REPORTING COVID-19 PANDEMIC INDICATOR

PHUSE Single Day Event 2022
Spring House, PA
Thursday 21 July 2022

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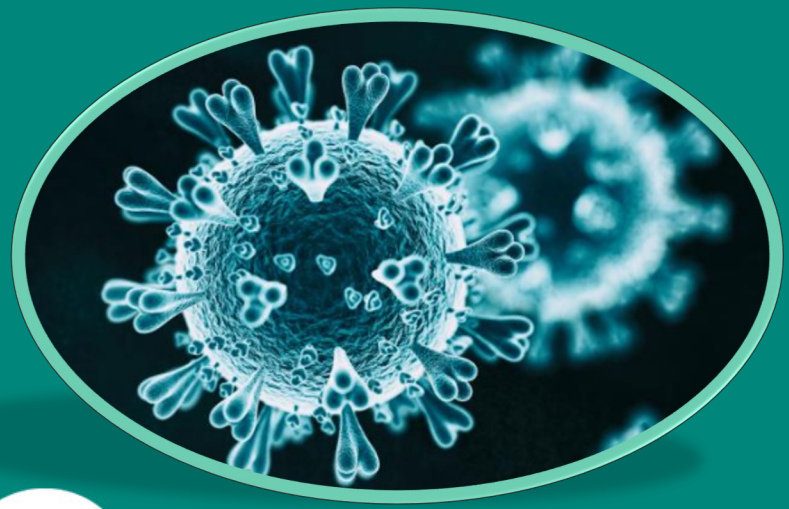

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Agenda

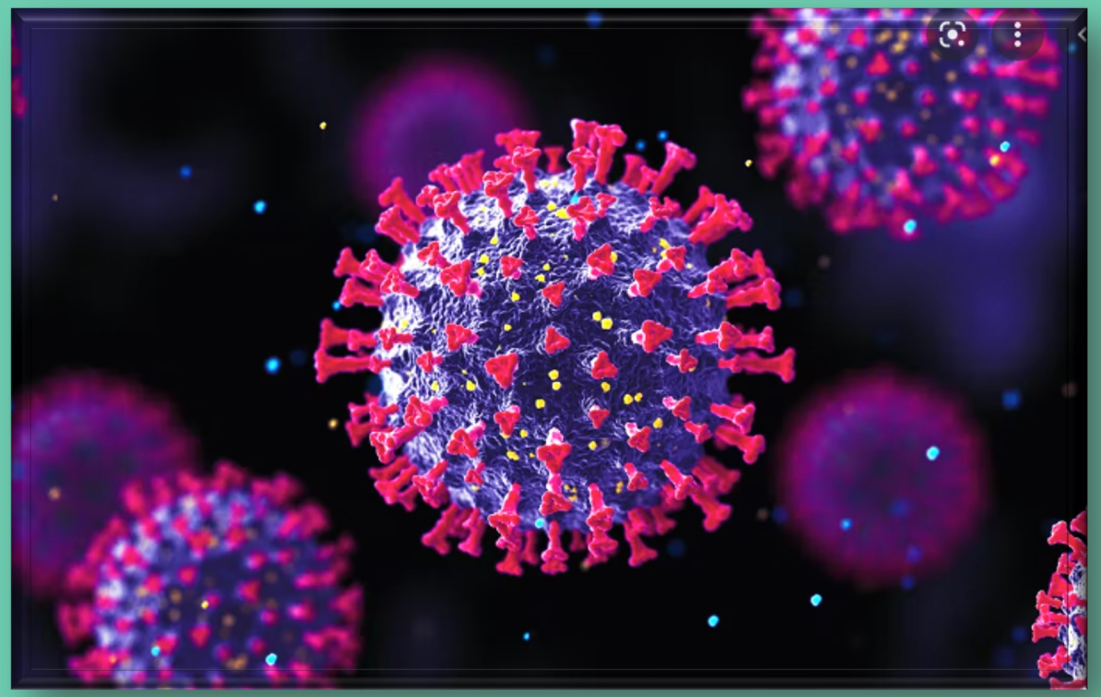
What you need to know about COVID-19 pandemic Indicator data that would be used for reporting:

1. Protocol Deviation associated with COVID-19

2. Discontinuations due to COVID-19
   - Overall Study Discontinuations
   - Study Medication Discontinuations
   - Trial Segment Discontinuations

3. Adverse Event

4. Trial Summary (TS) Domain Flag



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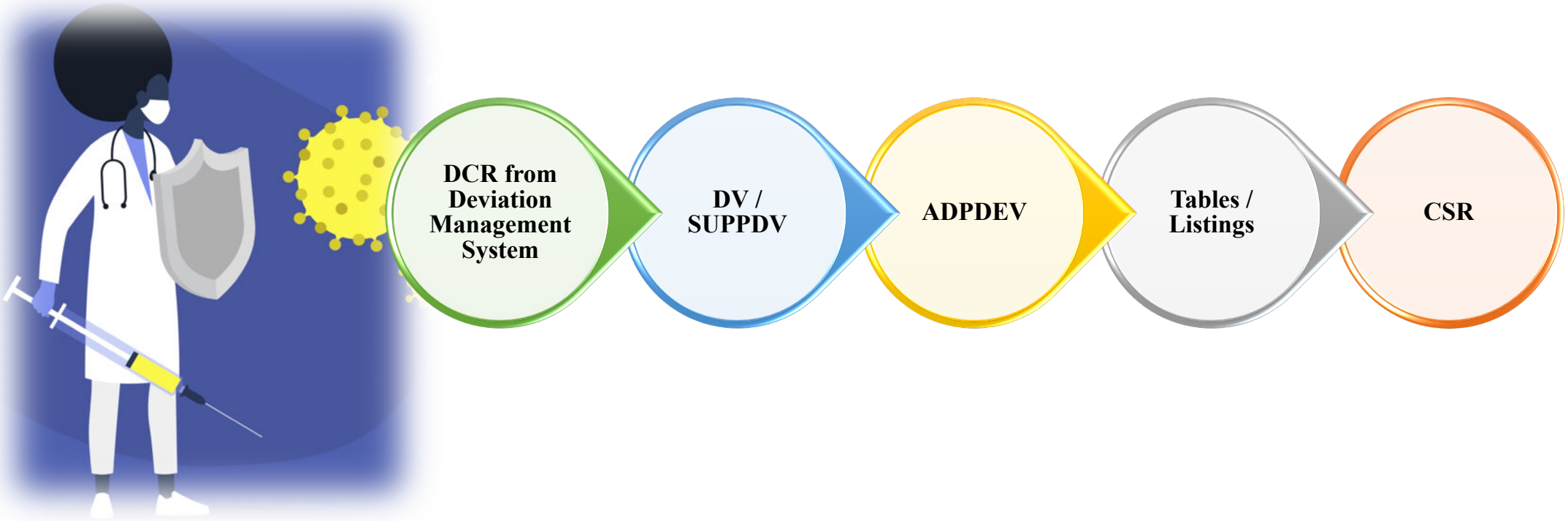
Protocol Deviation Associated with COVID-19



DCR: Deviations Cumulative Report

New Process

Plan	• Statistician calls COVID PD Term Customization meeting to initiate process. Discuss CSR TLF needs
Report	• CRA reports deviations with all required COVID-19 details
Review	• Clinical reviews deviations & Statistician and Clinical Scientist assesses the need for sensitivity analyses
Run	• Clinical runs & prepares the Deviations Cumulative Report for the Statistician & files in electronic Trial Master File
Create	• SDTM and Stat Programmers use the Deviations Cumulative Report to create SDTM to ADaM and Tables & Listings
Author	• Medical Writer uses the Tables & Listings to author the associated sections of the Clinical Study Report (CSR)

COVID PD Term Customization Meeting

- Called/led by statistician, ~4-6 weeks post FPE (or ASAP)
  - Discuss CSR needs and plan for COVID PD accounting table(s)
    - Discuss/revise COVID-19 related PD Accounting table mockup
  - Select terms that will be in the drop-down lists for the study from the TA-specific lists (Master Template of COVID PD Terms)
    - Discuss WHAT aspects of the study were impacted by the COVID PD (e.g. a visit), and HOW those aspects of the study were impacted (e.g., missed or delayed)
    - Remove any terms from the master list that are not applicable for the trial
    - Decide whether any new terms should be requested
    - If no terms requested, save the final *MK/V-XXX PXXX COVID PD Term List*
    - If new terms will be requested, contact PD SMEs, and upon approval of new terms, add the terms

