



End-to-End Traceability from Protocol Development to Submission

PhUSE Annual Conference, Edinburgh
10 October 2017

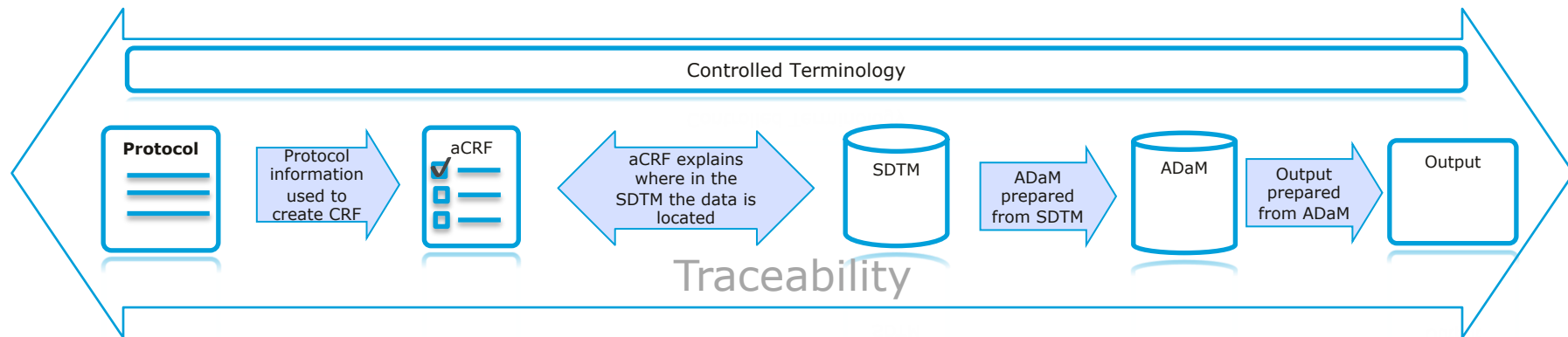
Mikkel Traun, Principal System Developer
Trine Danø Klingberg, Principal Standards Specialist
Francis D'sa, Standards Specialist

Novo Nordisk A/S

Implementation of CDISC in Novo Nordisk

- Right from the beginning

End-to-end traceability from protocol to the Clinical Study Report



Clinical versus Programmer language

Assessments

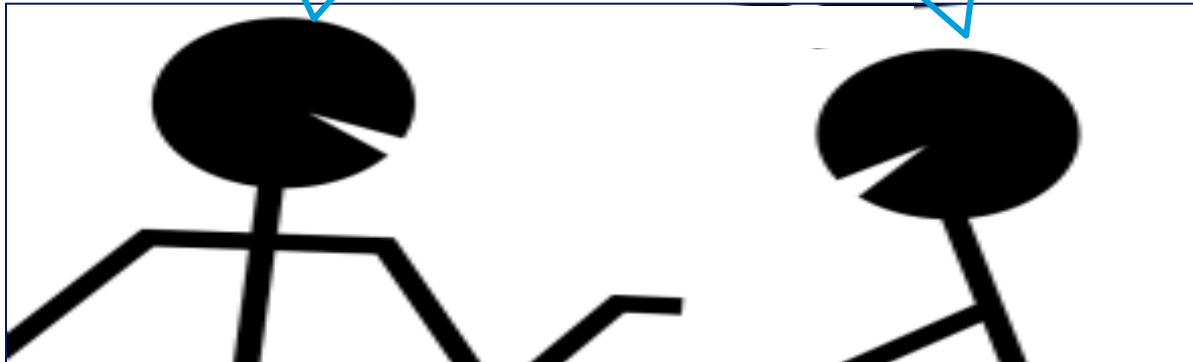
2 weeks

Why can't we just
add text to the CRF?

