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**EUROPE**  
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***The journey of 100 million records submission***

Sandeep Muttanna, Lead SDTM Programmer, Novo Nordisk A/S  
Vicky Poulsen, Principal Standards Specialist, Novo Nordisk A/S



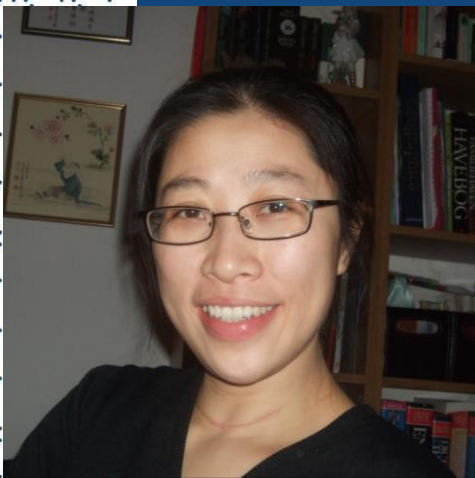
# Meet the Speakers

Sandeep Muttanna

**Title:** Lead SDTM Programmer

**Organization:** Novo Nordisk A/S

Joined Novo Nordisk A/S in 2012 with master's degree in computer science and keen interest in developing programming and SDTM competencies. In his current position, Sandeep leads submission preparations and planning of SDTM deliverables in the Diabetes Therapeutic Area.



Vicky Poulsen

**Title:** Principal Standards Specialist

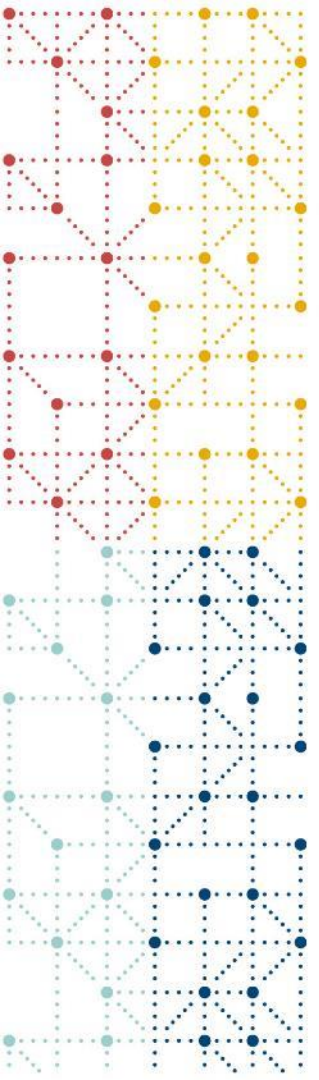
**Organization:** Novo Nordisk A/S

Joined Novo Nordisk A/S in 2015 after being a SAS consultant for a decade in the public health sector specialising in End-to-End BI solutions. She participated in the CDISC Implementation Project shortly after. In her present position, Vicky leads the standard programming strategy and development efforts that drive the SDTM Generation Framework for SDTM and define.xml automation.



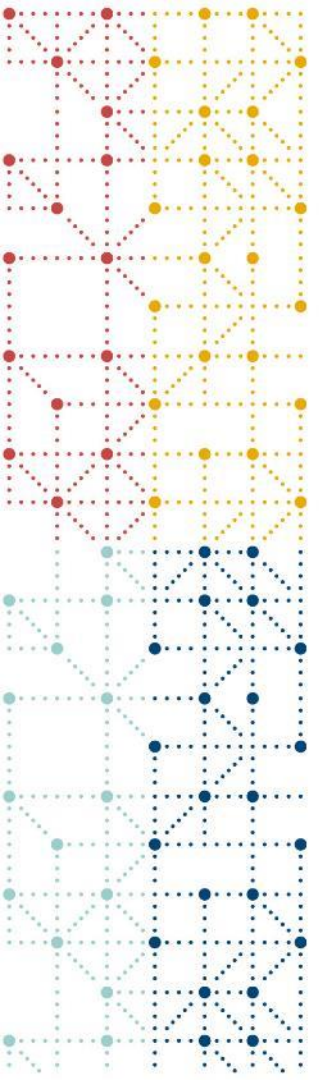
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- *The views and opinions expressed in this presentation are those of the authors' and do not necessarily reflect the official policy or position of CDISC/Novo Nordisk A/S.*



