End-to-end Traceability from Protocol Development to Submission

PhUSE SDE Copenhagen
1. June 2017

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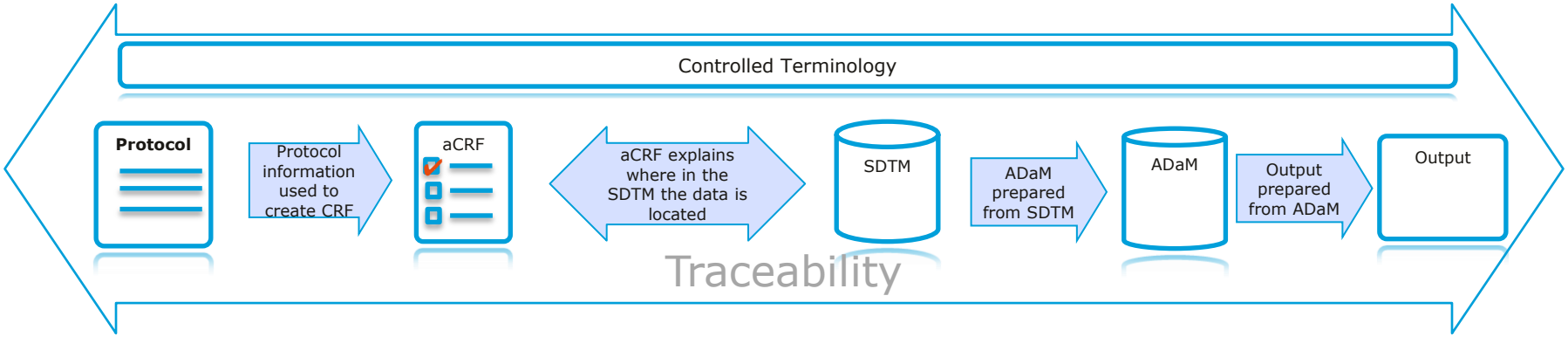
Mikkel Traun, Principal System Developer

