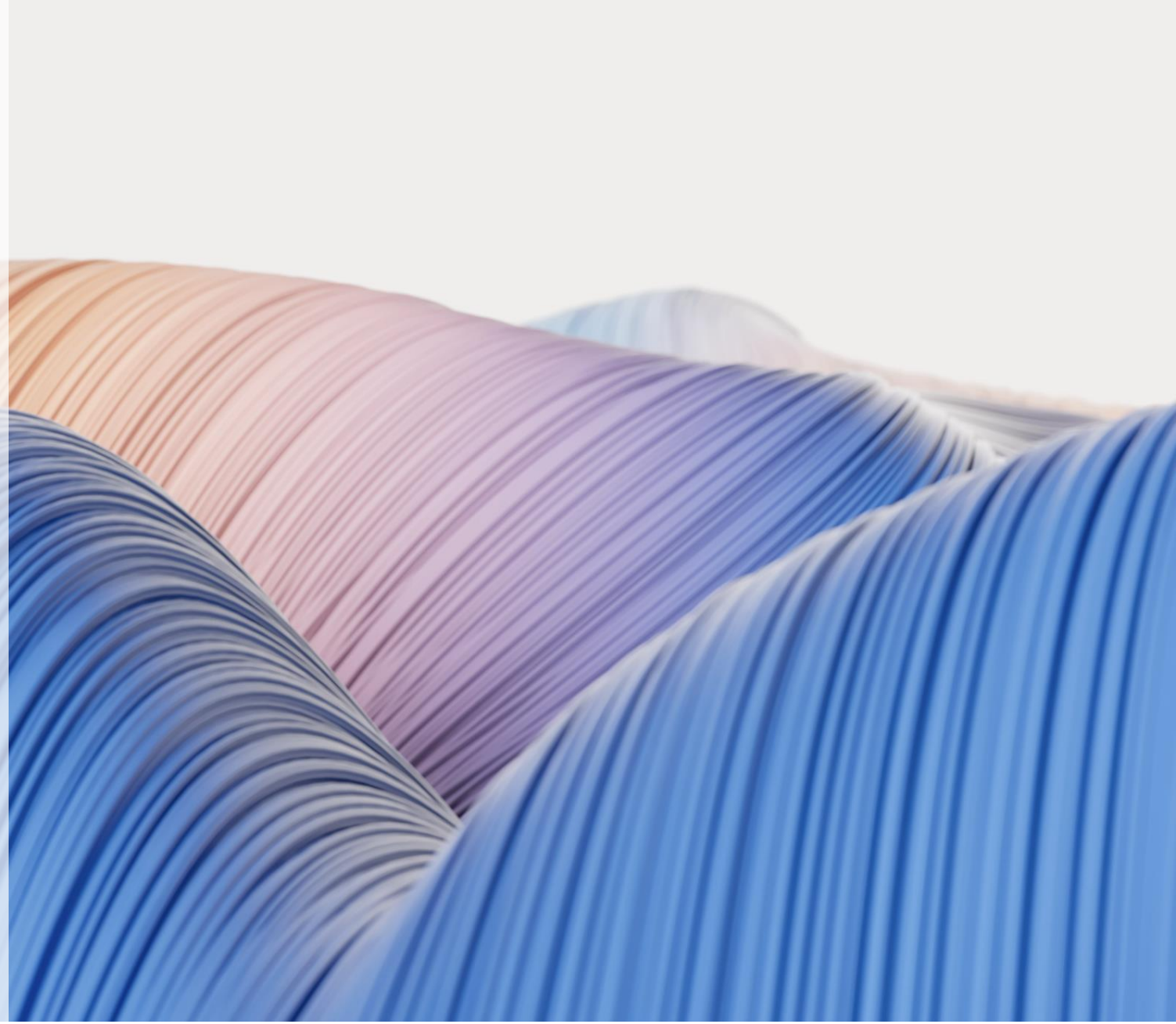
Automating SDTM Annotated CRF (aCRF) Creation

Leveraging Upstream Metadata

Christine Rossin

Collegeville, PA
August 29, 2024



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

- The process of annotating a Blank CRF with SDTM variables **is an industry-wide expectation** when submitting data to some regulatory agencies, e.g., FDA, PMDA, or NMPA.

- An annotated case report form (aCRF) is a PDF document that **maps the clinical data collection fields** used to capture subject data (electronic or paper) to the **corresponding variables or discrete variable values** contained within the **SDTM datasets**. Regardless of whether the clinical database is in a format supported by the Catalog, an aCRF should be submitted **preferably at the time a protocol is submitted**.*

- For **every user of the study data** the aCRF is a **critical part of the study documentation**. It 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.**

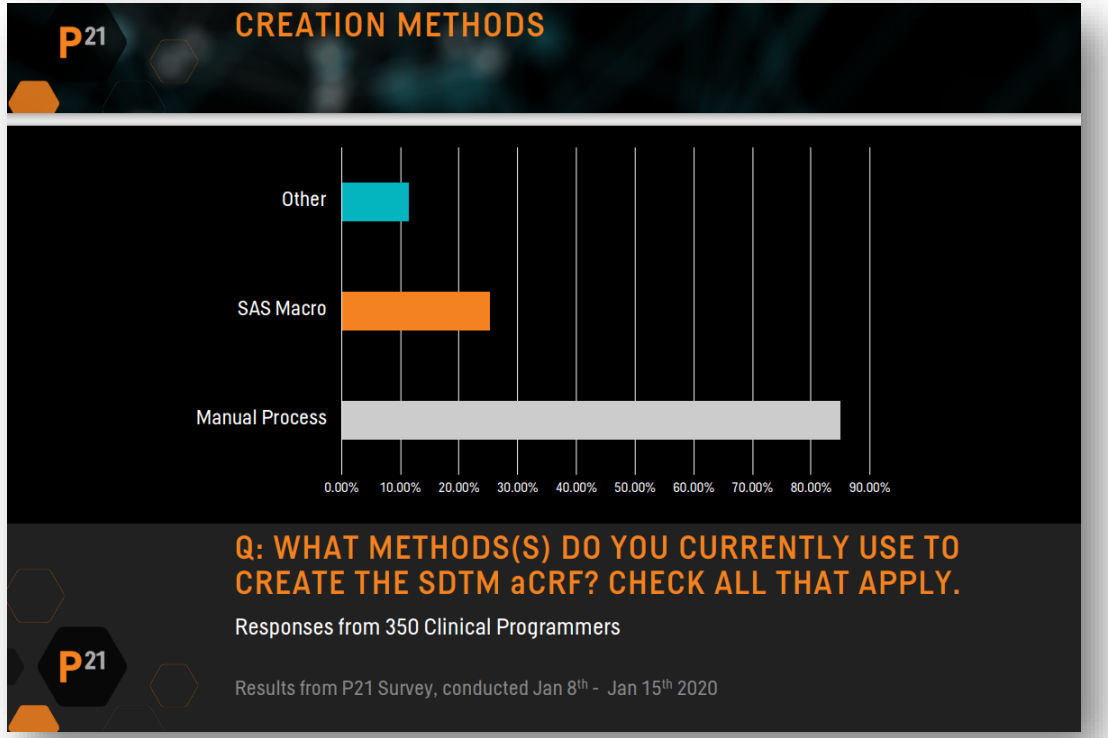
- It is obvious that making the **aCRF submission ready right from the beginning** will facilitate submission preparation and will save time and costs.**

