



PHUSE US Connect 2021

CSR Narrative automation



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This presentation covers

- CSR Narratives: Facts
- Challenges in creating narratives
- Plans to automate narrative writing
- Process developed
- Success stories



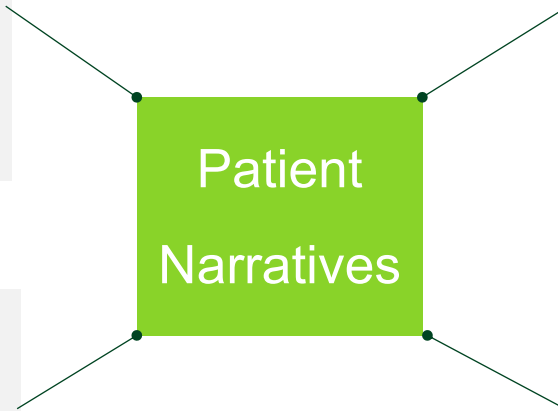
CSR narratives: facts



What is patient narrative

- Patient narratives are brief summary of pre-specified events experienced by patient throughout clinical trial.

- Patient narratives are written for all phases of clinical trials across all therapeutic areas.

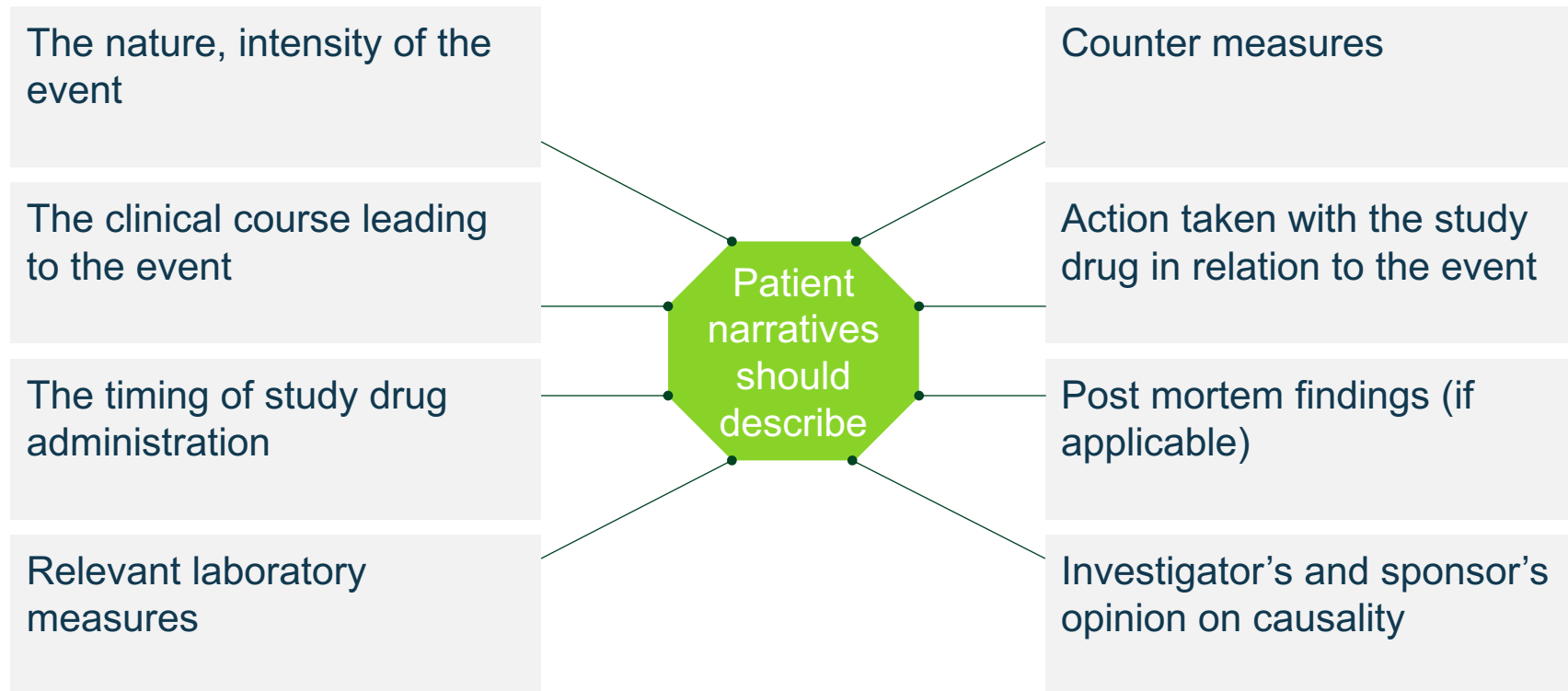


Patient Narratives

- Patient narratives are important part of clinical study reports (CSR). As per ICH guidelines narratives are included in CSR as
 - Text in section 12.3.2 of the CSR
 - An appendix in section 14.3.3
- They are generally written to include information on deaths, serious adverse events, adverse events of special interest and adverse events those leading to permanent discontinuation from clinical trial.

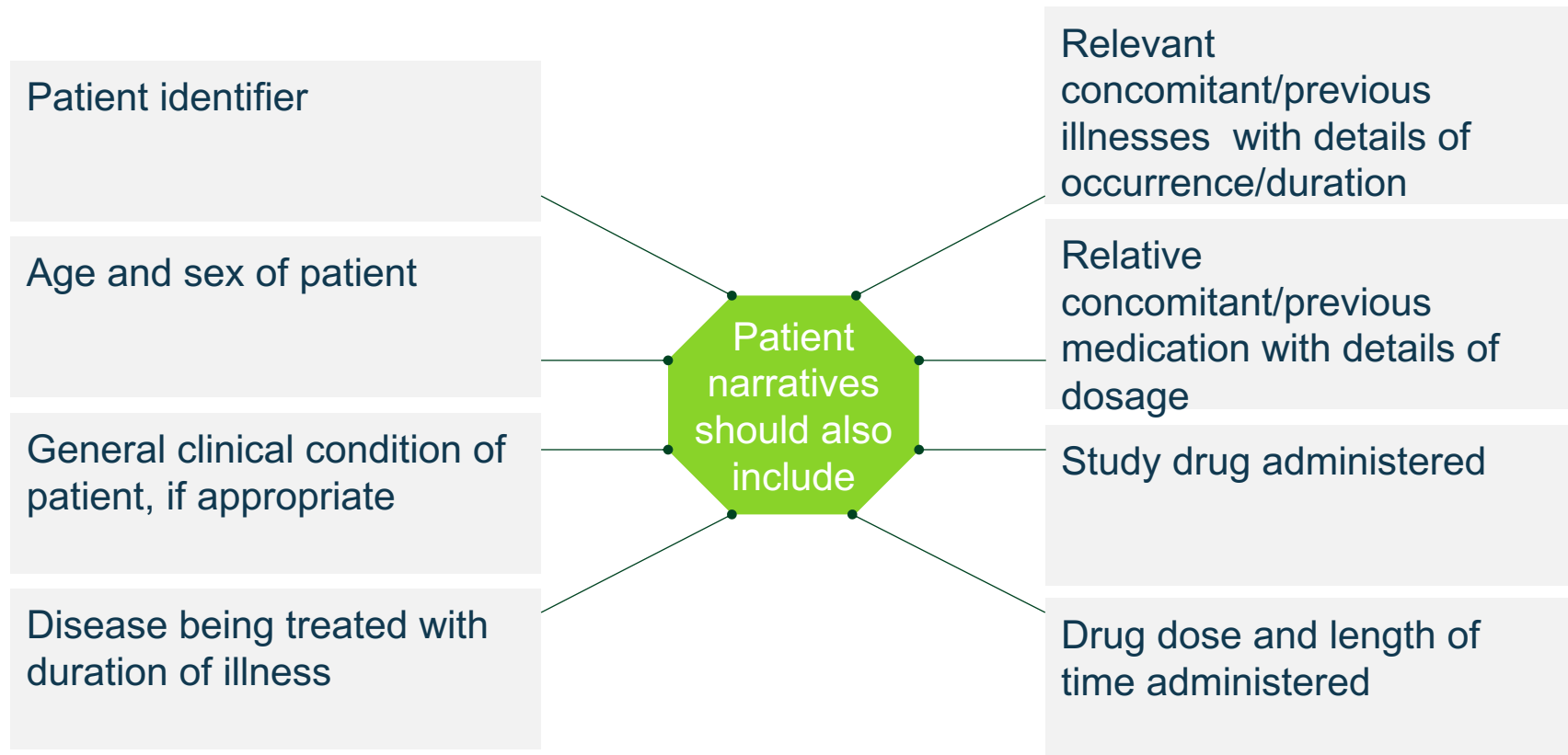


As per International Conference on Harmonization (ICH) E3 (section 12.3.2)