Novo Nordisk A/S

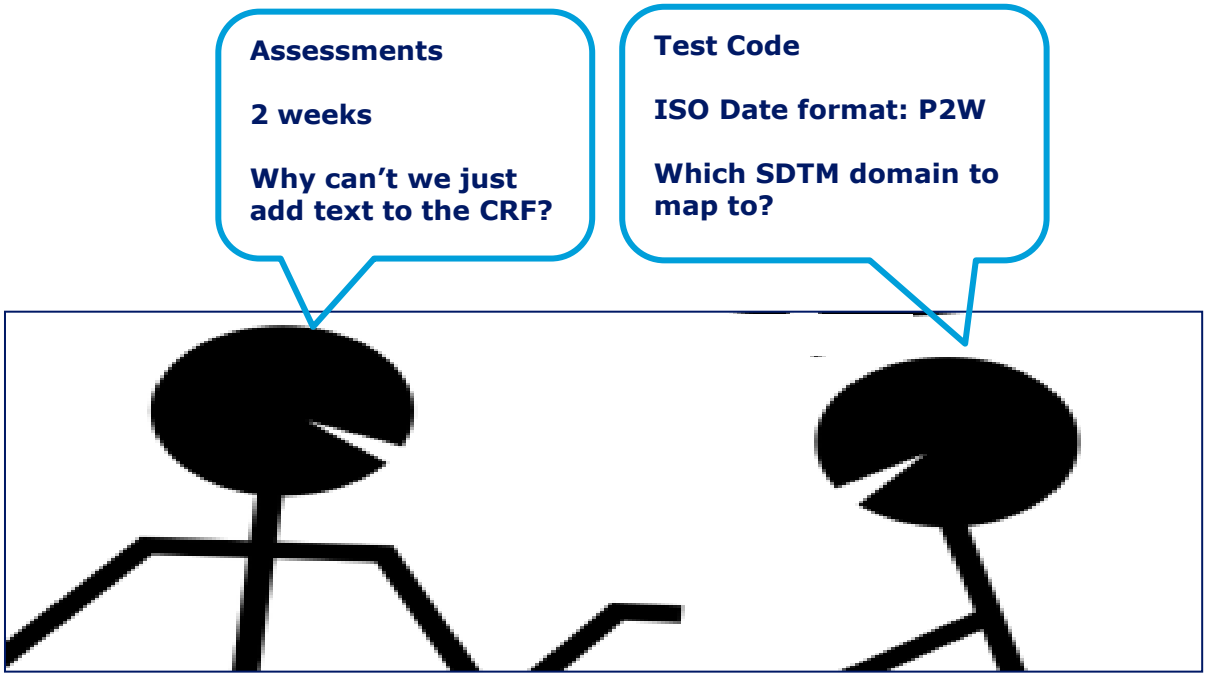
Implementation of CDISC in Novo Nordisk

- Right from the beginning

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



Clinical versus Programmer language



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

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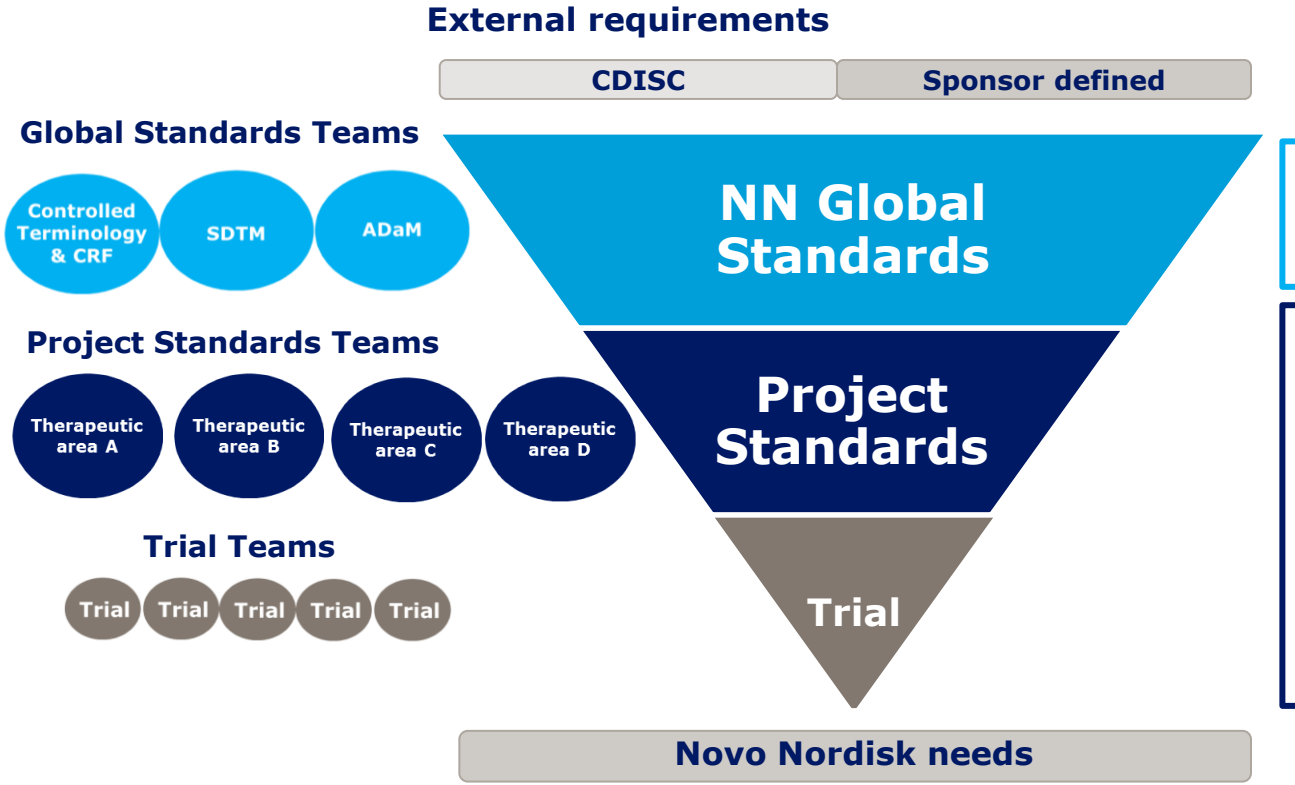
Global, Project and Trial Specific Standards



Maintain Global Standards and ensure consistent use across projects

Select and control project standards and ensure adherence to these.