*FDA Study Data Technical Conformance Guide, Technical Specifications Document, v5.7, March 2024
**SDTM aCRF Guideline, Guideline for SDTM annotation in Case Report Forms, Summary and Recommendations for Best Practice, v10 2020-11-20

Background and Context

Some notes about industry guidance and practices

- 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
- Guidance:
  - SDTM aCRF Guideline v1.0 (wiki.cdisc.org)
  - Study Data Tabulation Model Metadata Submission Guidelines (SDTM-MSG) v1.0 (cdisc.org)
  - Study Data Tabulation Model Metadata Submission Guidelines (SDTM-MSG): Human Clinical Trials v2.0 (cdisc.org)



Original Working Model: eSub QC Team Support

Partially automated approach

- Team of eSub specialist QC/ programmers supporting study teams
- Mostly manual creation of submission ready aCRF
- Study team involvement by reviewing annotations and confirming study specific details
- Leveraged only late-stage deliverables
  - Stable set of SDTM
  - Stable define.xlsx file
- Automation only via SAS programming
  - Driven by define Origin and CRF Page numbers
  - Annotations placed on Blank CRF in column along one side; each annotation manually moved to correct location
  - Adjustments done manually

Development of SDTM aCRF Annotator Tool

Ideation of an automation

Automation Opportunity

Team of 3 statistical programmers set out to automate aCRF creation

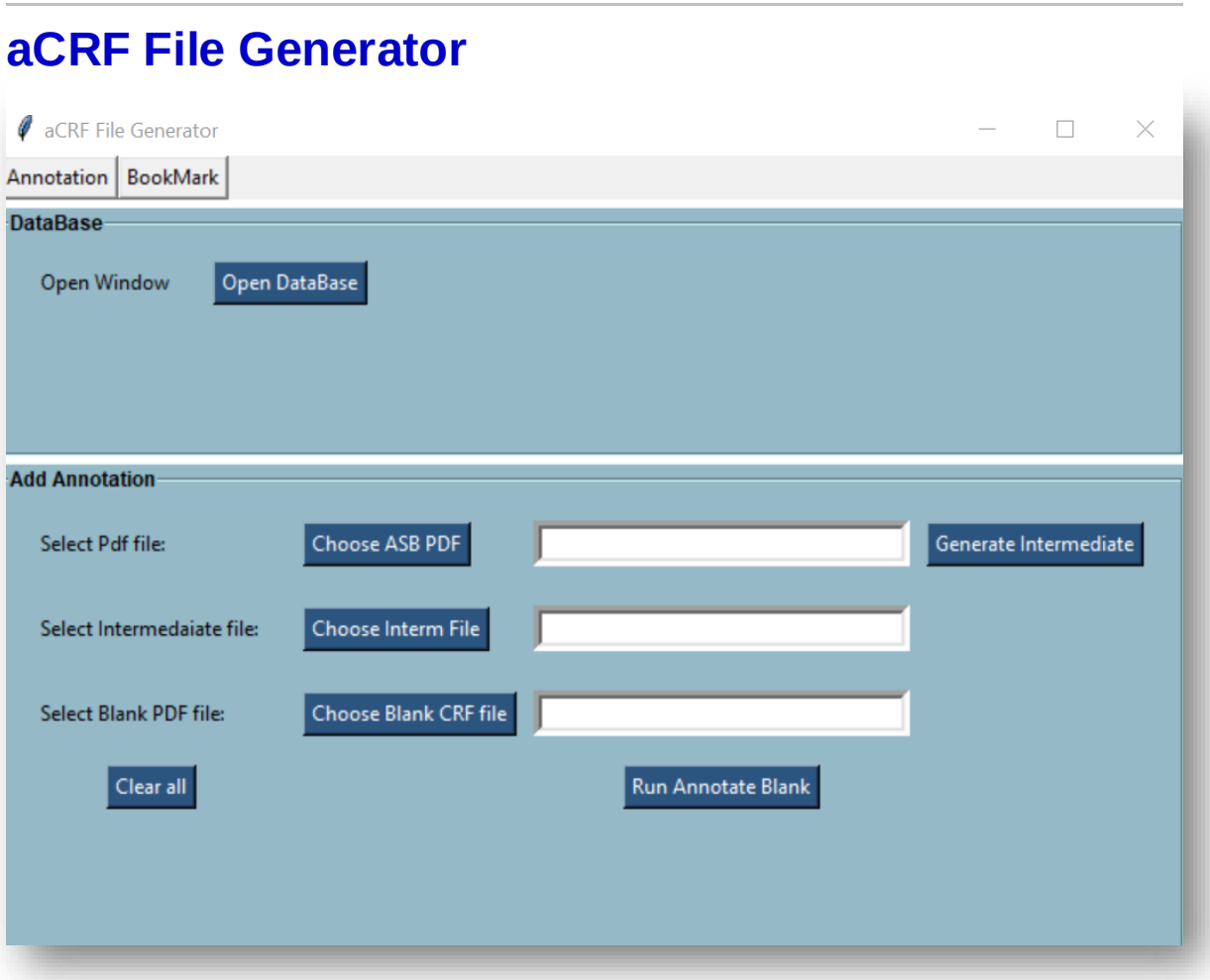
Vision

Web-based tool	Automate placing the SDTM variables	Hyperlinked TOC	Bookmarks by Visit and Domain	Page numbers

Development of SDTM aCRF Annotator Tool – Local Utility

Initial version – a locally executed utility

- Python scripts, behind a downloaded interface
- Attached SDTM variable annotations to database source variable fields to a blank Annotated Study Book (ASB)
- Used coordinates from field reference IDs on ASB to place SDTM variables on to corresponding Blank CRF pages
- Built a library of annotations repository over time using each study's aCRF annotations
  - Study-level annotation managed manually by interfile
  - Applied standard and repeating annotations to new studies, and continued to build with new annotations
  - Review and approval of annotation library done by repository manager team (labor intensive)
- Utilized Study Design Specifications (SDS), with sheet for time & events schedule, to create hyperlinked TOC, bookmarks by Visit and Domain
- Created footer for page numbers to reflect new electronic file page



