

Standard Implementation (SI07): Gear SDTM up with Digital Health Devices

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Introduction

Challenge and Considerations

Novo Nordisk's Approach

Learnings and Reflections

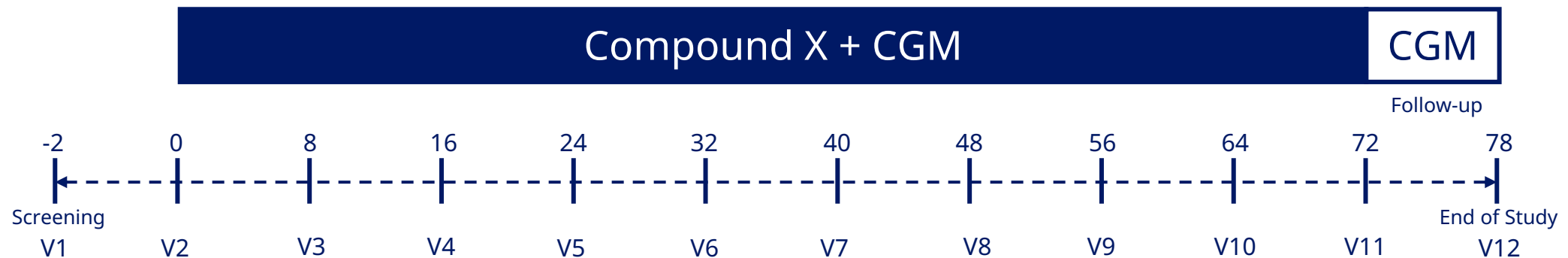
Agenda

The advance of Digital Health Technologies – A game changer in clinical studies



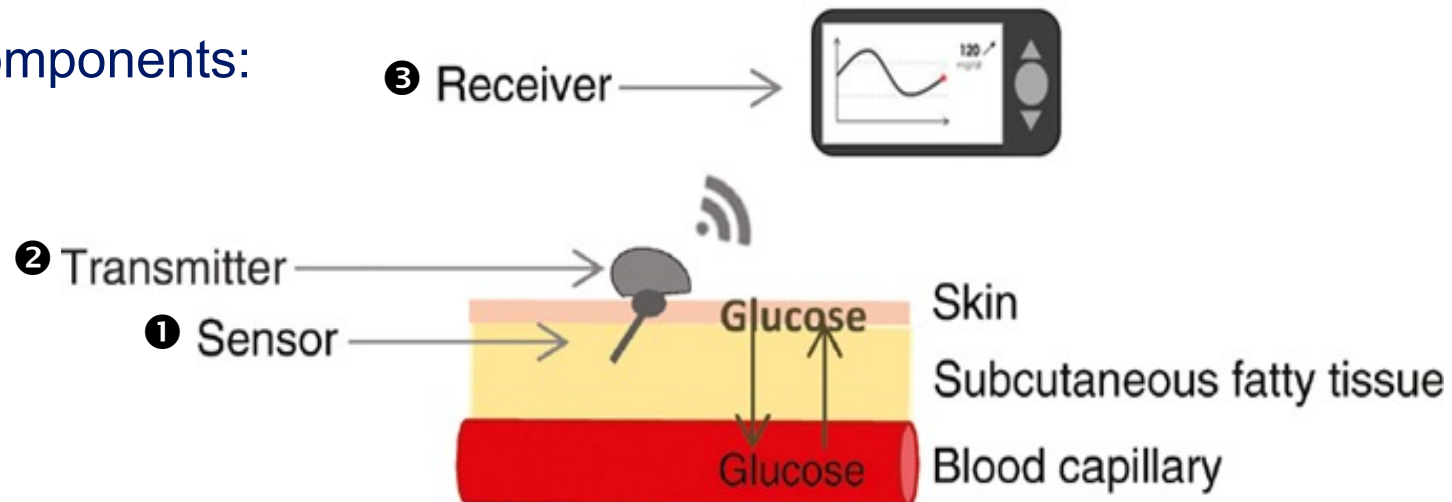
Study A

A Phase 3a study with 1000 participants and a primary objective to investigate the effect of *COMPOUND X* over 78 weeks. The study includes ten 14-day periods where glucose values are collected at 5-minute intervals using *CGM Model TX* to assess glycaemic control, a confirmatory secondary endpoint, of individual participants.