Perform assessment on change requests where project/global standards are not available or cannot be used.

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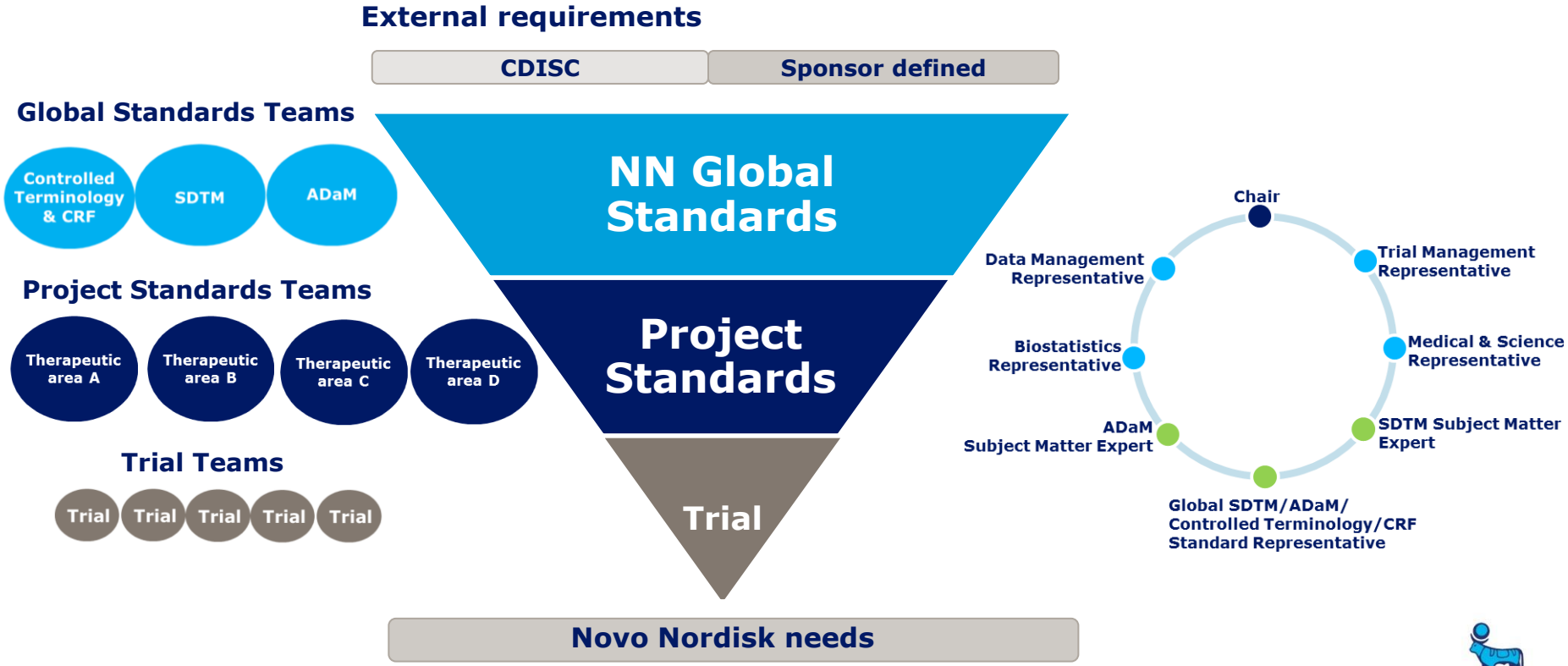
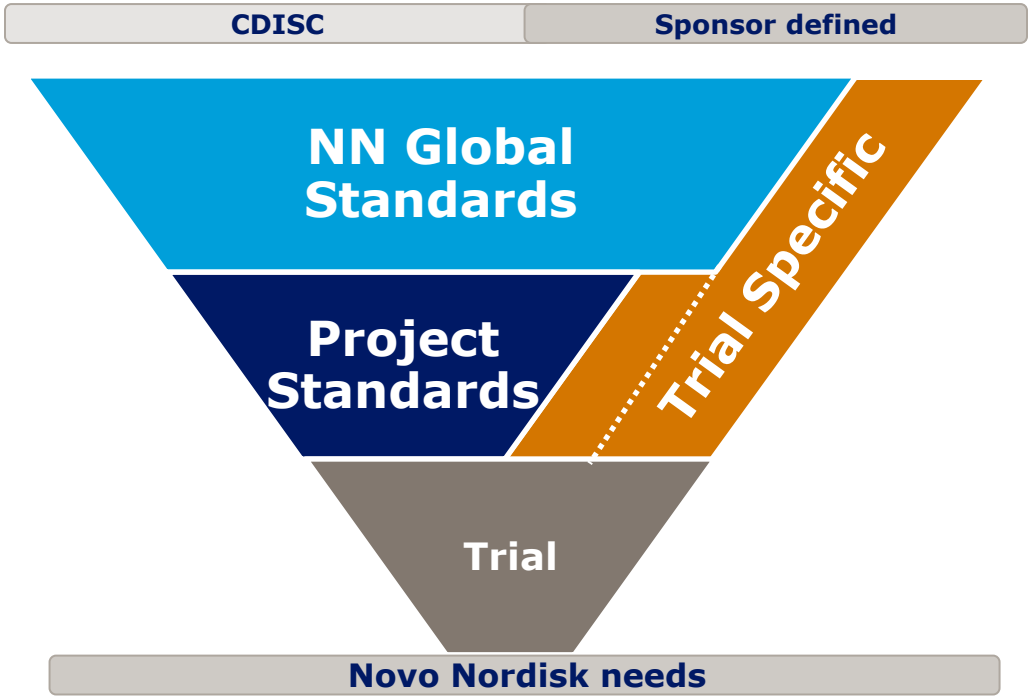
Global, Project and Trial Specific Standards