As per International Conference on Harmonization (ICH) E3 (section 12.3.2)





Challenges to write narratives



Challenges

- If large number of narratives needed for a study and writing process starts after clean database:

- Risk of missing CSR timelines due to lengthy and laborious work

- If narrative writing process start based on pre locked data then extra efforts needed to modify narratives based on locked data

- Narrative writing process can become very expensive if many narratives are need to be written for a study

- Writing a large number of narratives for a study can become very cumbersome

- Delay in template finalization due to difference in opinions of the reviewers

Patient
narratives



Plans to automate narrative writing



Our AIM

What	- “Automatic” generation of narratives after clean database (CDB) - Containing accurate data / information - Narrated in correctly phrased sentences
How	- “Automatic” retrieval of data from the Clinical database - By programming into a TEMPLATE composed to comply with ICH guidance
Why	For better efficiency at 2 levels after CDB (rate-limiting): 1. Single review round by SME with optional (minimum) editing if needed, without need for manual data QC 2. Straightforward compiling by MWSp as “CSR Section 15” containing Table of Contents & Abbreviations
Who	Statistical programming, Medical writing, Study medical expert



Final output

Subject identifier:

Age:

Sex:

Race:

Investigational product administered:

Date of randomization:

Narrative criteria:

Country:

Subject had the following diagnosis or diagnoses: type 2 diabetes mellitus, chronic kidney disease and peripheral arterial occlusive disease. Details of all medical history and concomitant medications of interest are tabulated below.

The subject received the first dose of Placebo on . Details of study treatment intake including titrations are displayed below. Details on vital signs are also provided below.

On , 266 day(s) after starting study treatment, the subject was reported with s which was a serious adverse event and resulted in death. The investigator considered this event to be not related to study treatment, and not related to protocol-required procedures. Additionally, the investigator also provided the following comment: "concomitant medication for this event was unknown because we could not obtain information from another hospital that subject had been hospitalized.". The reported date of death was . Other events that started or were ongoing up to 3 days prior to included dry eye, myalgia, oral candidiasis, pharyngitis, pneumonia and visual impairment.

The subject received the last dose of study treatment on . Study treatment was not completed by the subject. The primary reason for premature discontinuation of study treatment was death.

Concomitant medication of interest				
Ingredients	Indication	Start date	End date	Ongoing?
			-----	ONGOING
			-----	ONGOING

Exposure					
Actual treatment	Start date	End date	Dose per administration (mg)	Reason for dose adjustment	Adverse event/Outcome event
			10		
			20		
			0	ADVERSE EVENT / OUTCOME EVENT	Oral candidiasis

Vital signs				
Visit (month)	Date	Average systolic blood pressure (mmHg)	Average diastolic blood pressure (mmHg)	Average heart rate (bpm)
Visit 1				
Visit 2				
Visit 3				
Visit 4				
Per protocol vital signs were measured 3 times and averaged. The numbers displayed above were rounded to the nearest whole number.				

Medical history				
MedDRA PT	Reported term	Start date	End date	Ongoing?



Final output

Subject identifier:

Age:

Sex:

Race:

Investigational product administered:

Date of randomization:

Narrative criteria:

Country:

Subject had the following diagnosis or diagnoses: type 2 diabetes mellitus, chronic kidney disease, coronary artery disease and myocardial infarction. Details of all medical history and concomitant medications of interest are tabulated below.

The subject received the first dose of Finerenone on . Details of study treatment intake including titrations are displayed below. Details on vital signs are also provided below.

On 280 day(s) after starting study treatment, the subject was reported with which the investigator considered serious because it met the following seriousness criterion or criteria: "Is life threatening; Requires or prolongs hospitalization". The investigator also considered this event to be severe in intensity, not related to study treatment, and not related to protocol-required procedures. The subject received benzonatate, chlorphenamine maleate;dextromethorphan hydrobromide;phenylephrine hydrochloride, dextromethorphan hydrobromide;promethazine hydrochloride and olodaterol hydrochloride;tiotropium bromide monohydrate as remedial therapy. Action taken with the subject's study treatment was as follows: drug withdrawn. The last recorded outcome was not recovered/not resolved, and there is no recorded end date. Additionally, the investigator also provided the following comment: "patient began chemotherapy". Other events that started or were ongoing up to 3 days prior to included chronic obstructive pulmonary disease and pneumonia.