Test Code

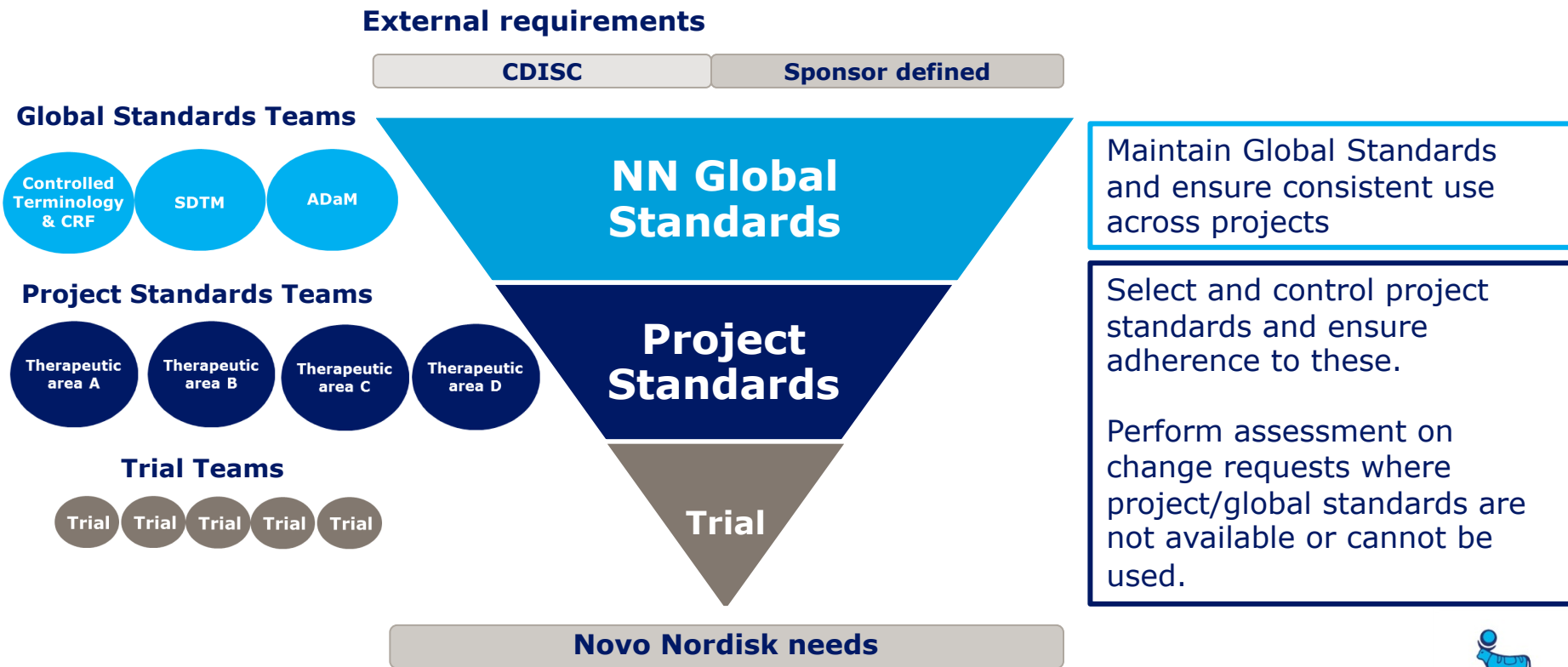
ISO Date format: P2W

Which SDTM domain to
map to?