Development of SDTM aCRF Annotator Tool – a GUI

For study teams to use utility required a validated tool

Needed a shared server for global access

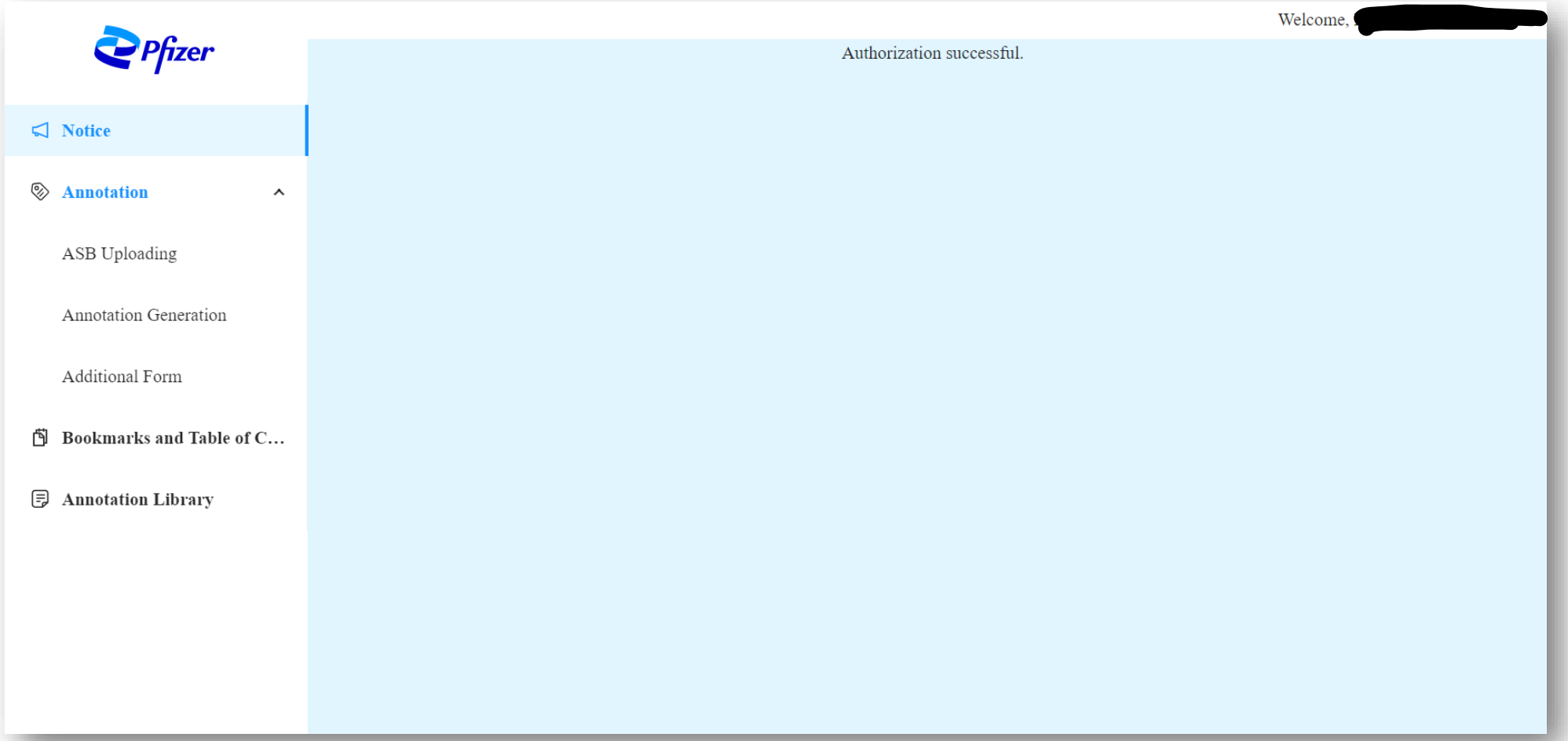
Digital group required a validated tool since creating regulatory deliverable

Developed GUI interface to be hosted on an internal server

Established formal support ticketing process to address issues or receive requests for enhancement

Development of SDTM aCRF Annotator Tool – a GUI

Second version – globally accessible tool



Pilot to Prepare for Rollout to Study Teams

Pressure testing

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

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

3. **Time commitment**: estimated 20% time over two weeks (i.e., should take total of < 2 days to complete; could be longer, depending on study complexity).

4. **Execution**: Programmers will be trained and will use pilot to test if the training materials are sufficient. 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.

5. **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

- User guide document updated
  - Mostly clarifications based on user feedback
  - Arranged sections to enable user to be walked through creation of aCRF from start to finish
  - Ensured additional software requirements for finalization of aCRF clarified and confirmed as expected
    - Adobe version confirmed for study team users (different from eSub specialist QC team)
    - Adobe toolbox not available for study team users, but is required for eSub special QC team (for QC activities)
- Addressed annotation gap (< 5 to <20 % CRF automated)
  - Create library of annotations repository using a direct extraction from MDR
  - MDR curated and fully functional for ASB creation
  - SDTM mapping referenced MDR
  - Extraction established required linkage between form reference IDs and SDTM variables
  - Offers a 80 – 90 % CRF automation

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

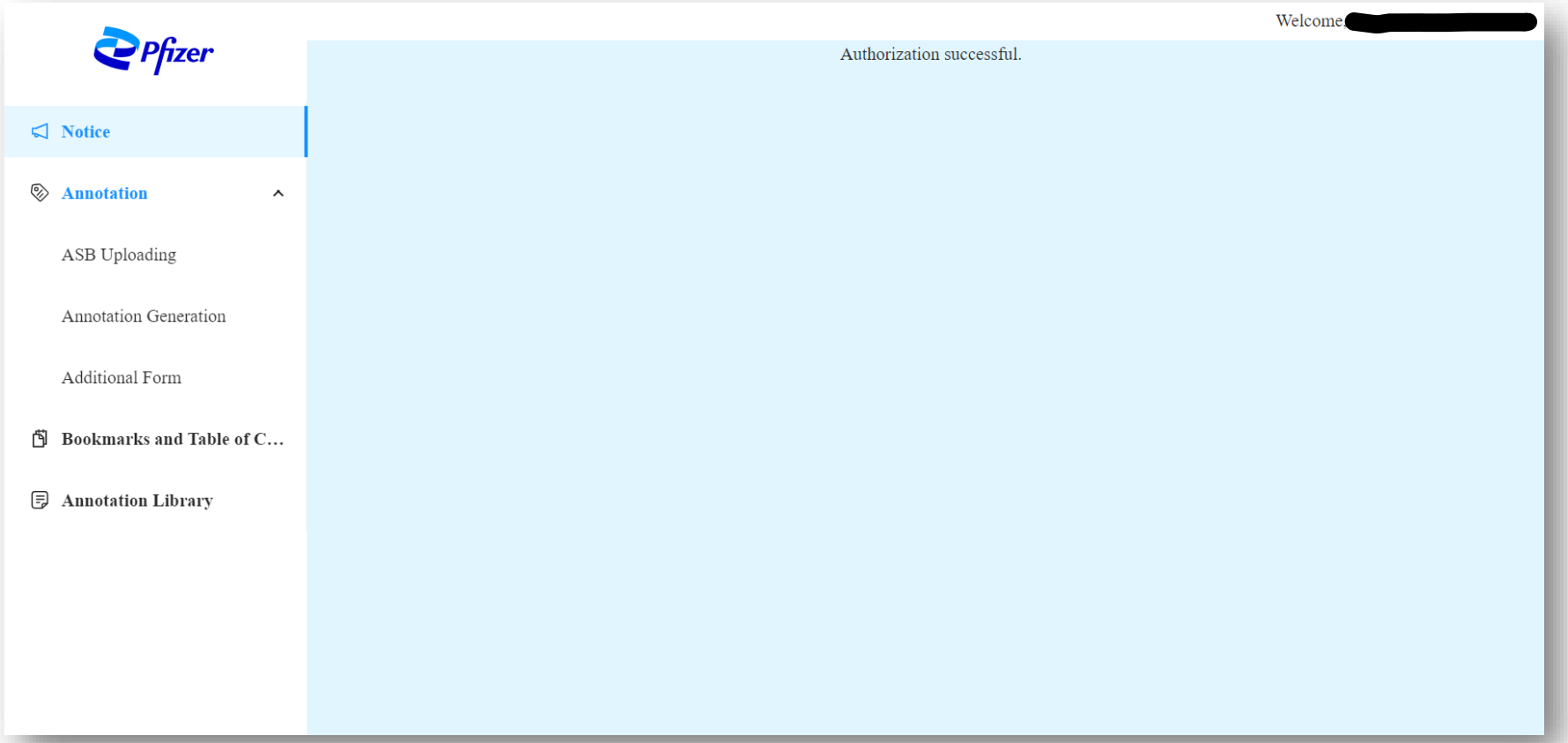
Overview of the value added using the tool