The subject received the last dose of study treatment on . Study treatment was not completed by the subject. The primary reason for premature discontinuation of study treatment was adverse event / outcome event (squamous cell carcinoma of lung).

On 189 day(s) after the last dose of study treatment, the subject was reported with which was a serious adverse event and resulted in death. The investigator considered this event to be not related to study treatment, and not related to protocol-required procedures. Additionally, the investigator also provided the following comment: "multi-factoral death involving saes #25, 26, 27, and 30". The

Concomitant medication of interest				
Ingredients	Indication	Start date	End date	Ongoing?
			-----	ONGOING
			-----	ONGOING

Exposure					
Actual treatment	Start date	End date	Dose per administration (mg)	Reason for dose adjustment	Adverse event/Outcome event
			10		
			20		
			0	ADVERSE EVENT / OUTCOME EVENT	Oral candidiasis

Vital signs				
Visit (month)	Date	Average systolic blood pressure (mmHg)	Average diastolic blood pressure (mmHg)	Average heart rate (bpm)
Visit 1				
Visit 2				
Visit 3				
Visit 4				
Per protocol vital signs were measured 3 times and averaged. The numbers displayed above were rounded to the nearest whole number.				

Medical history				
MedDRA PT	Reported term	Start date	End date	Ongoing?



Approaches

Patient Narratives

Approach 1:

// Inefficient manual programming

Approach 2:

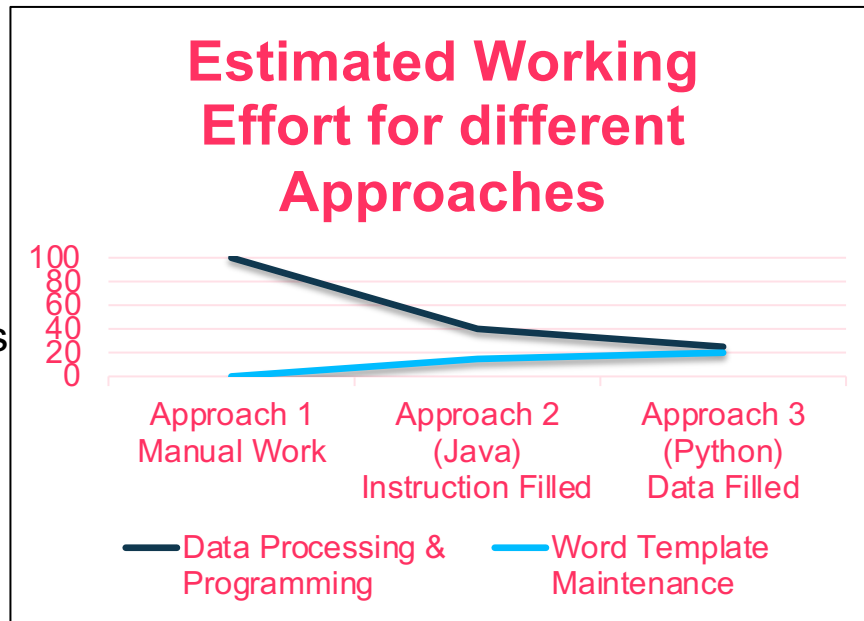
// Word template filled based on instructions

// Using Java based SAS macros

Approach 3:

// Word template filled based on data itself

// Using Python based SAS macros



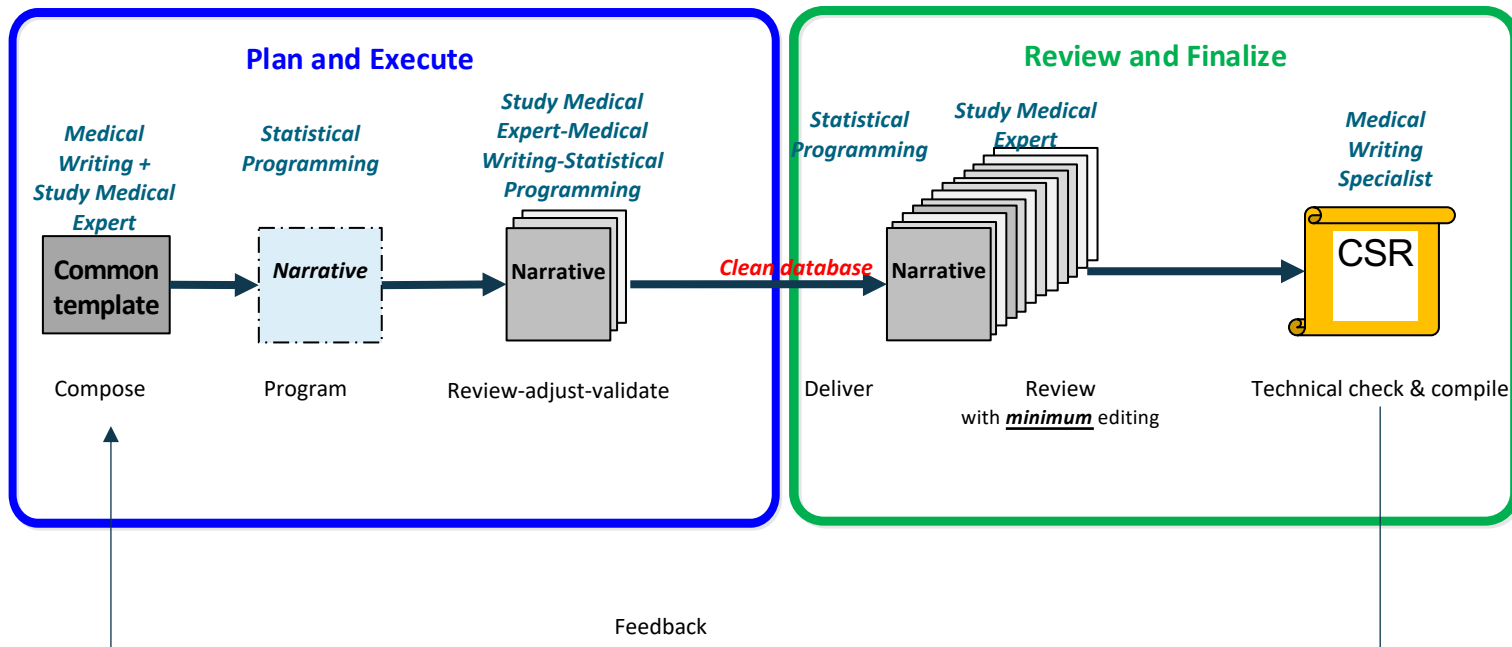


Developed process

Process (1 of 3)

Rule-based 'automation'

Process simplification





Process (2 of 3)

	FPLV				By each criterion			All criteria					
		Step 1			Step 2 (repeated if necessary)			Step 3					
SPA		Narrative strategy session	Align on Common template	Provide template	Program & Run	Review & Resolve	(optional) Validate	Program & Run	Review & Resolve	(optional) Validate			
MW													
SME													
MWS													
					≤5 narratives per criterion; check by criterion in Step 2 (i.e. Step 2a for Criterion 1, Step 2b for Criterion 2, etc.)			All narrative criteria (in total ≤5 narratives per criterion, review different subjects than those reviewed in Step 2)			TOTAL		
Working days		Start 5 months before CDB	5	0	1 to 3	2 to 5	2	1	3 to 5	2	10	Complete at least 2 weeks before CDB	
Date													
Holidays and OOO		Note: the frontloading would not take 5 months											

SPA: Statistical Programming & Analytics
 MW: Medical Writer
 SME: Study Medical Expert
 MWS: Medical Writing Specialist