Global, Project and Trial Specific Standards

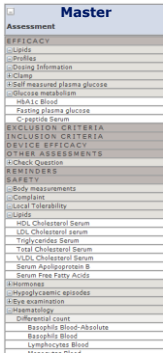
External requirements



Protocol Development

Final Protocol

Global standards



Project specific schedule of activities

Project Standards Team(PST)

Programmer

Iterative process

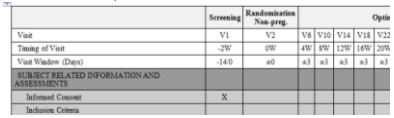
Study group

Protocol Metadata Document (PMD):

- High level schedule of activities
- Detailed schedule of activities
- Trial Design
- Visit
- Compounds
- Dosage
- Profile
- CDISC Trial Summary

Trial specific schedule of activities Report (Word)

High level Schedule of activities copied into the Protocol



	Screening	Randomisation Non-preg.					Optio
Visit	V1	V2	V6	V10	V14	V18	V22
Timing of Visit	-2W	0W	4W	8W	12W	16W	20W
Visit Window (Days)	-14/0	±0	±3	±3	±3	±3	±3
SUBJECT RELATED INFORMATION AND ASSESSMENTS							
Informed Consent	X						
Inclusion Criteria							

PMD QC'ed against the protocol

PMD archived

Version controlled

Trial metadata repository

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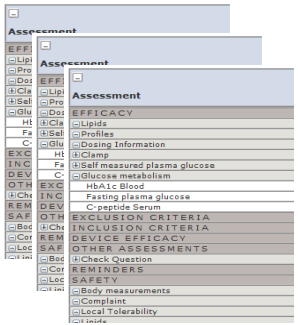
Project Standards

Lifecycle of Trial

Trial Planning | Trial Conduct | Analysis & Reporting

Project Standards Team (PST)



Protocol metadata | **Conduct metadata** | **Analysis metadata**

Global metadata repository

Trial metadata repository

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Project Standards

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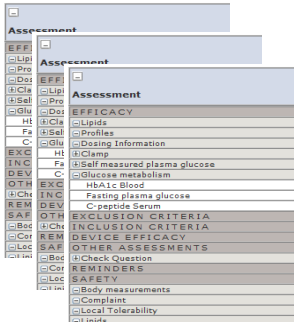
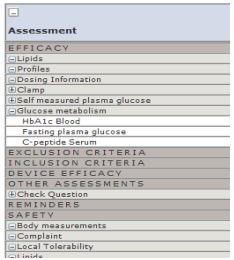
Study Group