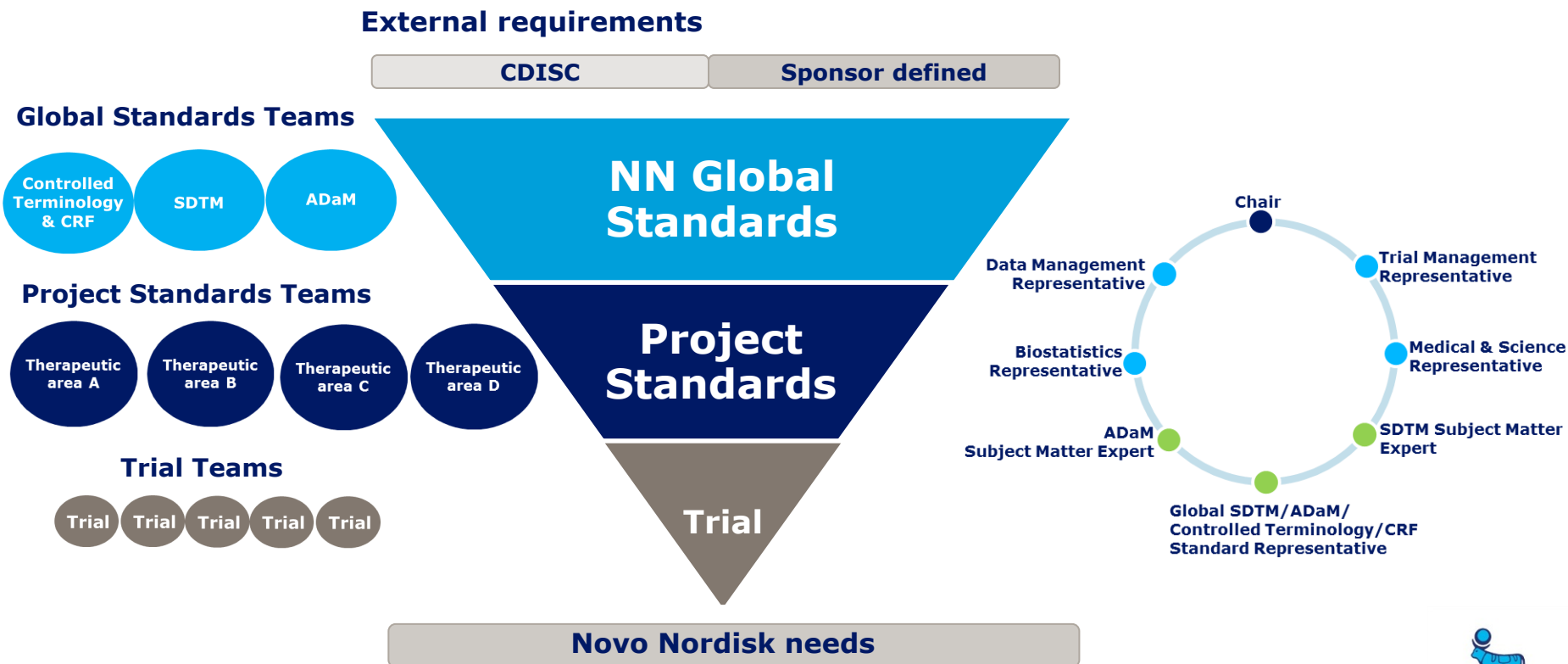


Reports have been developed to to facilitate end-2-end communication

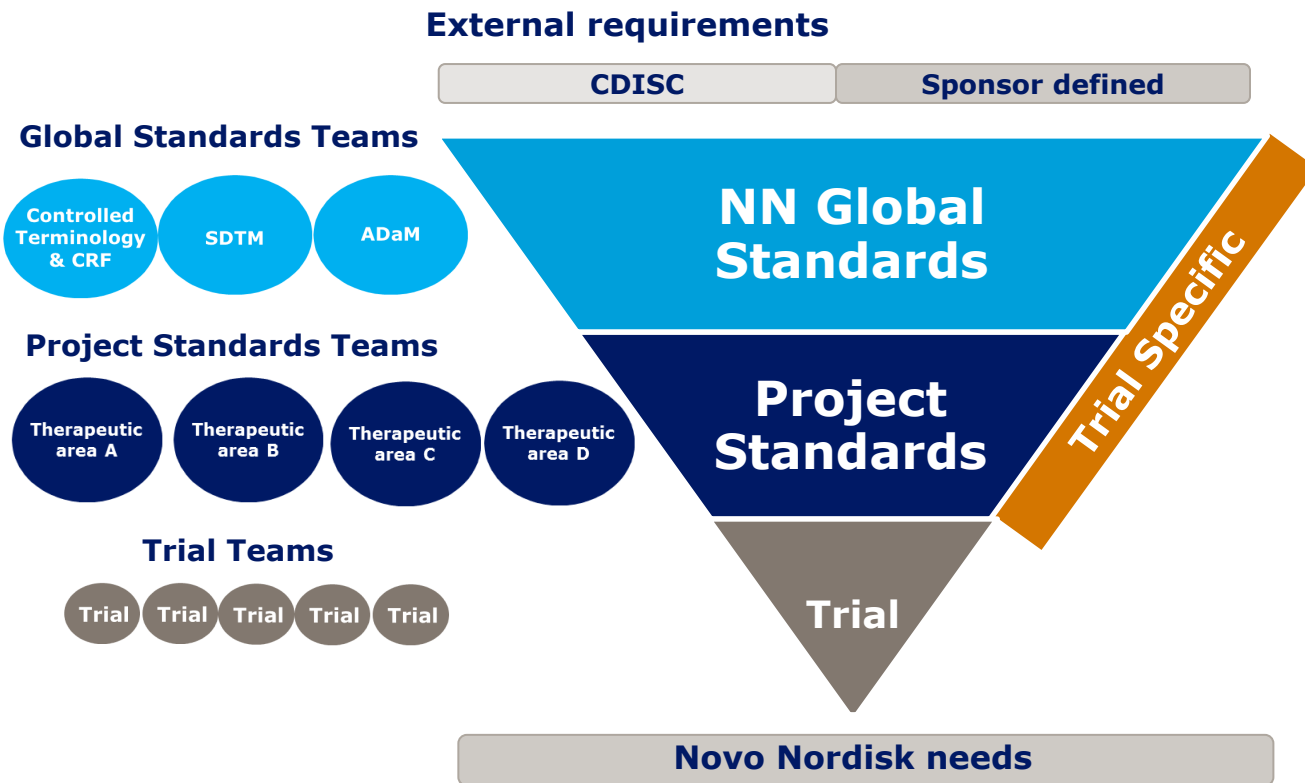
Global, Project and Trial Specific Standards



Global, Project and Trial Specific Standards



Global, Project and Trial Specific Standards



Protocol Development

Global standards

Project specific schedule of activities

Programmer

Protocol Metadata Document (PMD):

Trial specific schedule of activities Report (Word)

Final Protocol

Master

Assessment
EFFICACY
-Lipids
-Proteins
-Osteo Information
-C-Comp
-Self measured plasma glucose
-Glucose metabolism
-HbA1c Blood
-Fasting plasma glucose
-C-reactive Serum
EXCLUSION CRITERIA
INCLUSION CRITERIA
DEVICE EFFICACY
OTHER ASSESSMENTS
-Check Question
REVIEWERS
SAFETY
-Body measurements
-Complaint
-Local Tolerability
-SARs
-HDL Cholesterol Serum
-LDL Cholesterol Serum
-Triglycerides Serum
-Total Cholesterol Serum
-VLDL Cholesterol Serum
-Serum Apolipoprotein B
-Serum Free Fatty Acids
-Homocysteine
-Hypoglycaemic episodes
-Eye examination
-Hematology
-Differential count
-Basophilic Blood-Absolute
-Basophilic Blood
-Lymphocytes Blood

Project Standards Team (PST)