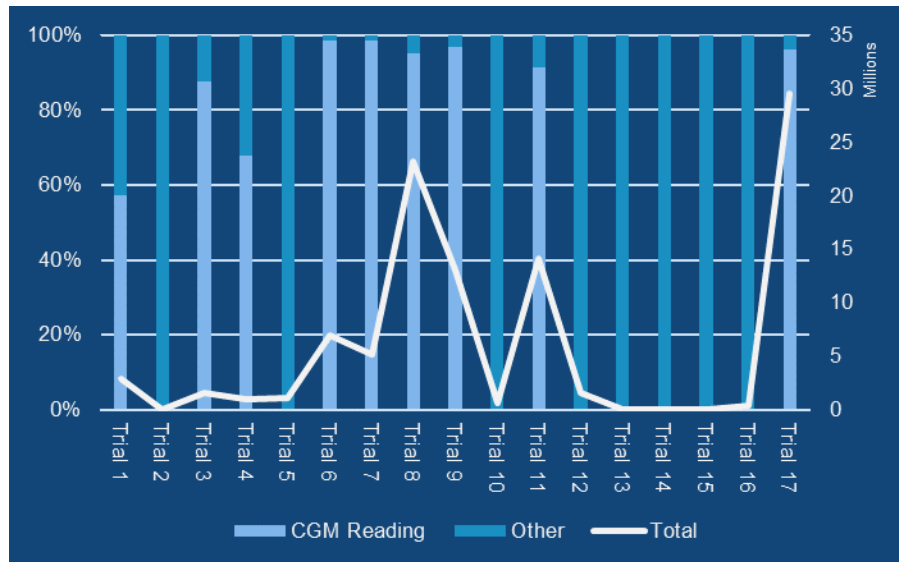
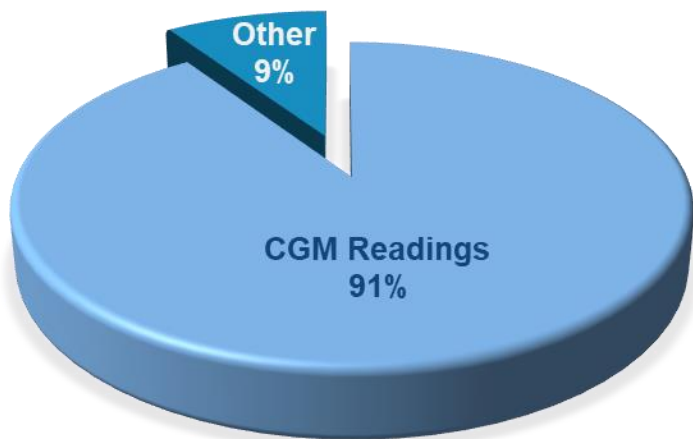
# Agenda