Continuous Glucose Monitoring (CGM)

- 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
- Together with ambulatory glucose profile (AGP) enables evaluation of glycaemic control by assessing glycaemic variation
 - Requires 10-14 days CGM readings
 - A minimum of 70% activity of the overall CGM periods to achieve reliable analysis of glycaemic indices
- Consists of three components:



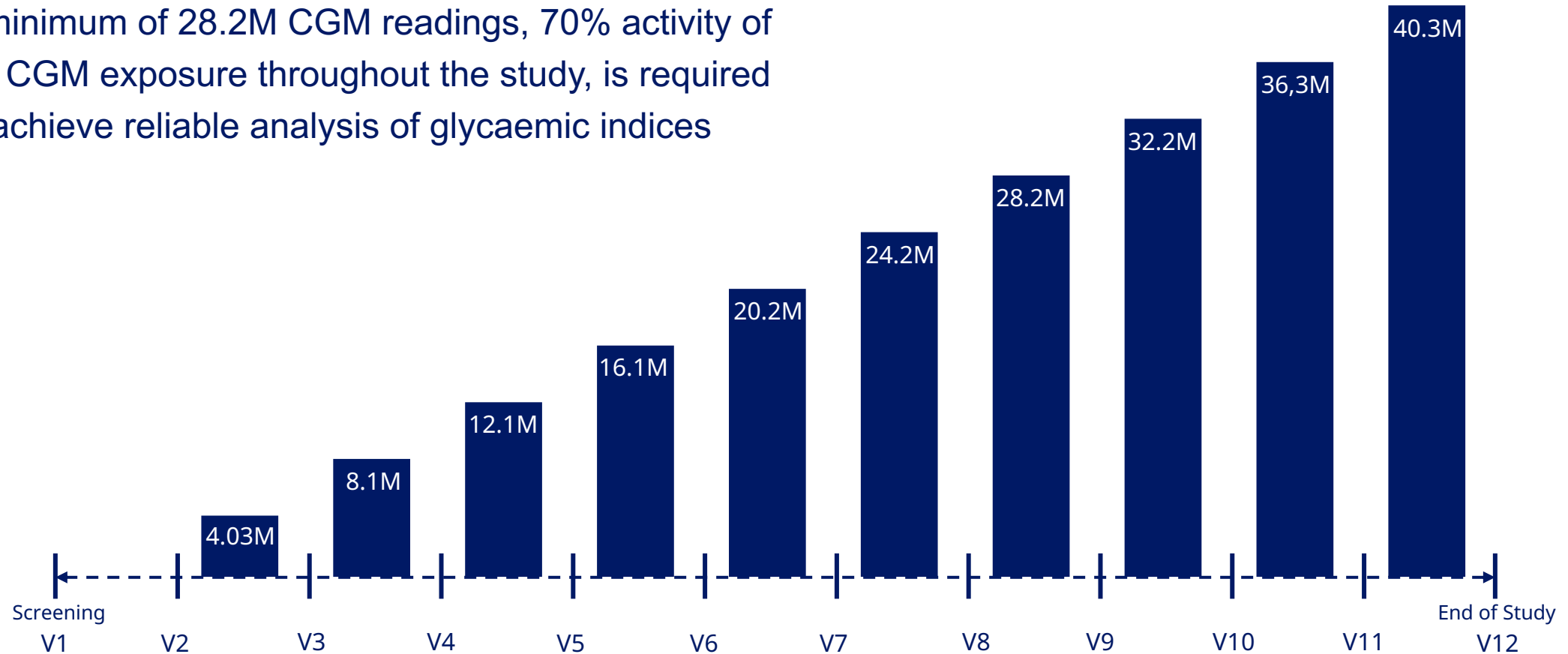
Challenges and Considerations

- Data volume
- Processing time
- Standard compliance



Volume of CGM Readings in Study A

A minimum of 28.2M CGM readings, 70% activity of full CGM exposure throughout the study, is required to achieve reliable analysis of glycaemic indices