COVID-19 Related PD Accounting Table Mockup

Accounting of Selected Protocol Deviations Associated With COVID-19

<<Rows with zero counts should not display in the CSR report>>

	Treatment A	Treatment B	Total
Subjects in population			
Subjects with ≥1 visit deviation			
≥1 visit missed			
≥1 visit where a primary/secondary efficacy assessment was scheduled[a]			
≥1 visit delayed			
≥1 visit where XXX was scheduled			
Subjects with ≥2 visit deviations			
Subjects with ≥3 visit deviations			
Subjects with ≥1 dose deviation			
≥1 dose missed			
≥1 dose delayed			
Subjects with ≥2 dose deviations			
Subjects with ≥3 dose deviations			
Etc. (additional blocks of rows for each value of the what variables)			

[a]*Safety assessments were scheduled for all visits.* /
<Other endnotes / footnotes as needed>

This table reflects all protocol deviations reported as associated with COVID-19 that are deemed to have the potential to impact interpretation of study results.

Each block of rows (i.e., within horizontal grid lines) reflects deviations recorded according to the bolded text (e.g., visit, dose). Impacts of COVID-19 counted in the blocks of rows subsequent to visit deviations may or may not also be counted within the block of rows for visit deviations, and vice versa, depending on whether the impacts were reported both as visit deviations and as other deviations.

Data Source: [data_source_txt]

How/ ATERM

What/ ACAT1

ASTERM/ Derived in ADPDEV

ATERM/ Derived in ADPDEV

Example of DV/SUPPDV

DOMAIN	USUBJID	DVSEQ	DVTERM	DVDECOD	EPOCH
DV	1000-000_009200001	1	COVID-19 outbreak: C19 ePRO questionnaire was not completed due to PCoord being working remotely during the COVID-19 outbreak. Suggested the site to arrange with a staff who assist during the study	Other Deviation	TREATMENT CYCLE 19
DV	1000-000_010000002	1	COVID-19 - Subject is unable to complete the ePRO diaries without being translated. As a result, all ePRO diaries will be considered not completed (missed mode) as the ePRO doesn't provide an option	Not Important Trial Procedures deviation	TREATMENT CYCLE 1
DV	1000-000_010000002	2	COVID-19 - Subject is unable to complete the ePRO diaries without being translated. As a result, all ePRO diaries will be considered not completed (missed mode) as the ePRO doesn't provide an option	Not Important Trial Procedures deviation	TREATMENT CYCLE 4
			COVID-19-Sub006 (Cycle 3) - Subject did not complete ePROs at		

SUPPDV

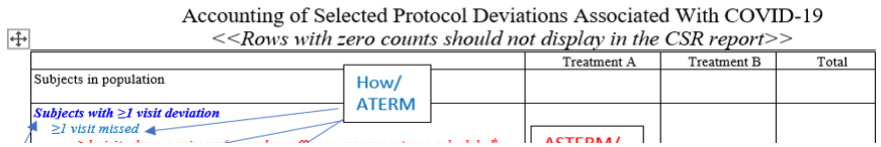
RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
DV	1000-000_009200001	DVSEQ	1	HDVI1	How Deviation Impact 1	MISSED
DV	1000-000_009200001	DVSEQ	1	WDVI1	What Deviation Impact 1	PATIENT-REPORTED OUTCOME
DV	1000-000_010000002	DVSEQ	1	HDVI1	How Deviation Impact 1	MISSED
DV	1000-000_010000002	DVSEQ	1	WDVI1	What Deviation Impact 1	PATIENT-REPORTED OUTCOME
DV	1000-000_010000002	DVSEQ	2	HDVI1	How Deviation Impact 1	MISSED
DV	1000-000_010000002	DVSEQ	2	WDVI1	What Deviation Impact 1	PATIENT-REPORTED OUTCOME

