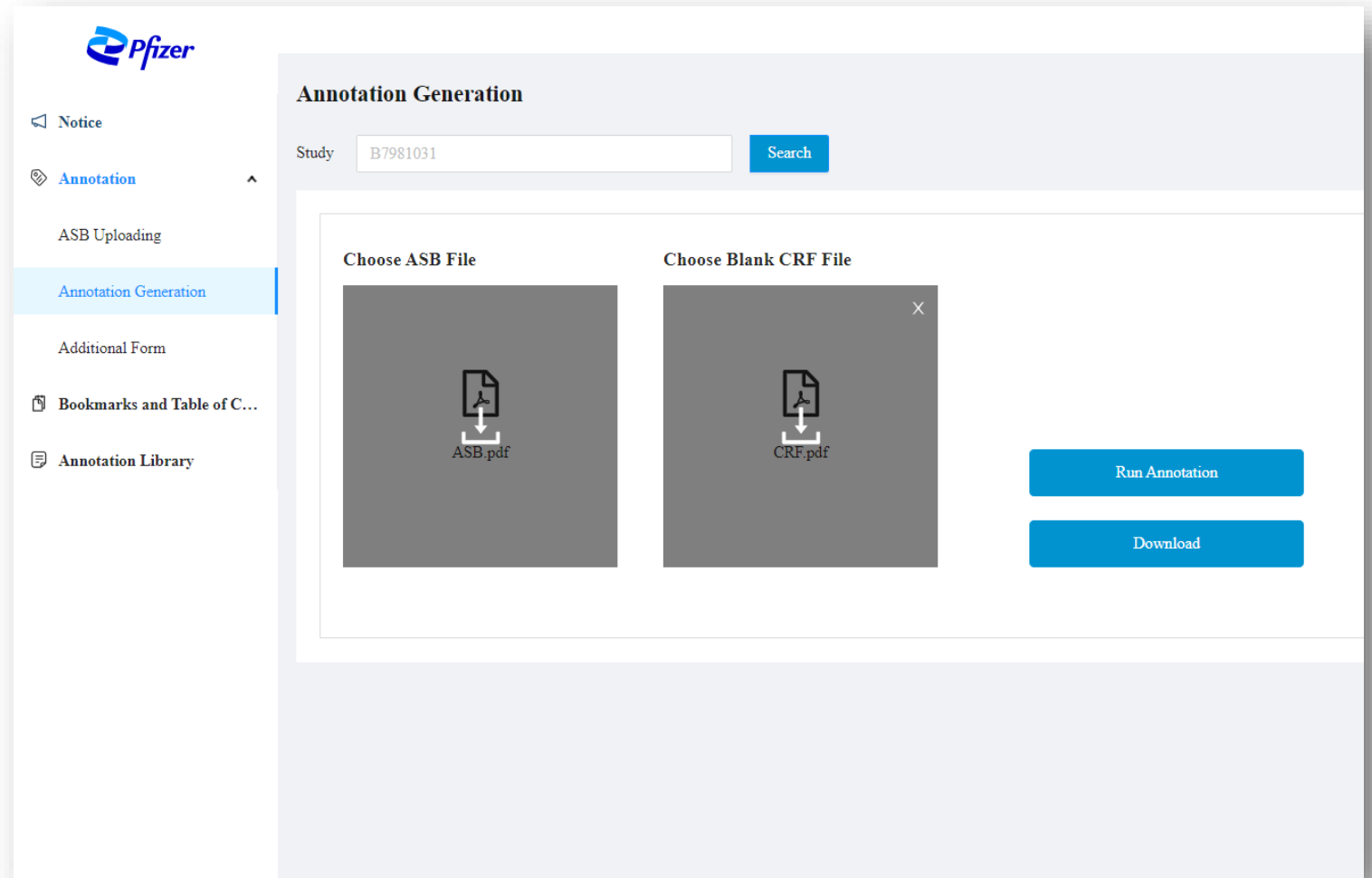
- Can be done online in tool or via downloaded file
- Some examples for updates: color column for pages with multiple domains, NOT SUBMITTED fields