- 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

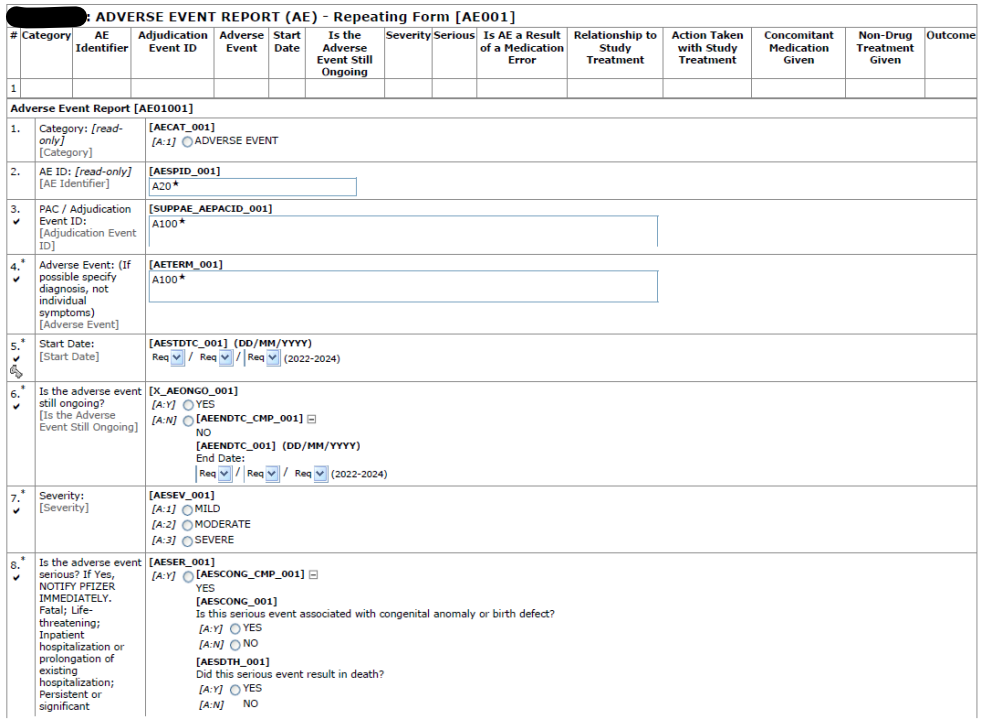


Generate an aCRF

Documents needed for annotations

Annotated Study Book (ASB)

- Contains field reference IDs and other metadata



[redacted]: ADVERSE EVENT REPORT (AE) - Repeating Form [AE001]

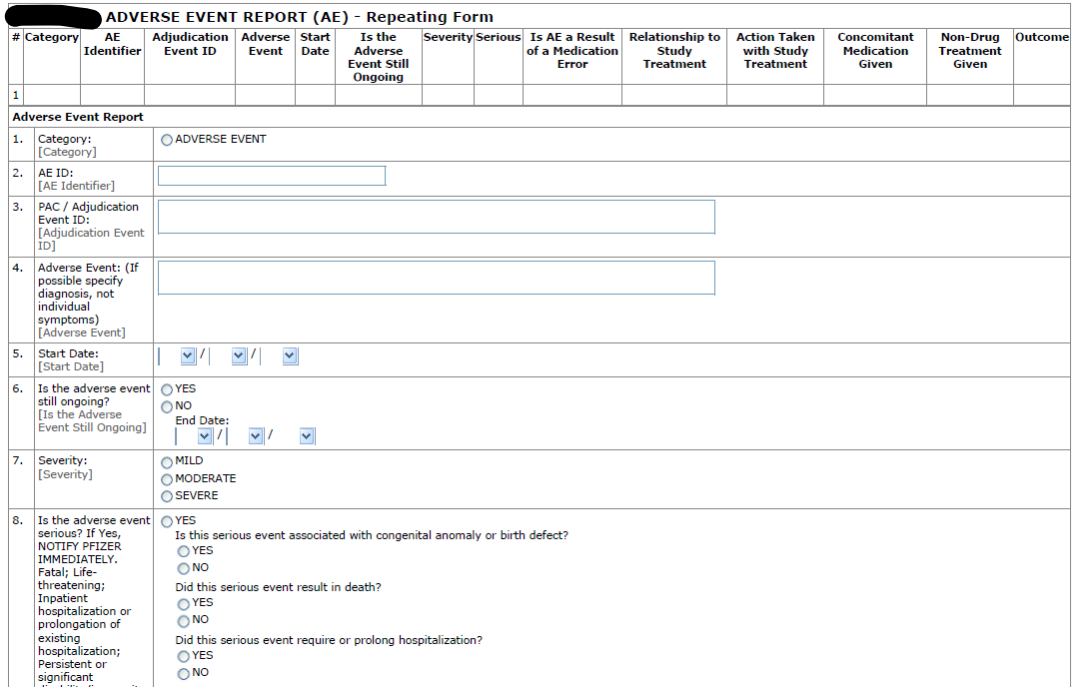
#	Category	AE Identifier	Adjudication Event ID	Adverse Event	Start Date	Is the Adverse Event Still Ongoing	Severity	Serious	Is AE a Result of a Medication Error	Relationship to Study Treatment	Action Taken with Study Treatment	Concomitant Medication Given	Non-Drug Treatment Given	Outcome
1														

Adverse Event Report [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] NO; [AEENDTC_CMP_001] [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