1. Introduction
2. Standard CGM Implementation
3. Submission Preparation
4. Learnings and Reflections



# Introduction

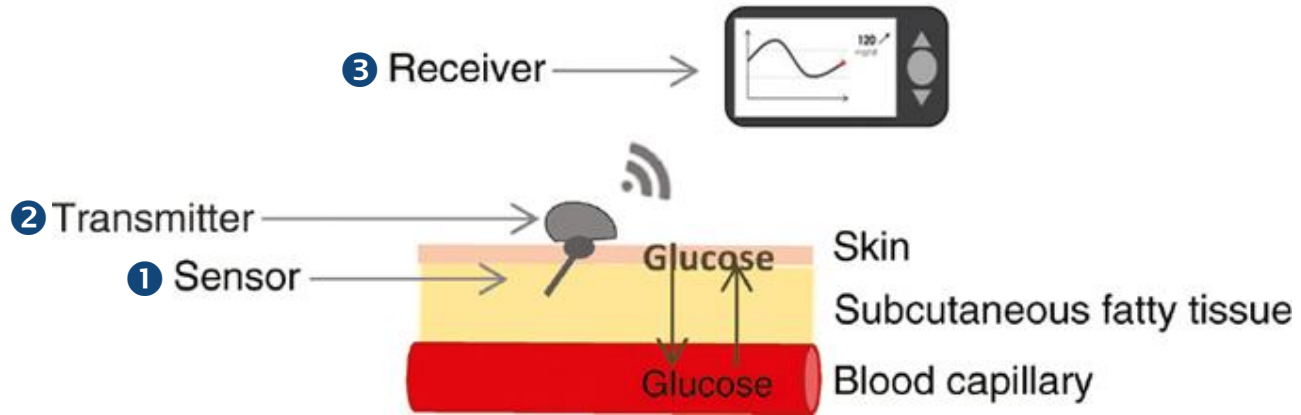
# 100 Million Records Submission



CGM: Continuous Glucose Monitoring

# Continuous Glucose Monitoring

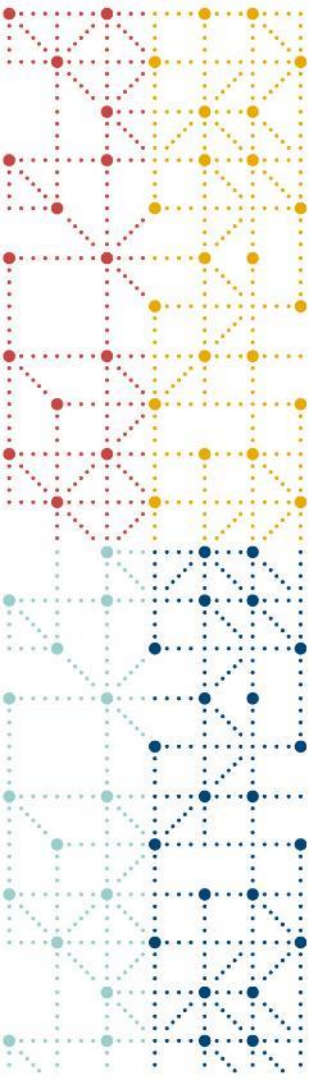
- Real-time, in 5-minute intervals, monitoring where the sensor glucose values are sent to a monitor, an app on a phone or an insulin pump continuously
- Enable evaluation of glycaemic regulation by assessing glycaemic variation
- CGM consists of 3 components:











# Standard CGM Implementation

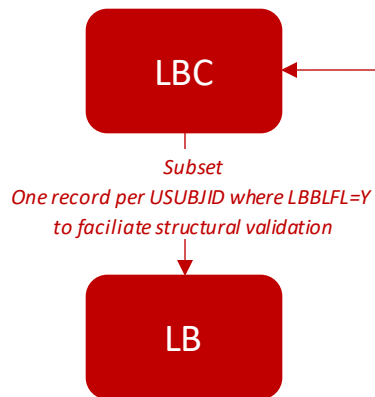
# Considerations

- Volume and usage of CGM data
  - Processing time
  - Validation
- Trial specific adjustments
- Conformance
  - SDTMIG 3.2/3.3
  - SDTMIG-MD 1.1
- Submission requirements

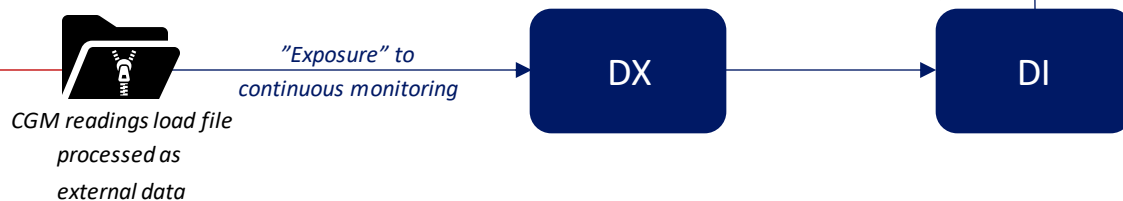


# CGM Data in SDTM

“Stack” dataset to LB domain  
Isolate CGM data from other Lab data



DOMAIN	SPDEVID	DISEQ	DIPARMCD	DIPARM	DIVAL
DI	401001-MX04607332	1	DEVTYPE	Device Type	CGM Manufacturer
DI	401001-MX04607332	2	MANUF	Manufacturer	Dexcom
DI	401001-MX04607332	3	MODEL	Model Number	G6
DI	401001-MX04607332	4	SERIAL	Serial Number	MX04607332