Laboratory Test Results (LB)



Code	Codelist Code	Codelist Extensible (Yes/No)	Codelist Name	CDISC Submission Value	CDISC Synonym(s)	CDISC Definition
C174310	C67154		Laboratory Test Name	Glucose Management Indicator	Glucose Management Indicator	An approximate measure (expressed as a % or mmol/mol) of an individual's expected hemoglobin A1c/hemoglobin level, based on the mean glucose measured over a period of at least 10 days by continuous glucose monitoring.
C105585	C67154		Laboratory Test Name	Glucose	Glucose	A measurement of the glucose in a biological specimen.
C142275	C67154		Laboratory Test Name	Glucose, Estimated Average	EAG; Estimated Average Glucose; Glucose, Estimated; Glucose, Estimated Average	A computed estimate of the blood glucose based on the value of the glycated hemoglobin
C186054	C67154		Laboratory Test Name	Glucose, Radiolabeled/Glucose	Glucose, Enriched/Glucose; Glucose, Radiolabeled/Glucose	A relative measurement (ratio or percentage) of radiolabeled glucose to total glucose in a biological specimen.
C139065	C67154		Laboratory Test Name	Glucose-6-Phosphate Dehydrogenase Act	Glucose-6-Phosphate Dehydrogenase Act	A measurement of the biological activity of glucose-6-phosphate dehydrogenase in a biological specimen.
C80184	C67154		Laboratory Test Name	Glucose-6-Phosphate Dehydrogenase	Glucose-6-Phosphate Dehydrogenase	A measurement of the glucose-6-phosphate dehydrogenase in a biological specimen.
C106537	C67154		Laboratory Test Name	Glucose-dep Insulinotropic Pep, Intact	Glucose-dep Insulinotropic Pep, Intact; Intact Gastric Inhibitory Polypeptide; Intact GIP; Intact Glucose-dependent Insulinotropic Peptide	A measurement of the intact (containing amino acids 1-42) glucose-dependent insulinotropic peptide in a biological specimen.

Device Domains

SDTMIG-MD version 1.1

STUDY REFERENCE

- *Device Identifiers (DI)*: contains consistent sponsor-defined variable (SPDEVID) for linking data across domains. DEVTYPE DIPARMCD must be included as a minimum.

EVENTS

- *Device Events (DE)*: contains information about various kinds of device-related events, such as device malfunctions.
- *Device Tracking (DT)*: represents a record of tracking events for a given device (e.g., initial shipment, deployment, return, destruction).

FINDINGS

- *Device-In-Use (DU)*: contains the values of measurements and settings that are intentionally set on a device when it is used.
- *Device Properties (DO)*: contains characteristics of the device.