Example of ADPDEV

	USUBJID	DVTERM	DVTERM1	WDVI	ACAT1	ACAT1N	HDVI	ATERM	ATERMN	DVSEQ	ANL01FL
1	1000-000_009200001	COVID-19 outbreak: C19 ePRO questionnaire was not completed due to PCoord being working remotely during the COVID-19 outbreak. Suggested the site to arrange with a staff who assist during the study	visit and obtain the questionnaires using a paper copy of questionnaire. Then, PCoord can update the ePRO later.	Patient-Reported Outcome	Subjects with >=1 Patient-Reported Outcome deviation	2	Missed	>=1 Patient-Reported Outcome Missed	7	1	Y
2	1000-000_010000002	COVID-19 - Subject is unable to complete the ePRO diaries without being translated. As a result, all ePRO diaries will be considered not completed (missed mode) as the ePRO doesn't provide an option	in a language the subject understands.	Patient-Reported Outcome	Subjects with >=1 Patient-Reported Outcome deviation	2	Missed	>=1 Patient-Reported Outcome Missed	7	1	Y
3	1000-000_010000002	COVID-19 - Subject is unable to complete the ePRO diaries without being translated. As a result, all ePRO diaries will be considered not completed (missed mode) as the ePRO doesn't provide an option	in a language the subject understands.	Patient-Reported Outcome	Subjects with >=1 Patient-Reported Outcome deviation	2	Missed	>=1 Patient-Reported Outcome Missed	7	2	Y

A sample call

- Use population_where, observation_where, subtitle
- All the text description in the first column except the first row “Subjects in population” are based on ADPDEV data.
  - Users need to derive these variables in ADPDEV



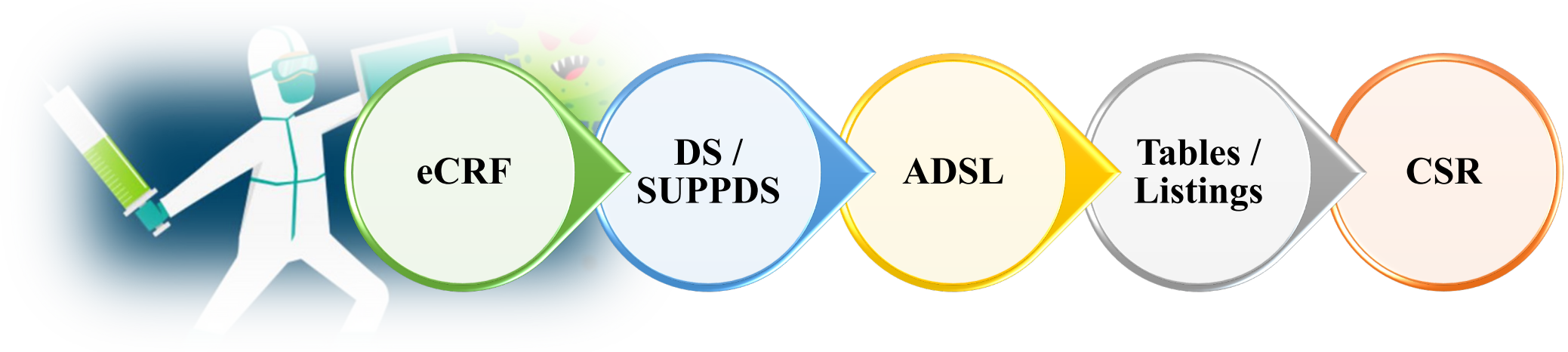
- Variable ASTERM and ASTERMN are not in all studies.
  - If these variables not exist in your studies, then third level rows will not be displayed.

```
%asr0pd0account0covid19(
 population_from=
,population_where=%str(trtfl='Y')
,observation_from=
,observation_where=%str(anl01fl='Y')
,therapy_des_var=
,therapy_cd_var=
,rename_output=&tnum
,output_fileref=
,rel_col_widths=
,display_totals=y
,data_source_txt=
,create_output_dataset= Y
,support_listing_fileref=
,page_orientation=p
,pagesize_adjust=
,landscape_max_width=
,subtitle=%str(Sub-title1| Sub-title2)
,end_notes=%str({\super a}End-note1| {\super b}End-note2)
,debug=y );
```