Iterative process

Study group



High level schedule of activities

Detailed schedule of activities

Trial Design

Visit

Compounds

Dosage

Profile

CDISC Trial Summary

High level Schedule of activities copied into the Protocol

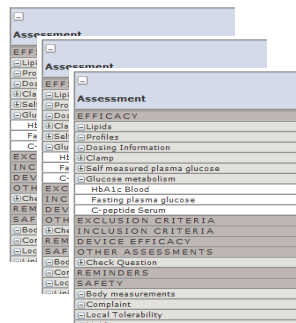
PMD QC'd against the protocol

Version controlled

PMD archived

	Screening	Randomization	Non-pkg.				Optin
	V1	V2	V6	V10	V14	V18	V22
Visit							
Timing of Visit	-2W	0W	4W	8W	12W	16W	20W
Visit Window (Days)	-14.0	n0	n3	n3	n3	n3	n3
SUBJECT RELATED INFORMATION AND ASSESSMENTS							
Informed Consent	X						
Inclusion Criteria							

Trial metadata repository



Analysis metadata

Trial metadata repository



Project Standards Team (PST)



Study Group

Assessment	
EFF	Assessment
-Lipids	
-Pro	
-Dose	
-Clamp	
-Self measured plasma glucose	
-Glucose metabolism	
-HbA1c Blood	
-Fasting plasma glucose	
-C-peptide Serum	
-EXCLUSION CRITERIA	
-INCLUSION CRITERIA	
-DEVICE EFFICACY	
-OTHER ASSESSMENTS	
-Check Question	
-REMINDERS	
-SAFETY	
-Body measurements	
-Complaint	
-Local Tolerability	

Assessment	
EFFICACY	
-Lipids	
-Profiles	
-Dosing Information	
-Clamp	
-Self measured plasma glucose	
-Glucose metabolism	
-HbA1c Blood	
-Fasting plasma glucose	
-C-peptide Serum	
-EXCLUSION CRITERIA	
-INCLUSION CRITERIA	
-DEVICE EFFICACY	
-OTHER ASSESSMENTS	
-Check Question	
-REMINDERS	
-SAFETY	
-Body measurements	
-Complaint	
-Local Tolerability	

Protocol metadata

Conduct metadata

Analysis metadata

Global metadata repository

Trial metadata repository

Project standard compare program

Project Standard Compare



Enforce and control of Project Standard

Glimpse of our metadata system

CDW Operations Metadata Management

Metadata Trial Manage Logout Production/V2R5C2/FRD

Trial Flowchart Groups: 0 Assessments: 0 Collections: 0

Trial ID: NN1234-5678

Assessments: ☒ All ☐ Non-derived ☐ Derived Visits/page: 10 Refresh Filters

Trial Details
Trial Definition ID: CTR
Trial Metadata Version: 7
Trial Definition Status: Draft

Flowchart Template
Project: NN1234
Group: Therapeutic area 1
Project standard: ☐

Template: Phase 3
Import

Edit Attributes:

<< < First V2 P4 P8 P16 P32 P55B Last >>> Assessment Collection

	Visit Short Label	V1	V2	P3	P4	P5	V6	P7	P8	P9	V10
Assessment		Screening	Baseline	Phone Contact	Phone Contact	Phone Contact	Treatment	Phone Contact	Phone Contact	Phone Contact	Treatment
Thrombocytes		X									
Erythrocytes		X									
Biochemistry											
Potassium Serum		X									
Albumin Serum		X									
Sodium Serum		X									
Creatinine Serum		X									
Aspartate Aminotransferase Serum		X									
Alanine Aminotransferase Serum		X									
Alkaline Phosphatase Serum		X									
Total Bilirubin Serum		X									
Glomerular filtration rate		X									
Urinalysis											
Erythrocytes urine		X	X								
Albumin Urine		X	X								
Creatinine urine		X	X								
Albumin/Creatinine Ratio		X	X								
Body Weight											
Body Weight		X	X								
Eye examination											
Left eye ophthalmoscopy	Topic Code: BODY_WEIGHT Short Label: Body Weight CDISC: [VSTEST:Weight] [VSTESTCD:WEIGHT] Sponsor Defined: Not linked	CT Std	X								
Right eye ophthalmoscopy		CT Std	X								
Vital signs											
Pulse		X	X								
Systolic Blood Pressure		X	X								
Diastolic Blood Pressure		X	X								
Physical examination											
Gastrointestinal System incl. Mouth		CT Std	X								
Central and Peripheral Nervous System		CT	X								
Skin		CT	X								
Respiratory System		CT	X								
Head, Ears, Eyes, Nose, Throat, Neck		CT Std	X								
Cardiovascular System		CT	X								
Musculoskeletal System		CT	X								