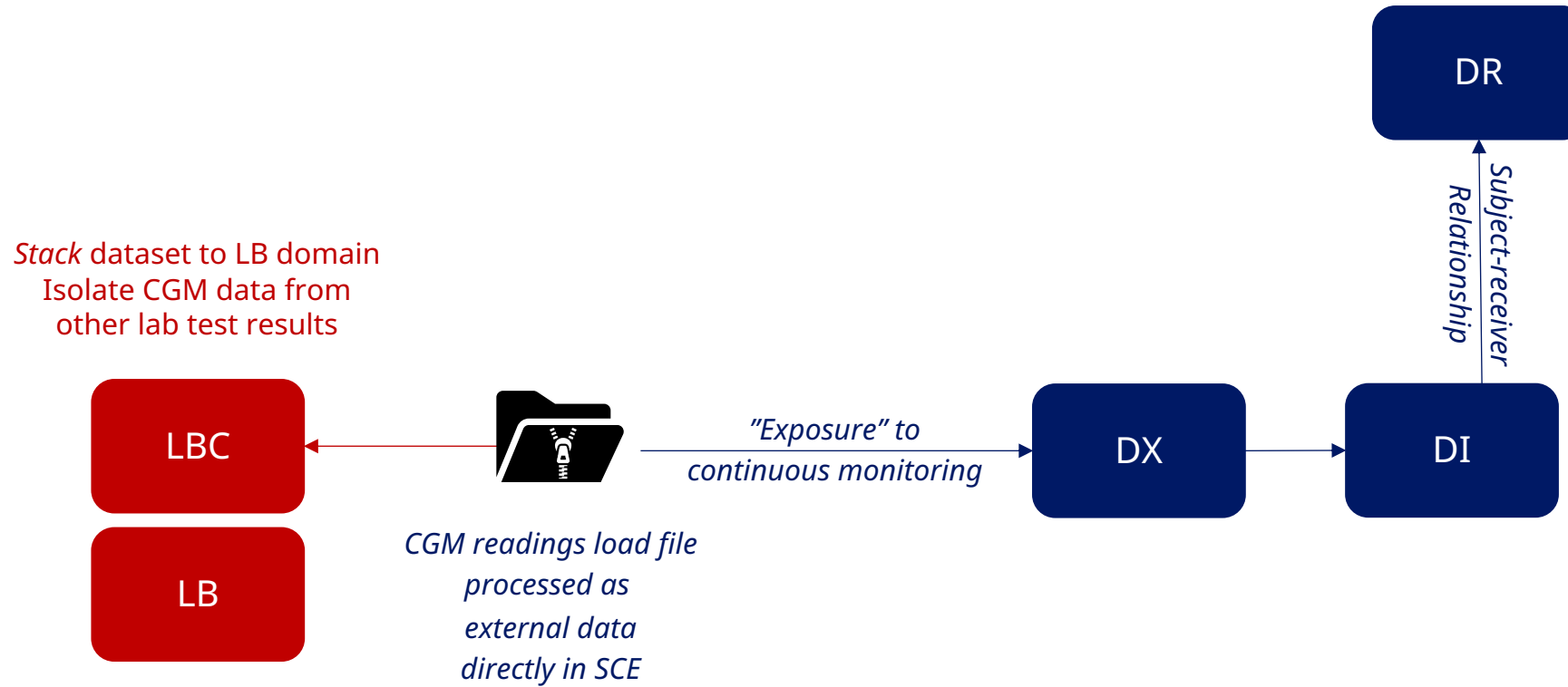
INTERVENTIONS

- *Device Exposure (DX)*: records the details of a subject's exposure to a medical device under study.

RELATIONSHIPS

- *Device-Subject Relationships (DR)*: links each subject to devices to which they have been exposed.

Novo Nordisk's Approach



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 required for data filtering
 - Worsens when supplemental qualifiers are involved



Stack Dataset Concept: What

- A general observation domain 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**



4.1.7 Splitting Domains

Sponsors may choose to split a domain of topically related information into physically separate datasets.

- A domain based on a general observation class may be split according to values in --CAT. When a domain is split on --CAT, --CAT must not be null.
- The Findings About (FA) domain (Section 6.4.4, [Findings About](#)) may alternatively be split based on the domain of the value in --OBJ. For example, FACM would store Findings About CM records. See Section 6.4.2, [Naming Findings About Domains](#), for more details.

Stack Dataset Concept: How

- *Stack* dataset concept can be expanded when need arises
 - LB: CGM / FGM
 - XO: OMICS Findings
- 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	LBBFL	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

- LBGRPID contains visit information provided in load file
- 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
- 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
- CGM data are classified as NON VISIT data
- LBTPT/LBTPTNUM populated with sequence number to circumvent P21 findings related to duplicated records, no actual meaning

SPDEVID

- A surrogate identifier that represents all the characteristics of a device
- To identify a device uniquely and consistently across domains

Unique identifier?

- Sensor☐
- Transmitter☒
- Receiver☒

STUDYID	DOMAIN	SPDEVID	DISEQ	DIPARMCD	DIPARM	DIVAL
STUDYA	DI	103-TX3101722	1	DEVTYPE	Device Type	CGM Receiver
STUDYA	DI	103-TX3101722	2	MANUF	Manufacturer	TX Manu.
STUDYA	DI	103-TX3101722	3	MODEL	Model Number	TX
STUDYA	DI	103-TX3101722	4	SERIAL	Serial Number	TX3101722
STUDYA	DI	119-TX03300629	5	DEVTYPE	Device Type	CGM Receiver
STUDYA	DI	119-TX03300629	6	MANUF	Manufacturer	TX Manu.
STUDYA	DI	119-TX03300629	7	MODEL	Model Number	TX
STUDYA	DI	119-TX03300629	8	SERIAL	Serial Number	TX03300629