[redacted] 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
1														

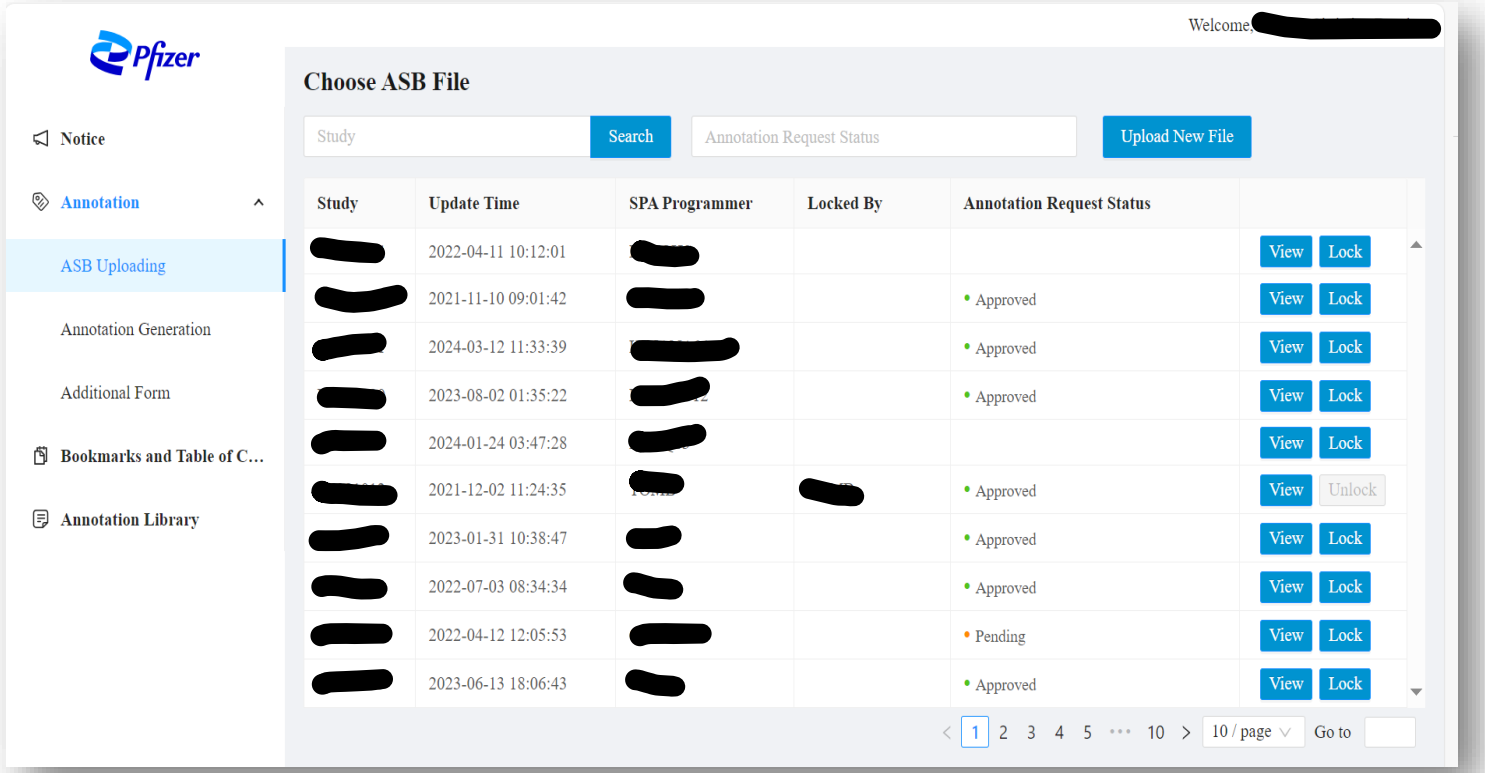
Adverse Event Report

1. Category: [Category] — ADVERSE EVENT
2. AE ID: [AE Identifier]
3. PAC / Adjudication Event ID: [Adjudication Event ID]
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

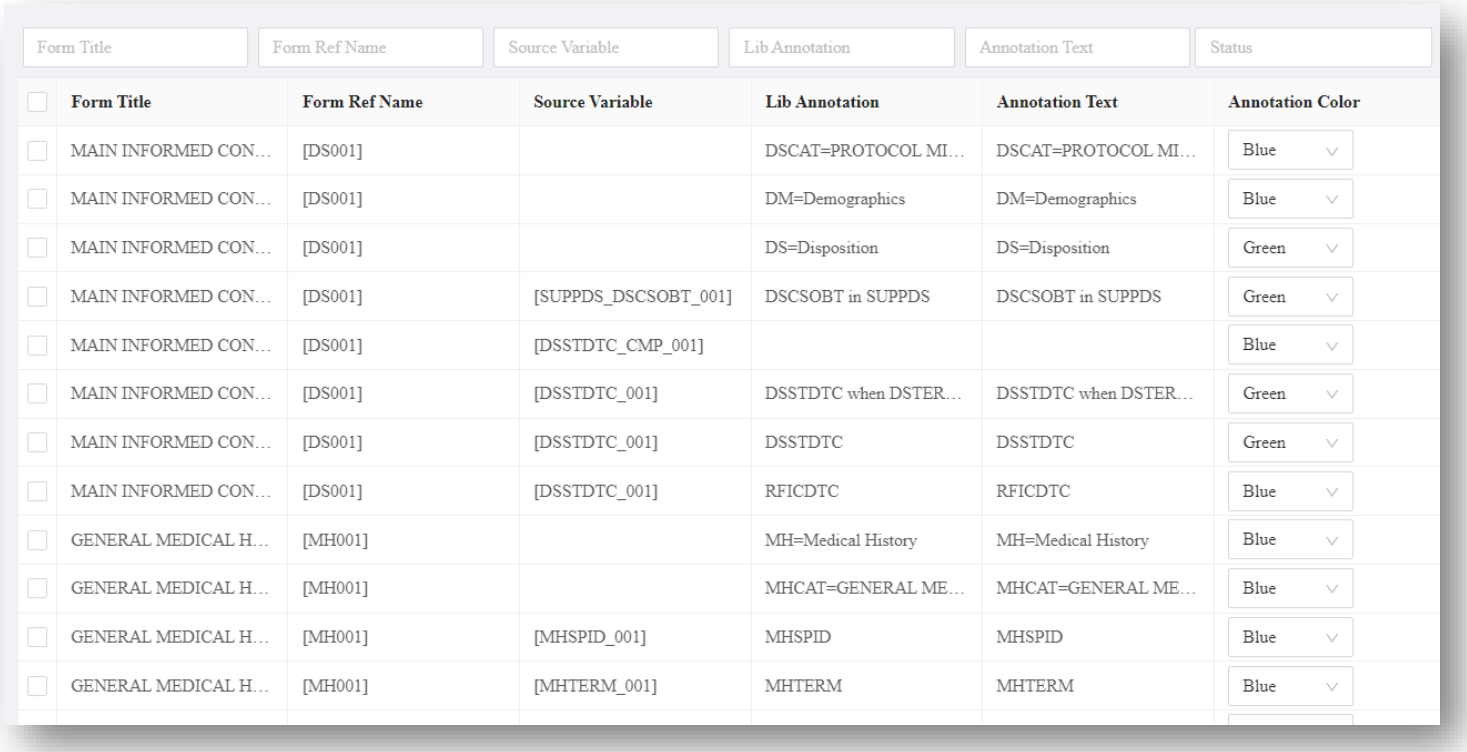
- Studies currently available will be listed
- New studies added using “Upload New File”
  - Will fetch annotations linked to study ASB fields using the library of annotations
- Review study annotations metadata file
  - May require manual updates