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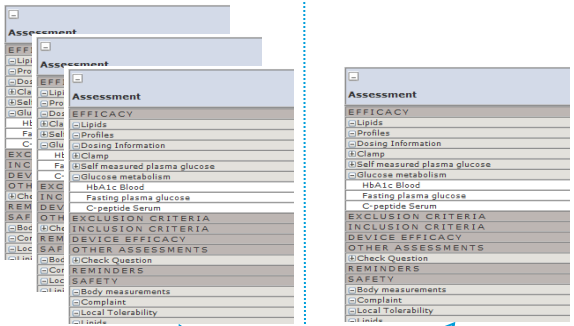

Protocol metadata | **Conduct metadata** | **Analysis metadata**

Global metadata repository

Trial metadata repository

Project standard compare program

Project Standard Compare

Enforce and control of Project Standard

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	A	B
1	Project Standard Report	
2	Trial ID	NN1234-5678
3	Trial Definition ID	CTR
4	Trial Definition Status	Draft
5	Trial Metadata Version	1
6	Project Code	NN1234
7	Project Label	Drug X
8	Timestamp	22-jul-16
9		
10		
11		

cover | Project stand

Ready 100%

	A	B	C	D	E	F	G	H	I	J	K	L
1		NN1234-5678 (CTR)				Project standard						
2	Change Type	Flowchart Group	Assessment Group	Assessment Subgroup	Assessment (Topic Code)	Template Name	Template Type	Flowchart Group	Assessment Group	Assessment Subgroup	Assessment (Topic Code)	Mandatory
3	Difference in flowchart group found	EFFICACY	Body measurements		Body Weight	NN1234 project standard.	Project Standard	SUBJECT RELATED INFORMATION AND ASSESSMENTS	Body measurements	Body measurements	Body Weight	N
4	Assessment not in project standard	EFFICACY	Body measurements		Neck Circumference							
5	Mandatory assessment missing					NN1234 project standard.	Project Standard	SUBJECT RELATED INFORMATION AND ASSESSMENTS	Body measurements		Height	Y

Project standard

Ready 100%

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Project Standards

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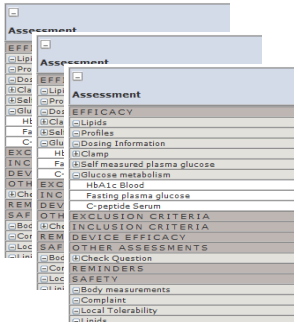