Project Standards Team (PST)

Protocol

Protocol Amendments

Schedule of activities



Study Group

Assessment
EFF
-Lipids
-Pro
-Dev
-Clamp
-Self
-Glucose
-HbA1c
-Fasting plasma glucose
-C-peptide Serum
-Exclusion Criteria
-Inclusion Criteria
-Device Efficacy
-Other Assessments
-Check Question
-Reminders
-Safety
-Body measurements
-Complaint
-Local Tolerability

Assessment
EFFICACY
-Lipids
-Pro
-Dev
-Clamp
-Self measured plasma glucose
-Glucose metabolism
-HbA1c Blood
-Fasting plasma glucose
-C-peptide Serum
EXCLUSION CRITERIA
INCLUSION CRITERIA
DEVICE EFFICACY
OTHER ASSESSMENTS
+Check Question
REMINDERS
SAFETY
-Body measurements
-Complaint
-Local Tolerability

Protocol metadata

Conduct metadata

Analysis metadata

Global metadata repository

Trial metadata repository

Trial setup reports program

Trial Outline



Protocol



Protocol Metadata Document



Supports all the business deliverables and review/approval



	A	B	C	D	E	F	G
1		Screenin	Randomisation	Dose escalation	Phone Contact	Treatment	Follow-up
2	Visit	V1	V2	V4	P61 ^a	Visit 8 - Visit 9 ^b	V11
3	Timing of Visit	14D	0D	56D	112D	154D-168D	182D
4	Visit Window	±14D	±7D	±14D	±14D		±7D
5	EFFICACY						
6	Glucose metabolism ^d			X	X		
7	HbA1c Blood						
8	SAFETY						
9	Hypoglycaemic episodes				X		
10	Vital signs						
11	Pulse or Heart Rate	X		X	X	X	
12	Pulse	X		X	X	X	
13	Adverse event						
14	Adverse event	X			X		
15	Adverse event	X			X		
16	SUBJECT RELATED INFORMATION AND ASSESSMENTS						
17	Body measurements	X	X	X	X	X	X
18	Body Weight	X	X	X	X	X	X
19							
20	Footnote						
21	^a call subject if no phone call received						
22	^b Washout Period						
23	^d Patient needs to be fasting						

Protocol Metadata Document (PMD):

High level schedule of activities

Detailed schedule of activities

Trial Design

Visit

Compounds

Dosage

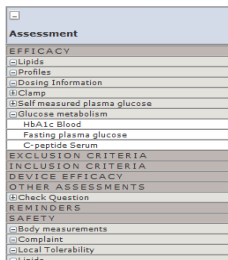
Profile

CDISC Trial
Summary

1	Planned Trial Visits for NN1234-5678										
2	Trial Period Label (Epoch)	Trial Period Short Label (Epoch)	Visit Short Label	Visit ID (MMA)	Visit Type	Visit Type Alias	Visit Label	Visit Sub-label	Visit Description	Trial Time Reference	Pla Trial
3	Screening Epoch	Screening Epoch	V1	10	Screening	Screening	Visit 1 (week -2)	Visit 1 (week -2)		Baseline	14 Days
4	Treatment Epoch 1	Treatment Epoch 1	V2	20	Baseline	Randomisation	Visit 2 (week 0)	Visit 2 (week 0)		Baseline	0 Days
5	Treatment Epoch 3	Treatment Epoch 3	V4	40	Treatment	Dose escalation	Visit 4 (week 8)	Visit 4 (week 8)		Baseline	56 Days
6	Treatment Epoch 5	Treatment Epoch 5	P61	61	Phone Contact	Phone Contact	Visit 6 Day 1	Visit 6 Day 1		Baseline	112 Days
7	Treatment Epoch 7	Treatment Epoch 7	V80	80	Treatment	Treatment	Visit 8 (week 22)	Visit 8 (week 22)		Baseline 2	154 Days
8							Visit 9				