Form Title	Form Ref Name	Source Variable	Lib Annotation	Annotation Text	Status
☐ Form Title	Form Ref Name	Source Variable	Lib Annotation	Annotation Text	Annotation Color
☐ MAIN INFORMED CON...	[DS001]		DSCAT=PROTOCOL MI...	DSCAT=PROTOCOL MI...	Blue ▾
☐ MAIN INFORMED CON...	[DS001]		DM=Demographics	DM=Demographics	Blue ▾
☐ MAIN INFORMED CON...	[DS001]		DS=Disposition	DS=Disposition	Green ▾
☐ MAIN INFORMED CON...	[DS001]	[SUPPDS_DSCSOBT_001]	DSCSOBT in SUPPDS	DSCSOBT in SUPPDS	Green ▾
☐ MAIN INFORMED CON...	[DS001]	[DSSTDTC_CMP_001]			Blue ▾
☐ MAIN INFORMED CON...	[DS001]	[DSSTDTC_001]	DSSTDTC when DSTER...	DSSTDTC when DSTER...	Green ▾
☐ MAIN INFORMED CON...	[DS001]	[DSSTDTC_001]	DSSTDTC	DSSTDTC	Green ▾
☐ MAIN INFORMED CON...	[DS001]	[DSSTDTC_001]	RFICDTC	RFICDTC	Blue ▾
☐ GENERAL MEDICAL H...	[MH001]		MH=Medical History	MH=Medical History	Blue ▾
☐ GENERAL MEDICAL H...	[MH001]		MHCAT=GENERAL ME...	MHCAT=GENERAL ME...	Blue ▾
☐ GENERAL MEDICAL H...	[MH001]	[MHSPID_001]	MHSPID	MHSPID	Blue ▾
☐ GENERAL MEDICAL H...	[MH001]	[MHTERM_001]	MHTERM	MHTERM	Blue ▾

Annotation Generation Tab

Generate aCRF

- Upload existing ASB
 - Will be annotated with SDTM variables
- Upload Blank CRF to be annotated
- “Run Annotations” button
- Compare annotated ASB with aCRF
 - Any annotations missing
 - Ensure printed text is not obscured



The image shows a screenshot of the Pfizer Annotation Generation web application. On the left is a sidebar with the Pfizer logo at the top and a list of navigation items: Notice, Annotation (with a dropdown arrow), ASB Uploading, Annotation Generation (highlighted in blue), Additional Form, Bookmarks and Table of C..., and Annotation Library. The main content area is titled 'Annotation Generation'. It features a 'Study' input field containing 'B7981031' and a blue 'Search' button. Below this, there are two large grey boxes for file uploads. The first box is labeled 'Choose ASB File' and contains a document icon with a download arrow and the text 'ASB.pdf'. The second box is labeled 'Choose Blank CRF File' and contains a similar document icon with a download arrow and the text 'CRF.pdf'. To the right of these boxes are two blue buttons: 'Run Annotation' and 'Download'.

Annotation Generation Tab

Reviewing and adjusting the aCRF

Annotated Study Book (ASB)

- SDTM variables placed next to field reference IDs

B7981031: ADVERSE EVENT REPORT (AE) - Repeating Form [AE001]														
#	Category	AE Identifier	Adjudication Event ID	Adverse Event	Start Date	Is the Adverse Event Still Ongoing	Severity	Serious	Is AE a Result of a Medication Error	Relationship to Study Treatment	Action Taken with Study Treatment	Concomitant Medication Given	Non-Drug Treatment Given	Outcome
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Adverse Event Report [AE01001]														
1.	Category: [read-only] [Category]	[AECAT_001] AECAT [A-1] ☐ ADVERSE EVENT												
2.	AE ID: [read-only] [AE Identifier]	[AESPID_001] AESPID A20 *												
3.	PAC / Adjudication Event ID: [Adjudication Event ID]	[SUPPAE_AEPACID_001] AEPACID in SUPPAE A100 *												
4.*	Adverse Event: (If possible specify diagnosis, not individual symptoms) [Adverse Event]	[AETERM_001] AETERM A100 *												
5.*	Start Date: [Start Date]	[AESTDTC_001] AESTDTC YY Req ☐ / Req ☐ / Req ☐ (2022-2024)												
6.*	Is the adverse event still ongoing? [Is the Adverse Event Still Ongoing]	[X_AEONGO_001] AEENRPT AEENTPT [A-1] ☐ YES [A-N] ☐ NO [AEENDTC_001] AEENDTC YY End Date: Req ☐ / Req ☐ / Req ☐ (2022-2024)												
7.*	Severity: [Severity]	[AESEV_001] AESEV [A-1] ☐ MILD [A-2] ☐ MODERATE [A-3] ☐ SEVERE												
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Annotated CRF