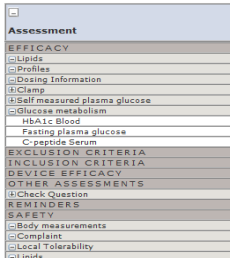

Protocol metadata | **Conduct metadata** | **Analysis metadata**

Global metadata repository

Trial metadata repository

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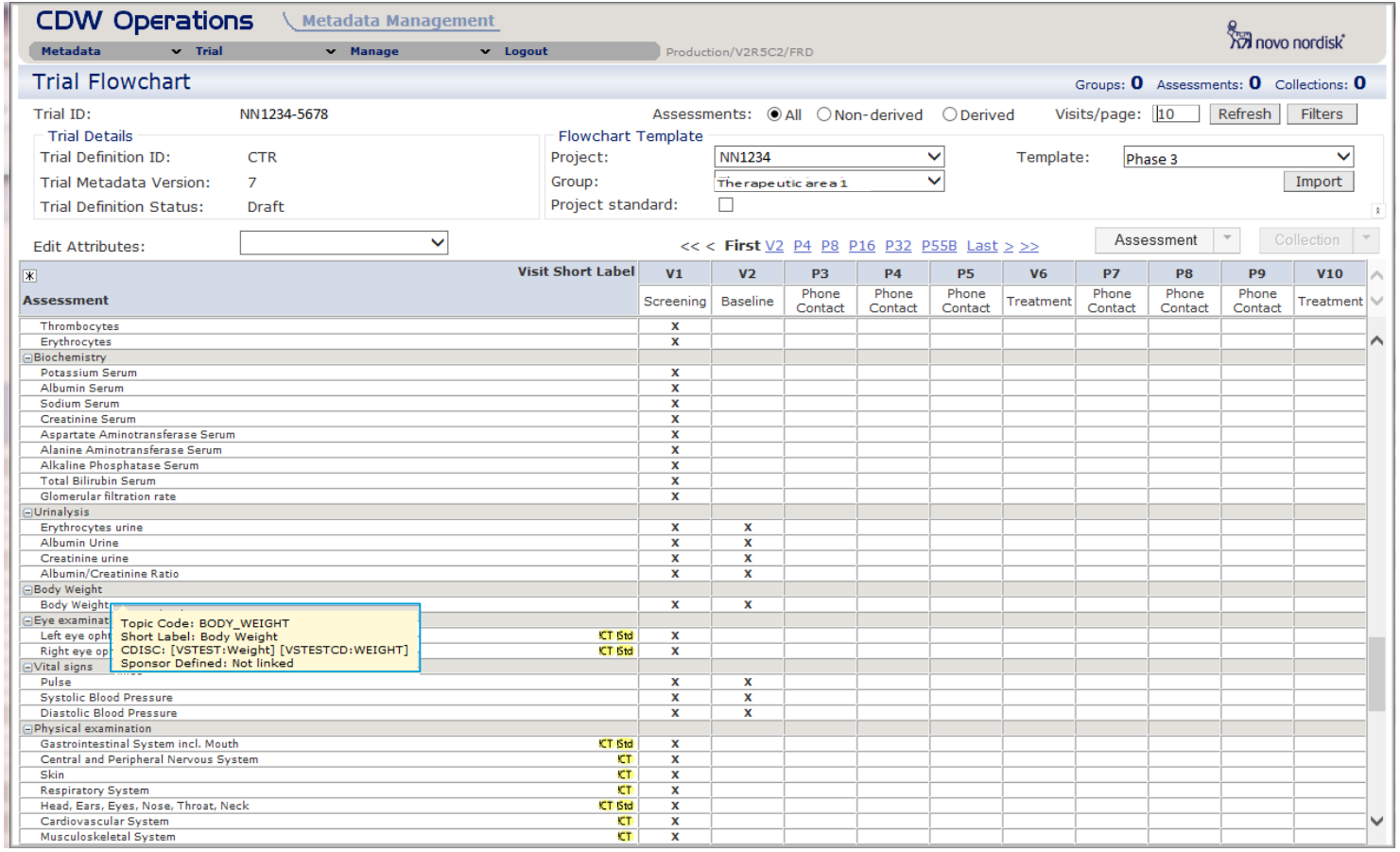
Glimpse of our metadata system



CDW Operations — Metadata Management

Metadata | Trial | Manage | Logout — Production/V2R5C2/FRD

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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

Assessment	Visit Short Label	V1 Screening	V2 Baseline	P3 Phone Contact	P4 Phone Contact	P5 Phone Contact	V6 Treatment	P7 Phone Contact	P8 Phone Contact	P9 Phone Contact	V10 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 examinat											
Left eye opht	ICT Std	X									
Right eye op	ICT Std	X									
Vital signs											
Pulse		X	X								
Systolic Blood Pressure		X	X								
Diastolic Blood Pressure		X	X								
Physical examination											
Gastrointestinal System incl. Mouth	ICT Std	X									
Central and Peripheral Nervous System	ICT	X									
Skin	ICT	X									
Respiratory System	ICT	X									
Head, Ears, Eyes, Nose, Throat, Neck	ICT Std	X									
Cardiovascular System	ICT	X									
Musculoskeletal System	ICT	X									

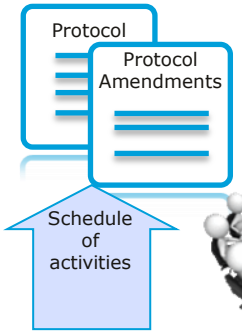
Topic Code: BODY_WEIGHT
Short Label: Body Weight
CDISC: [VSTEST:Weight] [VSTESTCD:WEIGHT]
Sponsor Defined: Not linked

Project Standards

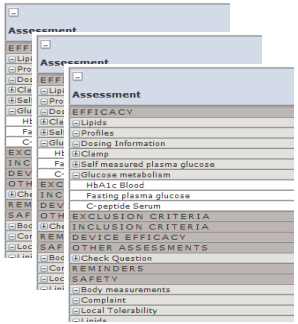
Lifecycle of Trial

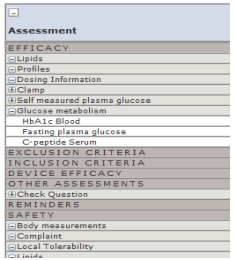
Trial Planning | Trial Conduct | Analysis & Reporting