Summary of Steps to Create DV Accounting Table

- **Approximately 4 to 6 weeks prior to LPLV, A&R SP will request Clinical for the draft DCR (Deviations Cumulative Report) file with new COVID PD specific columns populated for at least a small number of COVID PDs and share it via email**
  1. Clinical Scientist reconciles and consolidates all PD records into a final listing file (Deviations Cumulative Report; Excel)
  2. Clinical Scientist files the Excel file in the electronic Trial Master File (eTMF) system as source Protocol Deviation (DV and SUPPDV) data.
  3. A&R SP (Analysis and Reporting Programmer) with IT support (help desk ticket) moves the Excel file into computing platform
  4. SDTM SP (SDTM Programmer) executes DV dataset program
  5. A&R SP use DV and SUPPDV dataset as input for analysis dataset (ADPDEV)
  6. Use the analysis dataset to generate reports

Discontinuations Due to COVID-19



Sample CSR Table

This table was created using the standard macro

Discontinuations Associated with COVID-19

<Subtitle>

	ARM A n *(%)*	ARM B n *(%)*	Total n *(%)*
Participants in population	2,024	2,036	4,060
Status for Trial			
Discontinuations associated with COVID-19	xx (yy)	xx (yy)	xx (yy)
Reason 1	xx (yy)	xx (yy)	xx (yy)
Reason 2	xx (yy)	xx (yy)	xx (yy)
Etc.	xx (yy)	xx (yy)	xx (yy)
Discontinuations not associated with COVID-19	*xx (yy)*	*xx (yy)*	*xx (yy)*
Reason 1	*xx (yy)*	*xx (yy)*	*xx (yy)*
Reason 2	*xx (yy)*	*xx (yy)*	*xx (yy)*
Etc.	*xx (yy)*	*xx (yy)*	*xx (yy)*
Status for Study Medication in Trial			
Started	xx	xx	xx
Discontinuations associated with COVID-19	xx (yy)	xx (yy)	xx (yy)
Reason 1	xx (yy)	xx (yy)	xx (yy)
Reason 2	xx (yy)	xx (yy)	xx (yy)
Etc.			
Discontinuations not associated with COVID-19	*xx (yy)*	*xx (yy)*	*xx (yy)*
Reason 1	*xx (yy)*	*xx (yy)*	*xx (yy)*
Reason 2	*xx (yy)*	*xx (yy)*	*xx (yy)*
Etc.			