- Mirrors annotations from ASB and places onto Blank CRF

B7981031: ADVERSE EVENT REPORT (AE) - Repeating Form														
#	Category	AE Identifier	Adjudication Event ID	Adverse Event	Start Date	Is the Adverse Event Still Ongoing	Severity	Serious	Is AE a Result of a Medication Error	Relationship to Study Treatment	Action Taken with Study Treatment	Concomitant Medication Given	Non-Drug Treatment Given	Outcome
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Adverse Event Report														
1.	Category: [Category]	☐ ADVERSE EVENT AECAT												
2.	AE ID: [AE Identifier]	AESPID												
3.	PAC / Adjudication Event ID: [Adjudication Event ID]	AEPACID in SUPPAE												
4.	Adverse Event: (If possible specify diagnosis, not individual symptoms) [Adverse Event]	AETERM												
5.	Start Date: [Start Date]	/ / AESTDTC												
6.	Is the adverse event still ongoing? [Is the Adverse Event Still Ongoing]	☐ YES ☐ NO End Date: / / AEENRPT AEENTPT AEENDTC												
7.	Severity: [Severity]	☐ MILD AESEV ☐ MODERATE ☐ SEVERE												
8.	Is the adverse event serious? If Yes, NOTIFY PFIZER IMMEDIATELY. Fatal; Life-threatening; Inpatient hospitalization or prolongation of	☐ YES AESER Is this serious event associated with congenital anomaly or birth defect? ☐ YES ☐ NO Did this serious event result in death? ☐ YES AESDTH ☐ NO AESCONG												

Bookmarks and Table of Contents (TOC)

Submission readiness

- Upload required documents
 - Final version of the aCRF
 - Study design Specifications (SDS) file with 'Time and Events' sheet
- Generate TOC: “Run” under “Hyperlink”

Table of Content & Bookmarking

Study: B7981031 [Search] [Upload aCRF&SDS]

Study	Add Hyperlink	Add Page Number	Bookmarking	
B7981031	[Upload aCRF&SDS] [View SDS Detail]	[Run]	[Run]	[Download]

< 1 > 10 / page Go to

Bookmarks and Table of Contents (TOC)

Submission readiness

- Review and update bookmarks/TOC metadata file
 - Click 'View SDS Detail'
 - Is an updated metadata file used to generate bookmarks

Table of Content & Bookmarking

Study

Study	Add Hyperlink	Add Page Number	Bookmarking
B7981031	Upload aCRF&SDS View SDS Detail	Run	Run

< 1 > 10 / page Go to

Bookmarks and Table of Contents (TOC)

Review and update bookmarks/TOC metadata file

- Will have the forms sorted by two tabs: by Visits and by Domains.
- Can be done online in tool or via downloaded file

Visits	Domains	Duplicates		Add	Delete
Screening					
☐	DATE OF VISIT		12		
☐	DEMOGRAPHY		8		
☐	INFORMED CONSENT- MAIN		15		
☐	INFORMED CONSENT- ASSENT		14		
☐	PRIMARY DIAGNOSIS		32		
☐	GENERAL MEDICAL HISTORY		26		
☐	VITAL SIGNS - SCREENING		42		
☐	PHARMACODYNAMICS LAB SAMPLE COLLECTION - IP 10		29		
☐	DISPOSITION - SCREENING		10		
DAY1					
☐	DATE OF VISIT		12		

Bookmarks and Table of Contents (TOC)

Submission readiness

- Finalize by adding bookmarks and page numbers
 - Bookmarks added by Visit and by Domain to aCRF within tool
 - Page numbers will be placed at bottom of each page reflecting the electronic file page numbers (original CRF page numbers redacted)

Table of Content & Bookmarking

Study: B7981031 [Search] [Upload aCRF&SDS]

Study	Add Hyperlink	Add Page Number	Bookmarking	
B7981031	[Upload aCRF&SDS] [View SDS Detail]	[Run]	[Run]	[Download]

< 1 > 10 / page v Go to

Downloading & Locking a Study

- Once final the aCRF can be downloaded to be flattened for submission and archived as required
- At any time a study can be locked to ensure no other users can make changes
 - Once locked, other users can view annotations
 - Only the programmer that locked a study can unlock it

Study	Update Time	SPA Programmer	Locked By	Annotation Request Status	
A5481092	2021-11-10 09:01:42	MOTUPG		• Approved	View Lock
B5381012	2021-12-02 11:24:35	TOMB	TOMB	• Approved	View Unlock

Acknowledgements

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- Christine Rossin
- David Postma
- Abdallah Kinani
- Mercer Thorp
- Yao Huang

Questions?



Thank You