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 row per uninterrupted CGM exposure period per subject
- Derived based on CGM reading datetime

	STUDYID	DOMAIN	USUBJID	SPDEVID	DXSEQ	DXTRT	DXCAT	DXSTDTC	DXENDTC	DXSTDY	DXENDY	DXDUR	
1 ST PERIOD 100% Activity	STUDYA	DX	STUDYA/103	103-TX3101722	1	GLUCOSE MEASUREMENT	CGM	2021-03-23T07:43:58	2021-03-30T12:13:54	1	8	PT10350M	←
	STUDYA	DX	STUDYA/103	103-TX3101722	2	GLUCOSE MEASUREMENT	CGM	2021-03-30T12:34:01	2021-03-30T15:09:12	8	8	PT155M	←
	STUDYA	DX	STUDYA/103	103-TX3101722	3	GLUCOSE MEASUREMENT	CGM	2021-03-30T17:39:12	2021-04-06T12:09:04	8	15	PT9750M	←
2 ND PERIOD 100% Activity	STUDYA	DX	STUDYA/103	103-TX3101722	4	GLUCOSE MEASUREMENT	CGM	2021-04-06T12:54:11	2021-04-13T08:09:13	15	22	PT9795M	←
	STUDYA	DX	STUDYA/103	103-TX3101722	5	GLUCOSE MEASUREMENT	CGM	2021-04-13T08:44:20	2021-04-20T08:04:23	22	29	PT10040M	←
3 RD PERIOD 93% Activity	STUDYA	DX	STUDYA/103	103-TX3101722	6	GLUCOSE MEASUREMENT	CGM	2021-08-24T08:42:50	2021-09-01T22:37:58	155	163	PT12355M	←
	STUDYA	DX	STUDYA/103	103-TX3101722	7	GLUCOSE MEASUREMENT	CGM	2021-09-02T05:07:50	2021-09-03T08:43:01	164	165	PT1655M	←
	STUDYA	DX	STUDYA/103	103-TX3101722	8	GLUCOSE MEASUREMENT	CGM	2021-09-03T14:12:59	2021-09-03T23:43:00	165	165	PT570M	←
	STUDYA	DX	STUDYA/103	103-TX3101722	9	GLUCOSE MEASUREMENT	CGM	2021-09-04T04:57:51	2021-09-06T01:53:14	166	168	PT2695M	←
	STUDYA	DX	STUDYA/103	103-TX3101722	10	GLUCOSE MEASUREMENT	CGM	2021-09-06T04:28:14	2021-09-07T08:18:00	168	169	PT1670M	←

“Holes” in exposure

100% activity per period = 20 160 minutes CGM exposure

Standard Implementation

current

dm

data

external_data

sdtm

xprt

split

sdtm_map

sdtm_raw

tmp_define

document

output

program

lbc.sas7bdat9,268.784 KB

lbc_issue.sas7bdat128 KB

NNCGM-TRIAL_CGM_LOADFILE.zip227,229 KB

lbc.sas7bdat9,268.784 KB

Symbolic link

lbc.xpt15,861.113 KB

when

lbc1.xpt4,107.815 KB

lbc2.xpt4,110.715 KB

lbc3.xpt4,117.356 KB

lbc4.xpt3,525.245 KB

when

sdtm_parameter.dat

submit_stack=Y

param

sdtm_parameter.dat

submit_split=5!GB!5

param

LBC (Laboratory Test Results)

LBC (CGM Readings)

LBC1 (CGM Readings - LBC1)

LBC2 (CGM Readings - LBC2)

LBC3 (CGM Readings - LBC3)

PE (Physical Examination)

QS (Questionnaires)

RP (Reproductive System Findings)

VS (Vital Signs)

XL (Laboratory Test Results-US Units)

XV (Vital Signs-US Units)

FA (Findings About)

ZA (Event Adjudication Results)