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

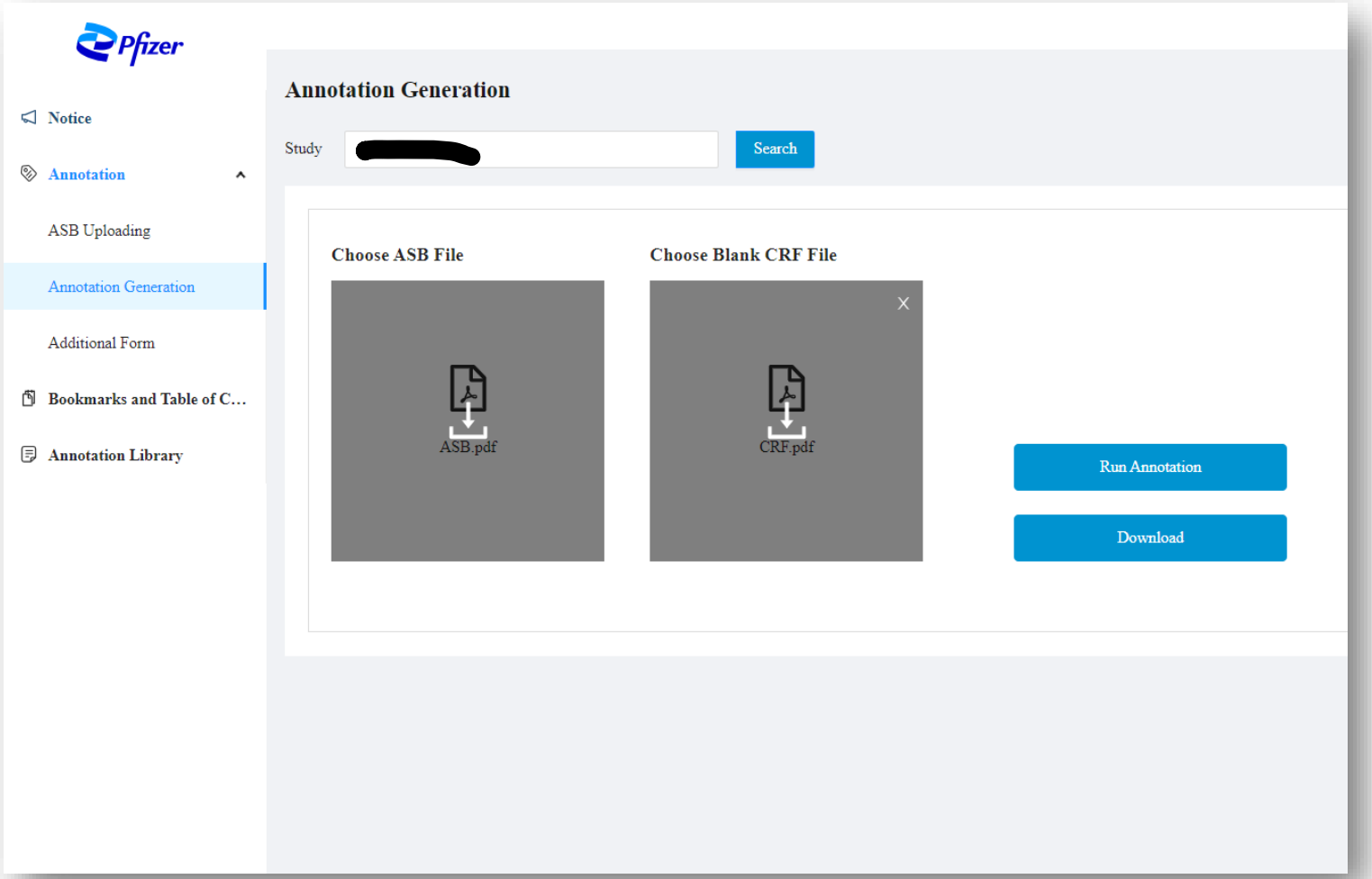


Form Title	Form Ref Name	Source Variable	Lib Annotation	Annotation Text	Annotation Color
MAIN INFORMED CON…	[DS001]		DSCAT=PROTOCOL MI…	DSCAT=PROTOCOL MI…	Blue
MAIN INFORMED CON…	[DS001]		DM=Demographics	DM=Demographics	Blue
MAIN INFORMED CON…	[DS001]		DS=Disposition	DS=Disposition	Green
MAIN INFORMED 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

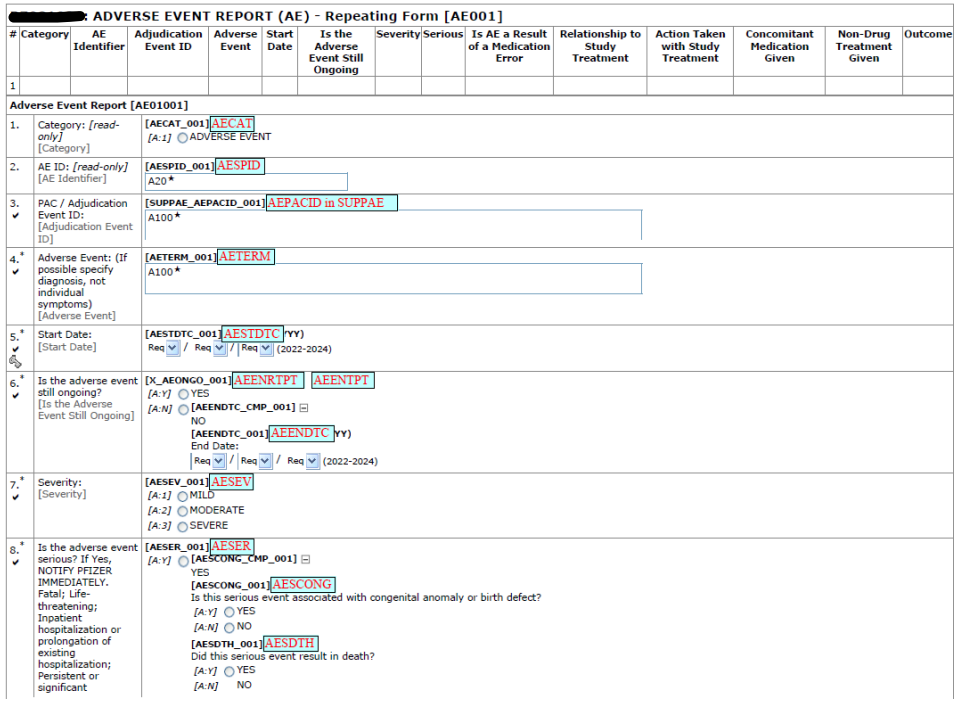


Annotation Generation Tab

Reviewing and adjusting the aCRF

Annotated Study Book (ASB)

- SDTM variables placed next to field reference IDs



[redacted]: ADVERSE EVENT REPORT (AE) - Repeating Form [AE001]