Assessment of Existing eCRFs

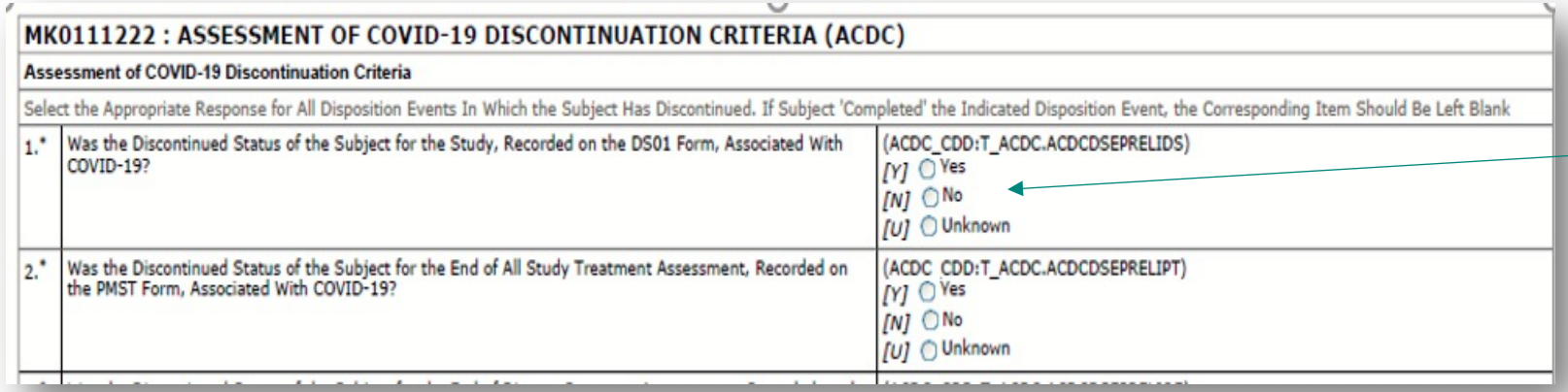
Data collection on the eCRF

Implement a simple Question(s) on a single eCRF Subject Discontinuation and/or Status of Study Medication at end of Trial Segment , and/or each Trial Segment associated with COVID-19 discontinuation, based on study design.

- Enables the data capture of COVID-19 association for **all** reasons for discontinuation
- Allows easier technical implementation for on-going studies
- Allows easier removal, if no longer needed
- Results will be mapped to SDTM and will utilize the “Y” value for the pandemic Indicator
- Records from the SDTM domain will be used in ADaM dataset to generate disposition tables

Mapping

Data from the eCRF will be merged with the parent record in DS domain



MK0111222 : ASSESSMENT OF COVID-19 DISCONTINUATION CRITERIA (ACDC)

Assessment of COVID-19 Discontinuation Criteria

Select the Appropriate Response for All Disposition Events In Which the Subject Has Discontinued. If Subject 'Completed' the Indicated Disposition Event, the Corresponding Item Should Be Left Blank

1.*	Was the Discontinued Status of the Subject for the Study, Recorded on the DS01 Form, Associated With COVID-19?	(ACDC_CDD:T_ACDC.ACDCDSEPRELIDS) [Y] ◯ Yes [N] ◯ No [U] ◯ Unknown
2.*	Was the Discontinued Status of the Subject for the End of All Study Treatment Assessment, Recorded on the PMST Form, Associated With COVID-19?	(ACDC_CDD:T_ACDC.ACDCDSEPRELIPT) [Y] ◯ Yes [N] ◯ No [U] ◯ Unknown

Y will be mapped to SUPPDS =DSEPRELI

N and U will be mapped to SUPPDS = DSEPRELN

Condition Required variables are added in ADSL

Variable Name	Variable Label
EP1BDCSI	Broad Study Disc Epi/Pandemic 1 Rel Ind
EP1BDCTI	Broad Treat Disc Epi/Pandemic 1 Rel Ind

Implementation of eCRF

In Scope

- All New & Ongoing EDC
- Discontinuation of Study/study Med /trial segment reported **December 1st, 2019 and later**
- Trials with Final Database locks April 1st, 2021 or Later