# “Stack” Dataset Concept: Why

Loading large volume of data into SDTM poses a number of challenges:

- Long processing time and storage
  - Burdens CDMS and SCE
  - Delayed availability of updated SDTM data
- Hampers usage when placed with other data within the same domain
  - Computing resources require for data filtering
  - Worsens when supplemental qualifiers are involved



# “Stack” Dataset Concept: What

- As per SDTM IG Section 4.1.1.7, a general observation domain, e.g. Findings, can be split into separate datasets by --CAT
  - All datasets will have the same structure of the domain to ensure data can be “stacked” back together, when necessary
- **Not the same as the split requirement (when dataset is above 5 GB) in FDA’s TCG**



## 4.1.1.7 Splitting Domains

Sponsors may choose to split a domain of topically related information into physically separate datasets. In such cases, one of two approaches should be implemented:

- 1) For a domain based on a general observation class, splitting should be according to values in --CAT (which must not be null).



# “Stack” Dataset Concept: How

- “Stack” dataset concept can be expanded when need arises
- Governed centrally by NN’s Global Standard Team
  - Approved “Stack” dataset is to be registered in the Metadata Repository to facilitate standardised implementation
  - Minimise administrative effort both at global and trial level
  - Maximise implementation flexibility and data friendliness

# LBC: CGM Readings

△ DOMAIN	△ USUBJID	△ SPDEVID	⊕ LBSEQ	△ LBGRPID	△ LBREFID	△ LBSPID	△ LBTESTCD	△ LBTEST	△ LBCAT	△ LBORRES	△ LBORRESU	△ LBSTRESC	⊕ LBSTRESN	△ LBSTRESU	△ LBSTAT	△ LBREASND
LB	NNCGM-TRIAL/401001	401001-MX04607332	24883	V1-V2	1	1-24	LBC-8Q2LGY-1945509911	GLUC	Glucose	CGM					NOT DONE	5-Sensor out of calibration
LB	NNCGM-TRIAL/401001	401001-MX04607332	24884	V1-V2	1-25	LBC-8Q2LGY-1945510211	GLUC	Glucose	CGM						NOT DONE	5-Sensor out of calibration
LB	NNCGM-TRIAL/401001	401001-MX04607332	24885	V1-V2	1-26	LBC-8Q2LGY-1945510511	GLUC	Glucose	CGM						NOT DONE	5-Sensor out of calibration
LB	NNCGM-TRIAL/401001	401001-MX04607332	24886	V1-V2	1-27	LBC-8Q2LGY-1945510811	GLUC	Glucose	CGM	246	mg/dL	13.651498335	13.651498335	mmol/L		
LB	NNCGM-TRIAL/401001	401001-MX04607332	24887	V1-V2	1-28	LBC-8Q2LGY-1945511111	GLUC	Glucose	CGM	248	mg/dL	13.762486127	13.762486127	mmol/L		
LB	NNCGM-TRIAL/401001	401001-MX04607332	24888	V1-V2	1-29	LBC-8Q2LGY-1945511411	GLUC	Glucose	CGM	247	mg/dL	13.706992231	13.706992231	mmol/L		
LB	NNCGM-TRIAL/401001	401001-MX04607332	24889	V1-V2	1-30	LBC-8Q2LGY-1945511711	GLUC	Glucose	CGM	248	mg/dL	13.762486127	13.762486127	mmol/L		