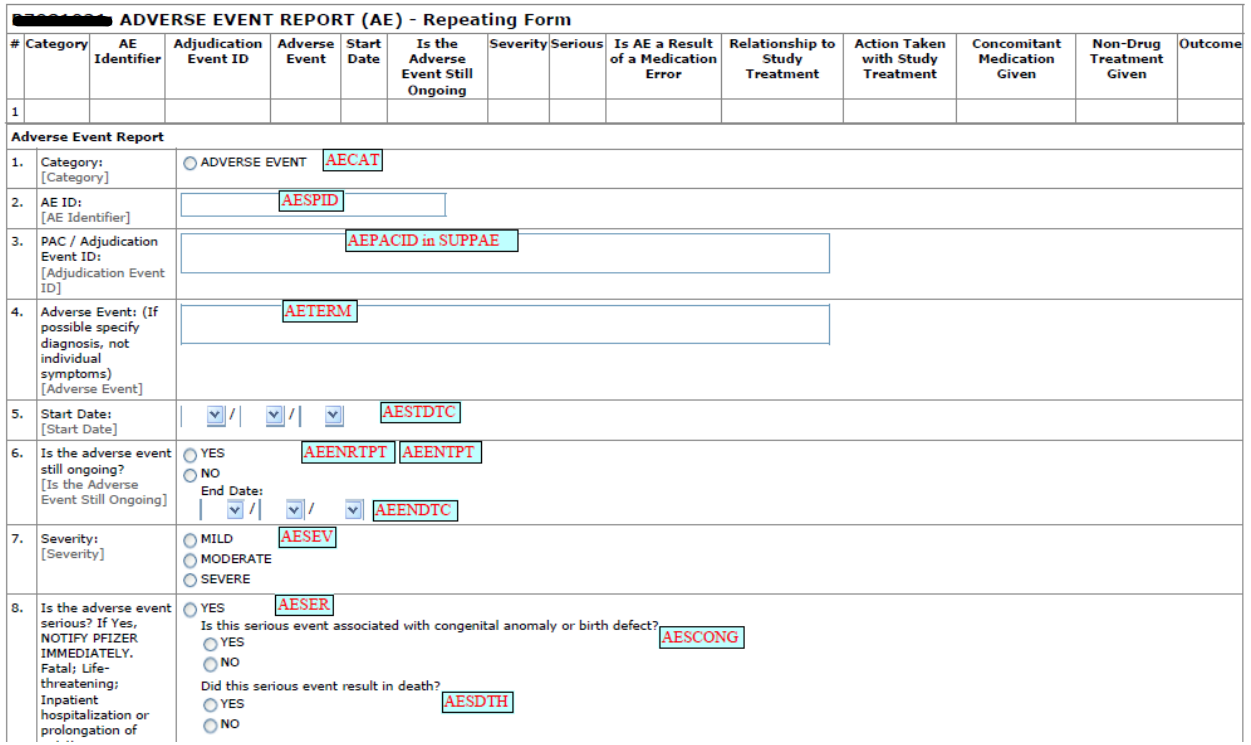
#	Category	AE Identifier	Adjudication Event ID	Adverse Event	Start Date	Is the Adverse Event Still Ongoing	Severity	Serious	Is AE a Result of a Medication Error	Relationship to Study Treatment	Action Taken with Study Treatment	Concomitant Medication Given	Non-Drug Treatment Given	Outcome
1														

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] AEENRTPT AEENTPT
   [A:Y] ○ YES
   [A:N] ○ [AEENDTC_CMP_001]
   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
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] AESER
   [A:Y] ○ [AESCONG_CMP_001]
   YES
   [AESCONG_001] AESCONG
   Is this serious event associated with congenital anomaly or birth defect?
   [A:Y] ○ YES
   [A:N] ○ NO
   [AESDTH_001] AESDTH
   Did this serious event result in death?
   [A:Y] ○ YES
   [A:N] NO

Annotated CRF

- Mirrors annotations from ASB and places onto Blank CRF



[redacted]: 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
1														

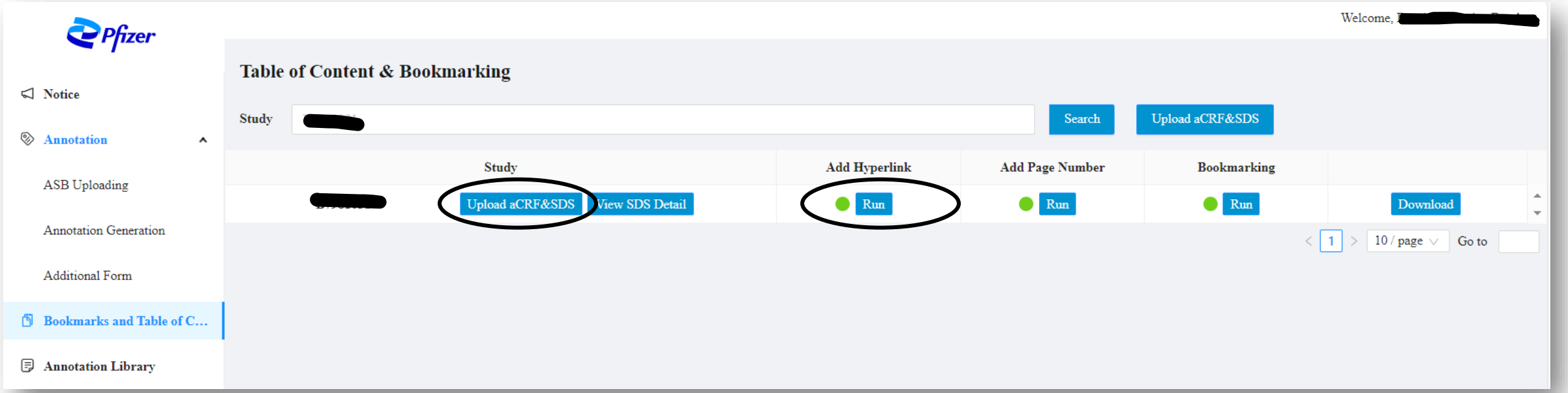
Adverse Event Report

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 AEENRTPT AEENTPT
   ○ NO
   End Date: / / 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? AESCONG
   ○ YES
   ○ NO
   Did this serious event result in death? AESDTH
   ○ YES
   ○ NO

Bookmarks and Table of Contents (TOC)

Submission readiness

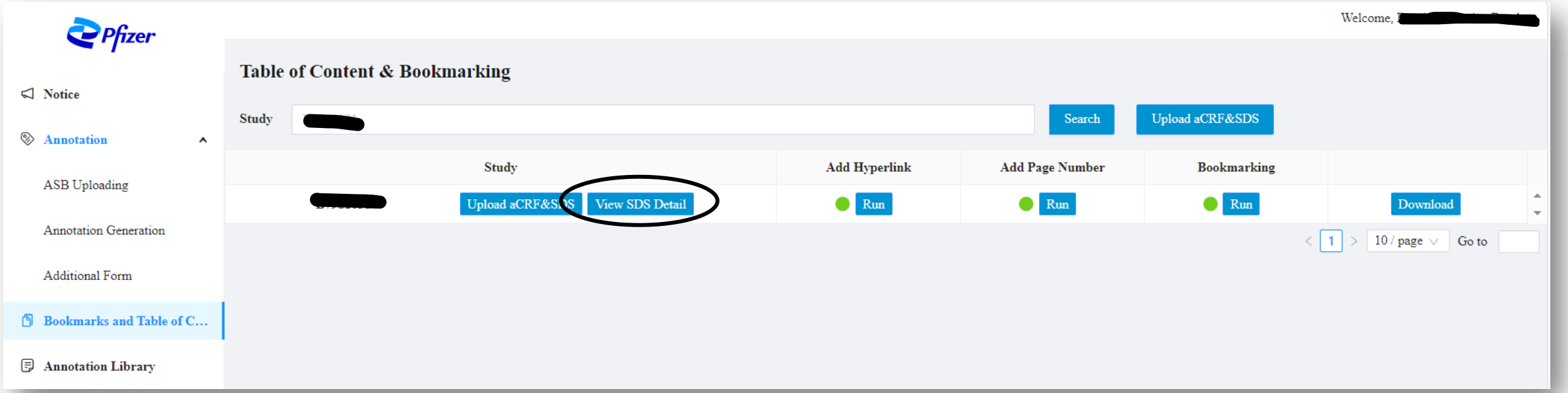
- Upload required documents
  - Final version of the aCRF
  - Study design Specifications (SDS) file with ‘Time and Events’ sheet
- Generate TOC: “Run” under “Hyperlink”