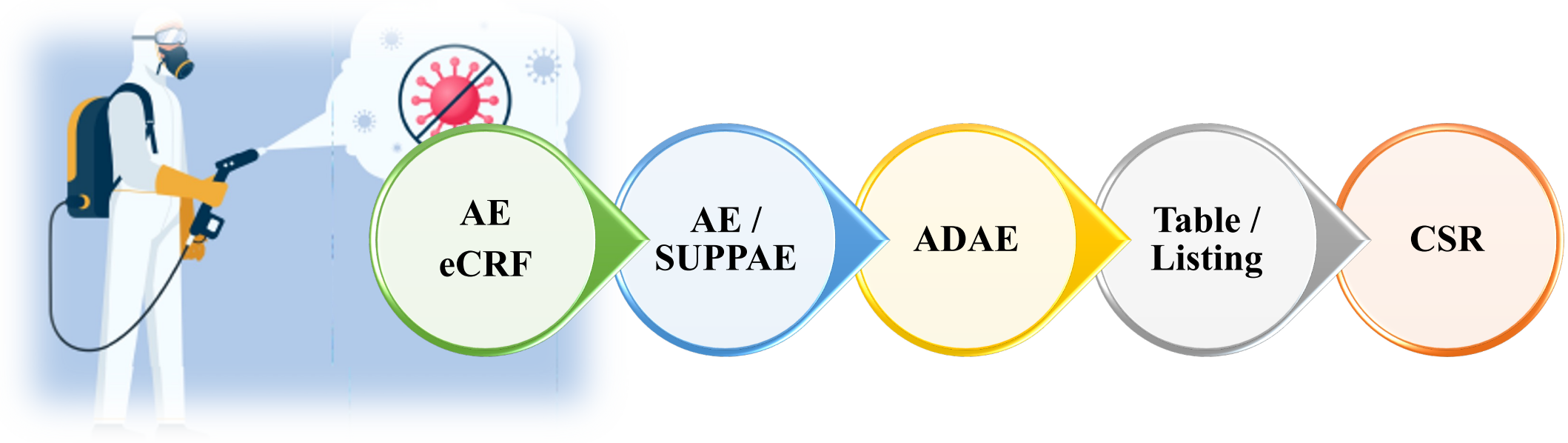
Out of Scope

- Trials with final Database lock completed prior to April 1, 2021
- non-IND
  Study that will not be submitted

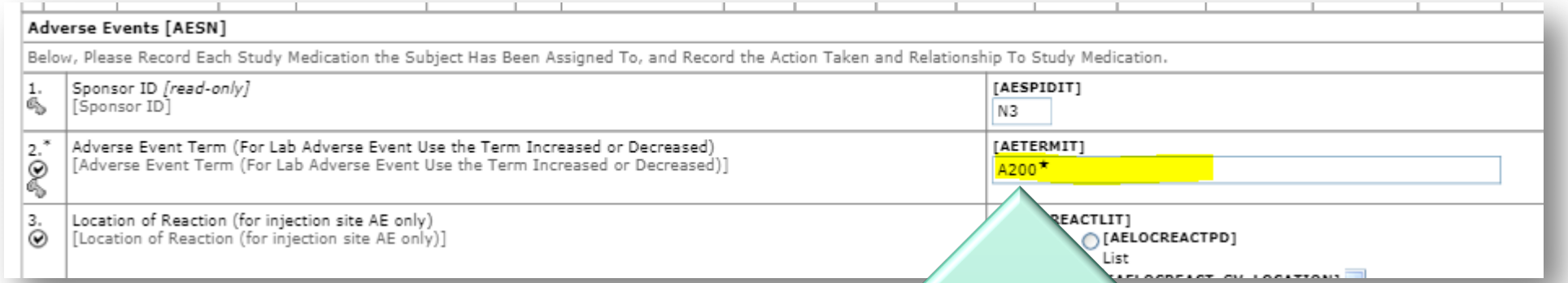
IMPORTANT: Trials with final DBL in 1Q2021 will not have mandatory implementation.

- **No trial should have a delay to DBL due to implementation of this eCRF**
- **Study team Impact assessment is needed to plan for the implementation**

Adverse Event (Collected on AE eCRF)



Adverse Event COVID Flag



Adverse Events [AESN]

Below, Please Record Each Study Medication the Subject Has Been Assigned To, and Record the Action Taken and Relationship To Study Medication.

1.	Sponsor ID *[read-only]* [Sponsor ID]	[AESPIDIT] N3
2.*	Adverse Event Term (For Lab Adverse Event Use the Term Increased or Decreased) [Adverse Event Term (For Lab Adverse Event Use the Term Increased or Decreased)]	[AETERMIT] A200*
3.	Location of Reaction (for injection site AE only) [Location of Reaction (for injection site AE only)]	REACTLIT] [AELOCREACTPD] List

Per the COVID Data Entry Guidelines, if an AE is COVID related then the Adverse Event Term should be entered in the AE eCRF:

- Enter “COVID-19” followed by clinical diagnosis in AE eCRF
- Example; “COVID-19 infection”, “COVID-19 respiratory infection”, “COVID-19 acute respiratory disease”, “SARS-CoV-2 test positive” etc.