△ LBNAM	△ LBLFL	△ ETCD	△ ELEMENT	⊕ VISITNUM	△ VISIT	⊕ VISITDY	△ EPOCH	△ LBDTC	⊕ LBDY	△ LBTPT	⊕ LBTPTNUM
IQVIA		E000	SCREENING	29999	NON VISIT		SCREENING	2021-08-25T11:25:11	-14	CGM-23	23
IQVIA		E000	SCREENING	29999	NON VISIT		SCREENING	2021-08-25T11:30:11	-14	CGM-24	24
IQVIA		E000	SCREENING	29999	NON VISIT		SCREENING	2021-08-25T11:35:11	-14	CGM-25	25
IQVIA	Y	E000	SCREENING	29999	NON VISIT		SCREENING	2021-08-25T11:40:11	-14	CGM-26	26
IQVIA		E000	SCREENING	29999	NON VISIT		SCREENING	2021-08-25T11:45:11	-14	CGM-27	27
IQVIA		E000	SCREENING	29999	NON VISIT		SCREENING	2021-08-25T11:50:11	-14	CGM-28	28

- 1 LBGRPID contains visit information provided in load file
- 2 Values 1-13 are not actual CGM readings but pre-defined status codes. Records reported as NOT DONE, LBREASND populated with EGV concatenated with pre-defined text
- 3 Baseline flag assigned to first record with non-missing LBORRES and LBDTC before RFXSTDTC or RFSTDTC (subjects without ARM assignment) to fulfil SDTM requirement, no actual meaning
- 4 CGM data are classified as NON VISIT data
- 5 LBTPT/LBTPTNUM populated with sequence number to circumvent P21 findings related to duplicated records, no actual meaning



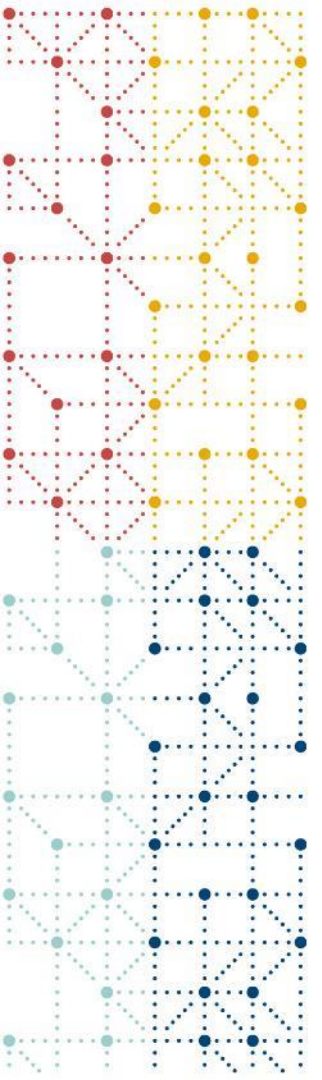
# DX: Exposure to Continuous Monitoring

- CGM readings can be disrupted for various reasons
- Exposure to continuous monitoring indicates if CGM data is collected as intended
- One record per period of continuous monitoring (5-minute intervals) per subject
- Derived based on recording datetime