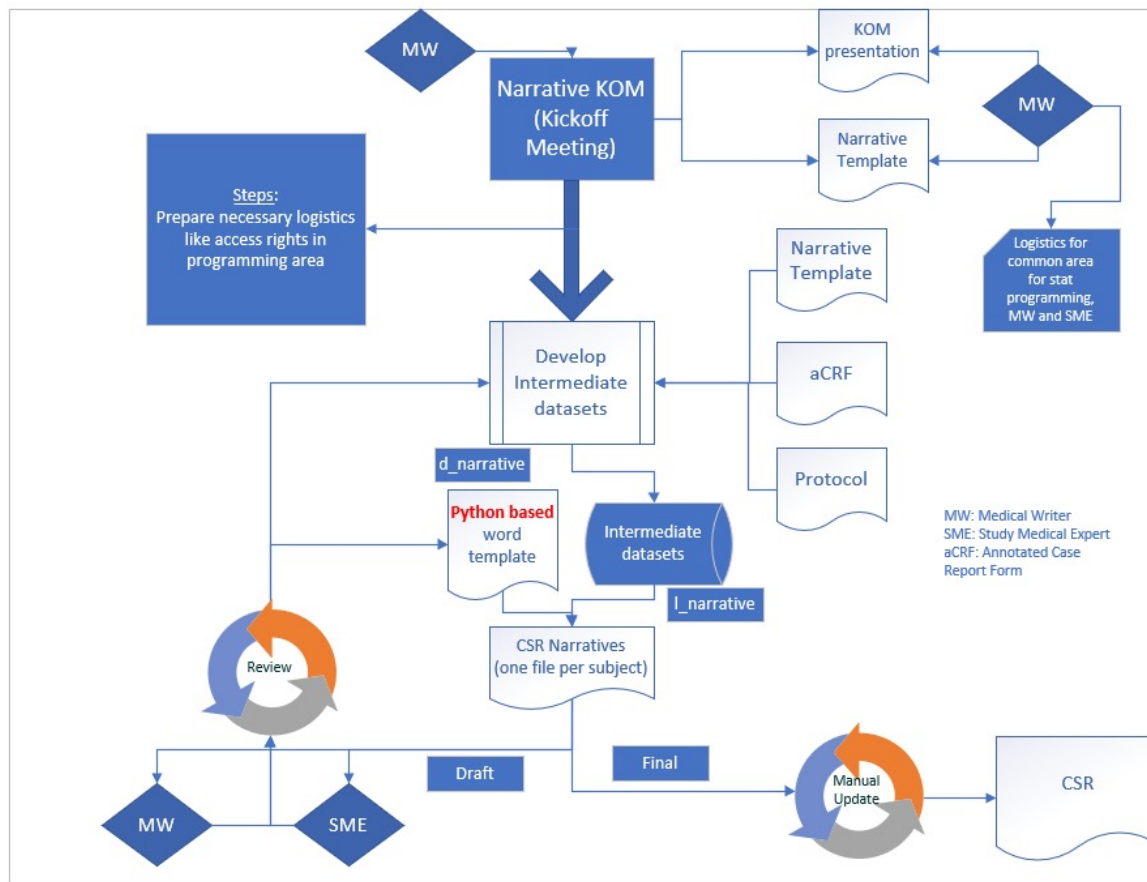
LPLV	CDB	CSR release						CSR		
			Step 4		Optional			Final step		
			Re-validate	Run		Resolve, update & validate	Re-Run			
					Spot review				Finalize	
								Final review, with minimal edits		
									Build	Finalize
			To check for stability e.g. mapping issues					Use 20 narratives per SME per week as a starting point. Check against timing for CSR management reviews		TOTAL
			5	1	5	4	1	Calculate according to the CSR timelines		22
										Complete before CSR management review

Process (3 of 3)

		FPFV							Deaths	related PDs + related SAEs	All 3 criteria		Japan		Japan				
			Step 1		Step 2		Step 3		Step 4		Step 5		Step 6		Step 7		Step 8		
SPA			Align on Common template		Program & Run		Program & Run		Program & Run		Program & Run		Program & Run		Program & Run		Program & Run		
MW																			
SME				Provide template		Review & resolve		Review & resolve		Review & resolve		Review & resolve		Review & resolve		Review & resolve		Review & resolve	
MWS																			
Planning for Finerenone					6 cases total, 3 criteria	Check all, resolve	Repeat <u>same</u> cases	Check all, resolve	10 <u>other</u> cases, 1 criterion	Check all, resolve	20 <u>other</u> cases total, 2 criteria	Check all, resolve	6 <u>other</u> cases total, 3 criteria	Check all, resolve	12 cases, 6 criteria	Check all, resolve	Repeat <u>same</u> cases	Check all, resolve	
<u>Working days</u>				0	0	1	4	3	2	3	2	2	5	2	3	2	3	2	3
dates					9/3/20	16/3/20	19/3/20	23/3/20	26/3/20	30/3/20	2/4/20	9/4/20	13/4/20	21/4/20	23/4/20	28/4/20	30/4/20	6/5/20	



Process





Python template

Subject identifier: `{{ ADSL.SUBJIDN }}`

Age: `{{ADSL.AGE}}`

Sex: `{{ ADSL.SEXC }}`

Race: `{{ADSL.RACE }}`

Investigational product administered: `{{ADSL.TRTDESC}}`

Date of randomization: `{{ADSL.RANDDT}}`

Narrative criteria: `{{CRITALL.CR_LIST}}`

Country: `{{ADSL.COUNTRYC}}`

Subject `{{ADSL.SUBJIDN}}` had the following diagnoses: `{% for MH in ADMH %}, {% endif %} {{ MH.MHDECOD | lowercase }} {% endfor %}`. Details of all medical history and concomitant medications of interest are tabulated below.