Bookmarks and Table of Contents (TOC)

Submission readiness

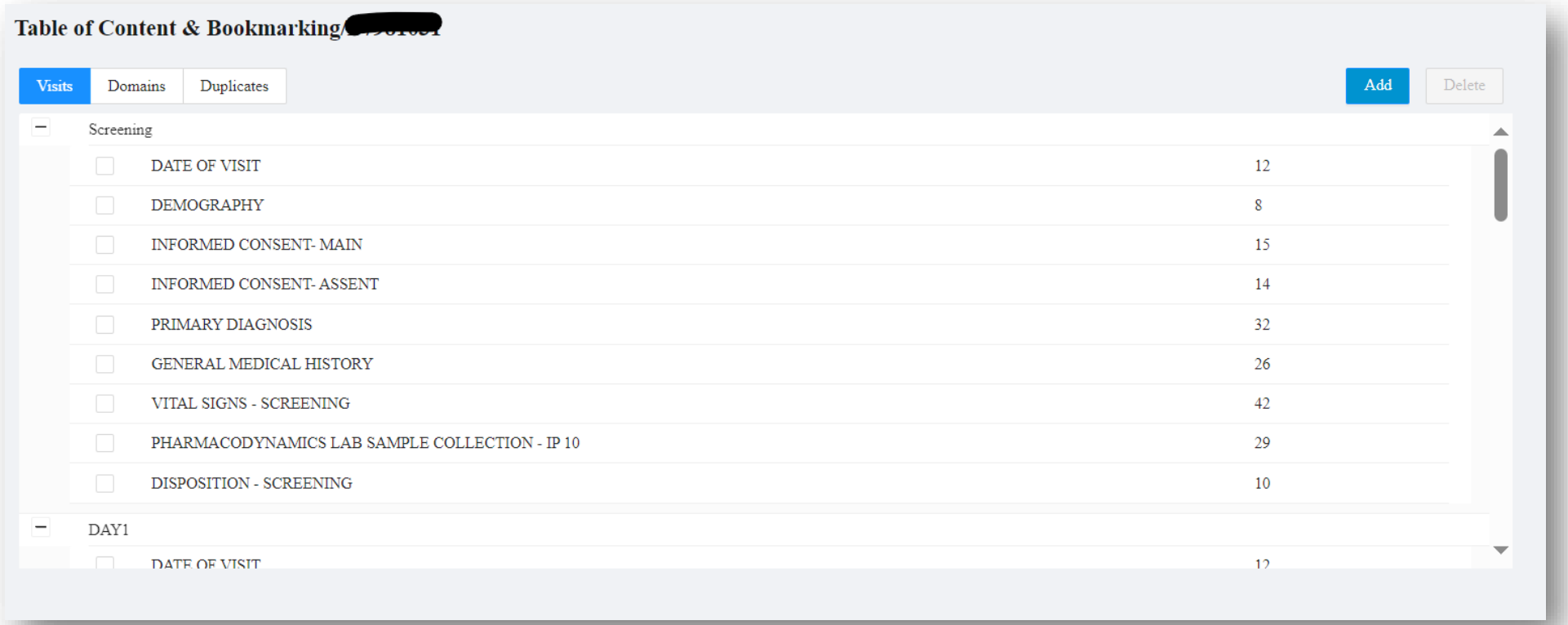
- Review and update bookmarks/TOC metadata file
  - Click ‘View SDS Detail’
  - Is an updated metadata file used to generate bookmarks



Bookmarks and Table of Contents (TOC)

Review and update bookmarks/TOC metadata file

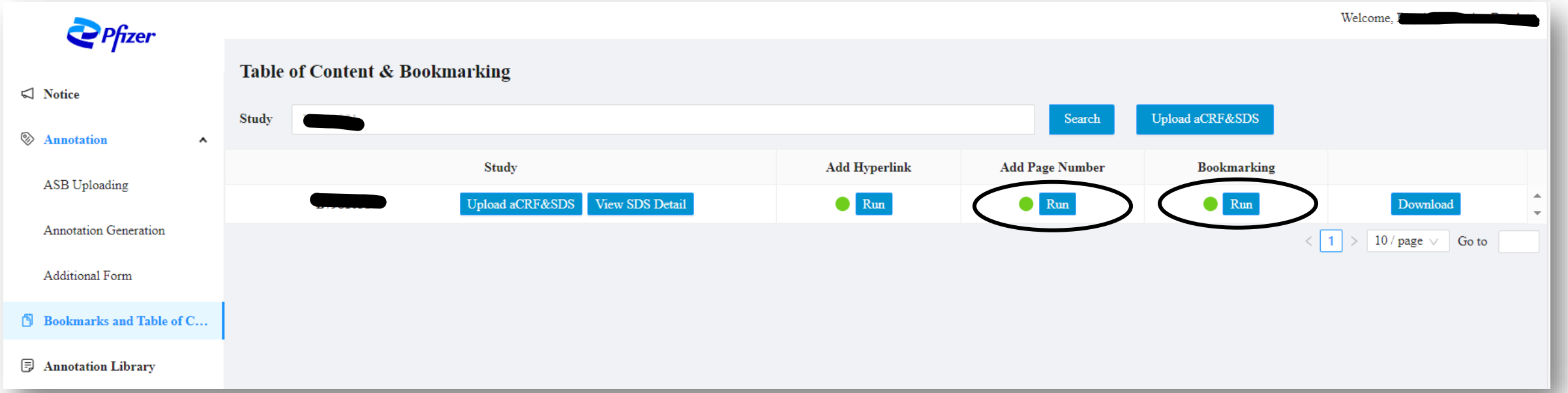
- Will have the forms sorted by two tabs: by Visits and by Domains.
- Can be done online in tool or via downloaded file



Bookmarks and Table of Contents (TOC)

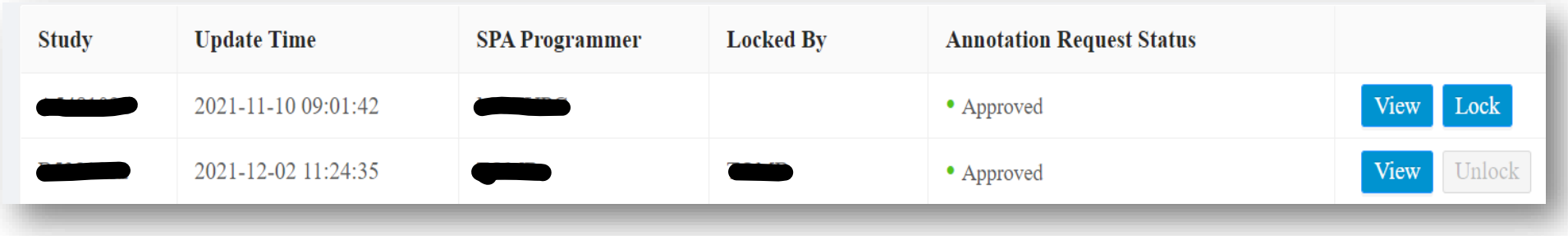
Submission readiness

- 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)



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



Acknowledgements

The team who made it happen

- Gauravbir Dogra
- Smriti Anand
- Suvathi Veerapandian
- Christine Rossin
- David Postma
- Abdallah Kinani
- Mercer Thorp
- Yao Huang

Questions?

Thank You