	△ DOMAIN	△ USUBJID	△ SPDEVID	△ DXGRPID	△ DXSPID	△ DXTRT	△ DXSTDTC	△ DXENDTC	⊕ DXSTDY	⊕ DXENDY	△ DXDUR	
	DX	NCCGM-TRIAL/401001	MX04607332	2883	DX-CGM--8Q2LGY-1	BLOOD GLUCOSE MEASUREMENT	2021-08-25T09:35:17	2021-09-04T09:35:13	-14	-4	PT14400M	
PT10D	DX	NCCGM-TRIAL/402001	MX04607391	3458	DX-CGM--8Q2M08-1	BLOOD GLUCOSE MEASUREMENT	2021-08-18T09:58:12	2021-08-20T09:48:07	-14	-12	PT2870M	Total: PT14285M
	DX	NCCGM-TRIAL/402001	MX04607391	5154	DX-CGM--8Q2M08-2	BLOOD GLUCOSE MEASUREMENT	2021-08-20T10:18:07	2021-08-26T07:33:06	-12	-6	PT8475M	
	DX	NCCGM-TRIAL/402001	MX04607391	5743	DX-CGM--8Q2M08-3	BLOOD GLUCOSE MEASUREMENT	2021-08-26T09:03:06	2021-08-28T10:03:06	-6	-4	PT2940M	
	DX	NCCGM-TRIAL/402001	MX04607391	5750	DX-CGM--8Q2M08-4	BLOOD GLUCOSE MEASUREMENT	2021-08-30T18:33:05	2021-08-30T18:58:05	-2	-2	PT25M	
	DX	NCCGM-TRIAL/402002	MX04607370	6323	DX-CGM--8Q2LHY-1	BLOOD GLUCOSE MEASUREMENT	2021-08-26T09:50:07	2021-08-28T09:29:55	.	.	PT2860M	
	DX	NCCGM-TRIAL/402002	MX04607370	7634	DX-CGM--8Q2LHY-2	BLOOD GLUCOSE MEASUREMENT	2021-08-28T09:59:55	2021-09-01T23:09:58	.	.	PT6550M	
	DX	NCCGM-TRIAL/402002	MX04607370	8558	DX-CGM--8Q2LHY-3	BLOOD GLUCOSE MEASUREMENT	2021-09-02T05:04:50	2021-09-05T09:54:59	.	.	PT4610M	
	DX	NCCGM-TRIAL/402003	MX04406120	8798	DX-CGM--8Q2M0G-1	BLOOD GLUCOSE MEASUREMENT	2021-08-30T10:14:50	2021-08-31T06:09:45	-14	-13	PT1195M	
	DX	NCCGM-TRIAL/402003	MX04406120	9286	DX-CGM--8Q2M0G-2	BLOOD GLUCOSE MEASUREMENT	2021-08-31T17:14:39	2021-09-02T09:44:47	-13	-11	PT2430M	

PT30M Gap  
PT90M Gap





# Submission Preparation

# Planning

- Consider requirements from various authorities
- Communicate to reviewers:

## Preliminary consultation meetings with authorities

- CGM implementation
  - Use of LBC dataset which contains both US conventional and standard units
  - Subset of CGM records in LB dataset
- Potential technical challenges
  - Size of submission package
  - Validation issues



# Bumps on the Road

A number of challenges when validating CGM data:

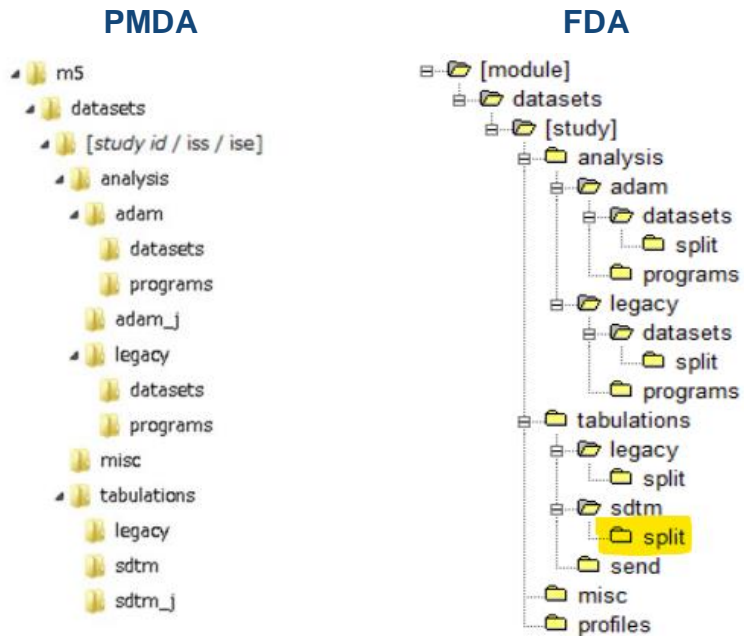
- Long processing time
- Pseudo issues

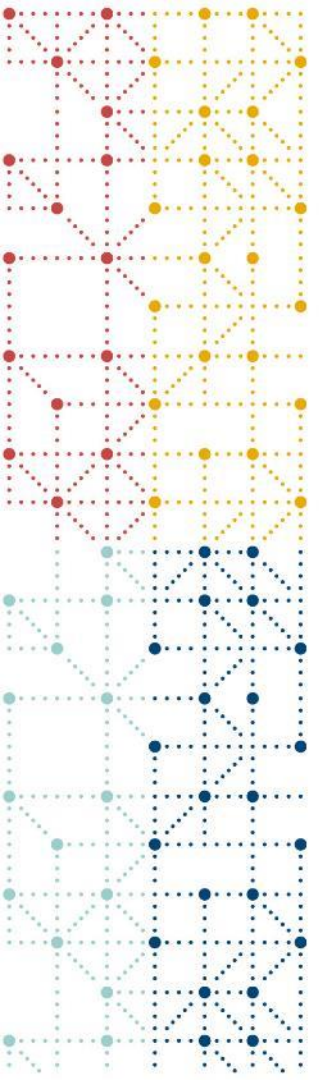
Scope	Rule ID	Message	Explanation
DEFINE	DD0115	Split and unsplit datasets are both listed	Check fired for LBC1, LBC2, LBC3 and LBC4 split datasets. LBC1, LBC2, LBC3 and LBC4 are listed in Define-XML to provide transparency. The split datasets are placed in the 'split' subdirectory and the location is correctly referenced.
DEFINE	DD0084	Referenced File is missing	Check fired for LBC dataset, and split datasets LBC1, LBC2, LBC3, and LBC4. The referenced datasets were excluded from the validation to avoid validation failure, but will be included in the submission.
DEFINE	SD0061	Domain referenced in define.xml but dataset is missing	Check fired for LBC1, LBC2, LBC3, LBC4, LBC split datasets. LBC1, LBC2, LBC3, LBC4, LBC are listed in Define-XML to provide transparency, but are placed in the 'split' subdirectory, which is not included in the validation.
DEFINE	DD0049	Name/Domain/SASDatasetName mismatch	Check fired for LBC dataset, which is part of a split domain. As per SDTMIG v3.2 Section 4.1.1.7, DOMAIN = 'LB' for both LB and LBC datasets, as if the two had not been split. This is to allow for the split dataset to be appended back into one domain dataset.

- Validation failure when XPT file exceed 30 GB (approx.) due to technical implementation in P21E
  - To mitigate, validate SDTM data in 2 rounds:
    - 1<sup>st</sup> Round - All datasets without LBC
    - 2<sup>nd</sup> Round - All datasets except LB/SUPPLB plus LBC

# Bumps on the Road

Differences in eCTD structure between authorities:





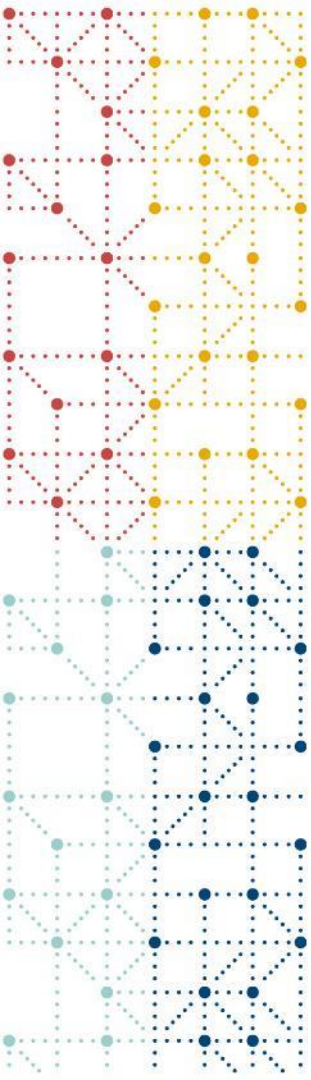
# Learnings and Reflections





# Learnings and Reflections

- Think End to End  
Trial design ➤ data collection ➤ processing ➤ reporting ➤ analysis ➤ output
- Consider systems constraints
  - Processing: CDMS/SCE
  - Archiving
- Be ready to adapt implementation strategy to overcome technical challenges
- Communicate, communicate, communicate
  - With vendors to streamline process
  - With internal stakeholders to ensure end-2-end standard implementation
  - With reviewers to understand the submission requirements and how to handle technical challenges
- Plan submission **in very, very good time**



# Thank You!

Sandeep Muttanna

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