1	CDISC Trial Summary parameters for NN1234-5678						
2							
3	#	Trial Summary Parameter Code	Trial Summary Parameter	Parameter Value (MMA)	Parameter Value Code	Reference Terminology	Par Null
4	1	REGID	Registry Identifier	1234-56		EUDRAC	
5	2	TITLE	Trial Title	0			
6	3	TPHASE	Trial Phase Classification	Phase II		CDISC	
7	4	OBJPRIM	Trial Primary Objective	To compare the efficacy on glycaemic control of Drug A against placebo in subjects with T2D.			
8	5	OBJSEC	Trial Secondary Objective	To compare the safety and tolerability of three dose escalation schemes using a single end dose level during 26 weeks administartion of Drug A in subjects with T2D.			
9	6	INTMODEL	Intervention Model	Parallel Group		CDISC	
10	7	TBLIND	Trial Blinding Schema	Single Blind		CDISC	
11	8	NARMS	Planned Number of Arms	9			

Analysis & Reporting



Analysis metadata

Trial metadata repository



Project Standards Team (PST)

Protocol

Protocol Amendments

Protocol information used to create CRF

CRF

Data captured in CRF

Data

Clinical System

Output

Schedule of activities



Study Group

Assessment group corresponds to CRF title

aCRF

aCRF explains where in the SDTM the data is located

SDTM

ADaM prepared from SDTM

ADaM

Traceability

Protocol metadata

Conduct metadata

Analysis metadata

Global metadata repository

Trial metadata repository

Trial Planning

Trial Conduct

Analysis & Reporting

Protocol

Protocol Amendments

Protocol information used to create CRF

CRF

Data captured in CRF

Data

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ADaM

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Traceability program

Traceability report

Traceability report during the lifecycle of trial



Traceability in Project Standard report

	A	B	D	J	K	L	M	N	O	P	Q	T	W	X	Y
1	Flowchart Group	Assessment Group	Topic Code Label	Status	Standard	Definition Completed	Linked to CT	Primary Assess- ment	Mand	Linked to domain	Category	CDISC CT Code Value	TESTCD Variable	TESTCD Value	TEST Variable
28	Efficacy	Glucose metabolism	HbA1c	Active	Y	N	Y	N	N	LB	GLUCOSE METABOLISM	C64849	LBTESTCD	HBA1C	LBTEST
29	Efficacy	Glucose metabolism	Fasting plasma glucose	Active	Y	N	Y	N	N	LB	GLUCOSE METABOLISM	C105585	LBTESTCD	GLUC	LBTEST

End-to-end traceability from protocol development to submission

Standards in MDR

- CDISC CT
- SDTM master model
- Sponsor concepts and labels, link to CDISC CT
- Sponsor defined CT submission values
- Project standards
- Trial setup reports and templates

Trial Setup in MDR

- Select SDTM and CDISC CT version
- Select project standard
- Define trial metadata for trial design and trial summary parameters
- Add trial specific assessments
- Manage changes
- Run trial setup reports

Learnings

- Getting it right from the beginning is possible and save time downstream
- Reports supporting end-to-end traceability helps bridging the communication gaps across skill area
- Development and maintenance of standards is key
- Processes for control of standards is needed
- Challenging to introduce a MDR system and reports for use of standards, compare to traditional document centric solutions
- Do not underestimate the effort for support and change management

Presenters

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