The subject received the first dose of `{{ADSL.TRTDESC | camelcase}}` on `{{ADSL.RFSTDT}}`. Details of study treatment intake including titrations are displayed below. Details on vital signs are also provided below.

`{%p if ADAE %}`

`{%p for AE in ADAE %}`

`{%p if AE.PREAE=="Y" %}`

On `{{AE.ASTDT | missing("unknown") }}`, `{% if AE.AESTDYIC != "" %} {{AE.AESTDYI}} day(s) after starting study treatment, {% endif %}` the subject was reported with `{{AE.AEDECOD | lowercase | missing("unknown event") }}` `{% if AE.AEOUT!="FATAL" %}` which the investigator considered `{{ AE.AESERN | label(1,"ADAE.AESERN") | missing("unknown") }}` `{% if AE.AE_CRIT.strip() %}` because it met the following seriousness criterion or criteria: `"{{ AE.AE_CRIT | missing("unknown") }}" {% endif %}`. The investigator also considered this event to



Narrative program

```
/* Macro to loop through different criteria to create outputs into different folders;
%MACRO _loop_output(select_data = , select_condition = , output_prefix = );

    %LOCAL select_list;
    %LET select_list = ;
    OPTIONS NOQUOTELENMAX;

    PROC SQL NOPRINT;
        SELECT DISTINCT subjidn INTO :select_list SEPARATED BY " " FROM &select_data WHERE &select_condition;
    QUIT;

    %IF %LENGTH(&select_list.) = 0
    %THEN %DO;
        %PUT ERROR: _loop_output - check selection condition, no subjects selected.;
    %END;
    %PUT The following subjects are selected: &select_list;

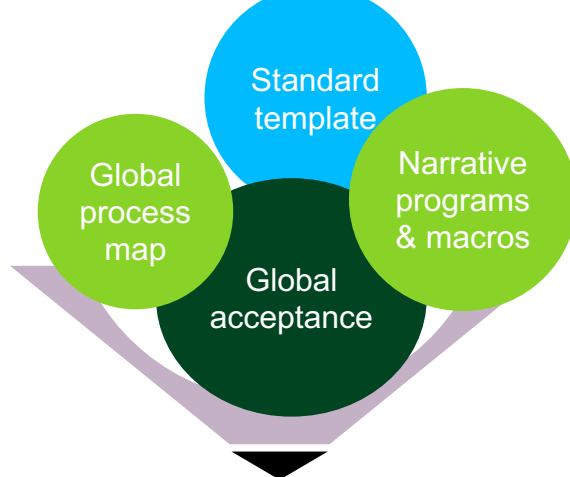
    %pete_wordupdate(
        indat_meta_data = doctemp_data
        , indat_meta_vars = doctemp_vars
        , indat_meta_fmtns = doctemp_fmtns
        , id_var = subjidn
        , id_var_select = &select_list
        , template_file = &template_file
        , outfiles_prefix = &output_prefix
        , debug = NO
    )

    OPTIONS QUOTELENMAX;
%MEND;

/*? Call the loop program for all criterias you want to create output for.;
/* for development, use a condition with few subjects;
/*_loop_output(select_data = data.critallp, select_condition = (critn=1 AND subjidn < 120017026), output_prefix = &outdir/crit_a/dev_16244_);
/*_loop_output(select_data = data.critall, select_condition = (critn=1), output_prefix = &outdir/crit_a/16244_narrative_);
/*_loop_output(select_data = data.critall, select_condition = (critn=2), output_prefix = &outdir/crit_b/16244_narrative_);
```



Success story



Success looks like

Manual approach

- Working group was formed and discussion started among working group members
- User requirements gathered and system availability were assessed.

Java based approach

- Development of process maps started
- Development of global standard template

Python based approach

- SAS program and macros were updated and finalized based on template requirements



Contact



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Thank you!