RELREC (Related Records)

SUPPAE (Supplemental Qualifiers - AE)

SUPPCE (Supplemental Qualifiers - CE)

SUPPCM (Supplemental Qualifiers - CM)

SUPPDM (Supplemental Qualifiers - DM)

SUPPDS (Supplemental Qualifiers - DS)

SUPPDT (Supplemental Qualifiers - DT)

SUPPDV (Supplemental Qualifiers - DV)

SUPPEC (Supplemental Qualifiers - EC)

SUPPEG (Supplemental Qualifiers - EG)

SUPPEA (Supplemental Qualifiers - FA)

SUPPHO (Supplemental Qualifiers - HO)

SUPPIE (Supplemental Qualifiers - IE)

SUPPLB (Supplemental Qualifiers - LB)

SUPPMH (Supplemental Qualifiers - MH)

SUPPPE (Supplemental Qualifiers - PE)

LB	Laboratory Test Results	FINDINGS	One record per analyte per planned time point number per time point reference per visit per subject	Tabulation	STUDYID, USUBJID, LCAT, LBSCAT, LBTESTCD, LBORRES, LBSPEC, VISITNUM, LBOTC, LBTPTRF, LBTPNUM	Laboratory test findings including, but is not limited to hematology, clinical chemistry and urinalysis data. This domain does not include microbiology or pharmacokinetic data, which are stored in separate domains.	Laboratory Test Results SAS Transact File #
LBC	CGM Readings (Laboratory Test Results)	FINDINGS	One record per reading per subject	Tabulation	STUDYID, USUBJID, LCAT, LBSCAT, LBTESTCD, LBORRES, LBSPEC, VISITNUM, LBOTC, LBTPTRF, LBTPNUM	Laboratory test findings including, but is not limited to hematology, clinical chemistry and urinalysis data. This domain does not include microbiology or pharmacokinetic data, which are stored in separate domains.	CGM Readings SAS Transact File #
LBC1	CGM Readings - LBC1 (CGM Readings)	FINDINGS	One record per reading per subject	Tabulation	STUDYID, USUBJID, LCAT, LBSCAT, LBTESTCD, LBORRES, LBSPEC, VISITNUM, LBOTC, LBTPTRF, LBTPNUM	Laboratory test findings including, but is not limited to hematology, clinical chemistry and urinalysis data. This domain does not include microbiology or pharmacokinetic data, which are stored in separate domains. This is a split dataset of LBC domain. This dataset contains records where USUBJID ge 101001* and USUBJID le 303010*. See [doc:SDRG].	CGM Readings - LBC1 SAS Transact File #
LBC2	CGM Readings - LBC2 (CGM Readings)	FINDINGS	One record per reading per subject	Tabulation	STUDYID, USUBJID, LCAT, LBSCAT, LBTESTCD, LBORRES, LBSPEC, VISITNUM, LBOTC, LBTPTRF, LBTPNUM	Laboratory test findings including, but is not limited to hematology, clinical chemistry and urinalysis data. This domain does not include microbiology or pharmacokinetic data, which are stored in separate domains. This is a split dataset of LBC domain. This dataset contains records where USUBJID ge 303011* and USUBJID le 701003*. See [doc:SDRG].	CGM Readings - LBC2 SAS Transact File #
LBC3	CGM Readings - LBC3 (CGM Readings)	FINDINGS	One record per reading per subject	Tabulation	STUDYID, USUBJID, LCAT, LBSCAT, LBTESTCD, LBORRES, LBSPEC, VISITNUM, LBOTC, LBTPTRF, LBTPNUM	Laboratory test findings including, but is not limited to hematology, clinical chemistry and urinalysis data. This domain does not include microbiology or pharmacokinetic data, which are stored in separate domains. This is a split dataset of LBC domain. This dataset contains records where USUBJID ge 701004* and USUBJID le 962009*. See [doc:SDRG].	CGM Readings - LBC3 SAS Transact File #

Learnings and Reflections

- Think End to End
 - Trial design ➤ data collection ➤ processing ➤ reporting ➤ analysis ➤ output
- Consider systems constraints - Processing: CDMS vs SCE
- 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!

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