Adverse Event COVID Flag in SDTM

During the **SDTM mapping step**

- Business Rule is executed per the logic below to create the Epi/Pandemic Related Indicator which will flag the AE that was COVID-19 related

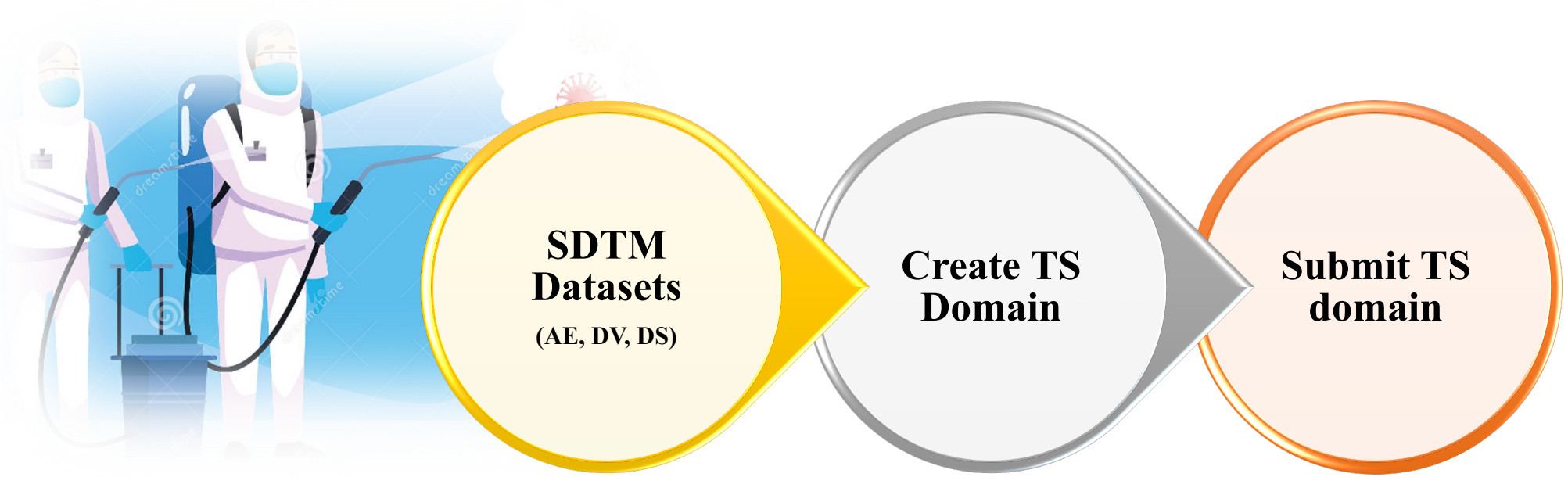
New SUPPQUAL variable was added to the SUPPAE domains to flag COVID-19

- **SUPPAE.AEEPRELI** - Epi/Pandemic Related Indicator
  - *If SDTM.AE.AETERM contains 'COVID' or SDTM.AE.AEDECOD contains ('COVID', 'Coronavirus', 'Corona', 'CoV-2', 'Patient isolation', 'Quarantine', 'Home isolation', 'Home quarantine') then QVAL = 'Y';*

New Conditional variable was added to ADAE

- ANL09FL - Analysis Flag 09 for COVID-19 Related AE

Trial Summary (TS) Domain Flag



Trial Summary (TS) Domain

Use standard Trial Summary Domain specifications to create the TS domain

- Two new conditional parameters added to flag COVID-19
  - **EPDISIND - Epi/Pandemic Related Disruption Ind**
    - Programming logic: Set TSVAL to 'Y'
      - if SUPPAE.QNAM='AEEPRELI' or SUPPDA.QNAM in('DACNTMOD', 'DAEPCHGI') or SUPPDM.QNAM='SITEID1' or SUPPDS.QNAM='DSEPRELI' or SUPPDV.QNAM in ('DVEPRELI', 'DVREAS') or SUPPEC.QNAM in ('ECEPADJI', 'ECEPDSCI' 'ECREASOC') or SUPPEX.QNAM in (EXEPADJI', 'EXEPDSCI', 'EXEPINTI', 'EXRSINT')
  - **EPDEMIC - Name of Epi/Pandemic**
    - Programming logic: If TSPARMCD:EPDISIND = Y then Hardcode to "COVID-19 PANDEMIC"

Note:

- Programming logic includes SUPPDA, SUPPDM, SUPPEC and SUPPEX domain logic to account for future updates if implemented by Merck for those domains
- TS domain is not used in the analysis, but rather created for the FDA submission

Acknowledgement

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THANK YOU