Project Standards Team (PST)



Study Group





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

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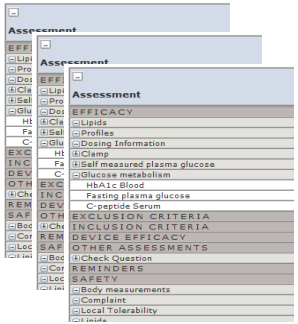
Project Standards

Lifecycle of Trial

Trial Planning | Trial Conduct | Analysis & Reporting

Project Standards Team (PST)

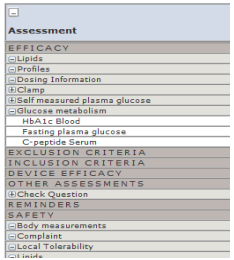


Protocol

Protocol Amendments

Schedule of activities

Study Group



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

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	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						

Cover | High level flowchart | Detailed flowchart

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High Level Flowchart without Phone Contact

	Screening	Randomisation	Dose escalation	Treatment	Follow-up
Visit	V1	V2	V4	Visit 8 - Visit 9[b]	V11
Timing of Visit	14D	0D	56D	154D-168D	182D
Visit Window	±14D	±7D	±14D		±7D
EFFICACY					
Glucose metabolism[d]			X		
HbA1c Blood					
SAFETY					
Hypoglycaemic episodes					
Vital signs					
Pulse or Heart Rate	X		X	X	
Pulse	X		X	X	
Adverse event					
Adverse event	X				
Adverse event	X				
SUBJECT RELATED INFORMATION AND ASSESSMENTS					
Body measurements	X	X	X	X	X
Body Weight	X	X	X	X	X

Footnote
[b] Washout Period
[d] Patient needs to be fasting

High Level Flowchart with only Phone Contact

	Phone Contact
Visit	P61[a]
Timing of Visit	112D
Visit Window	±14D
EFFICACY	
Glucose metabolism[d]	X
SAFETY	
Hypoglycaemic episodes	X
Vital signs	
Pulse or Heart Rate	X
Pulse	X
Adverse event	
Adverse event	X
Adverse event	X
SUBJECT RELATED INFORMATION AND ASSESSMENTS	
Body measurements	X
Body Weight	X

Footnote
[a] call subject if no phone call received
[d] Patient needs to be fasting

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Protocol Metadata Document (PMD):

- High level schedule of activities
- Detailed schedule of activities
- Trial Design
- Visit
- Compounds
- Dosage
- Profile
- CDISC Trial Summary

Planned Trial Visits for NN1234-5678

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 Tria
Screening Epoch	Screening Epoch	V1	10	Screening	Screening	Visit 1 (week -2)	Visit 1 (week -2)		Baseline	14 Day
Treatment Epoch 1	Treatment Epoch 1	V2	20	Baseline	Randomisation	Visit 2 (week 0)	Visit 2 (week 0)		Baseline	0 Days
Treatment Epoch 3	Treatment Epoch 3	V4	40	Treatment	Dose escalation	Visit 4 (week 8)	Visit 4 (week 8)		Baseline	56 Day
Treatment Epoch 5	Treatment Epoch 5	P61	61	Phone Contact	Phone Contact	Visit 6 Day 1	Visit 6 Day 1		Baseline	112 Da
Treatment Epoch 7	Treatment Epoch 7	V80	80	Treatment	Treatment	Visit 8 (week 22)	Visit 8 (week 22)		Baseline 2	154 Da
						Visit 9				

Detailed flowchart | Trial Design | Visit | Compound | Dosage | Profile | CDISC TS

CDISC Trial Summary parameters for NN1234-5678

#	Trial Summary Parameter Code	Trial Summary Parameter	Parameter Value (MMA)	Parameter Value Code	Reference Terminology	Para Null
1	REGID	Registry Identifier	1234-56		EUDRAC	
2	TITLE	Trial Title	0			
3	TPHASE	Trial Phase Classification	Phase II		CDISC	
4	OBJPRIM	Trial Primary Objective	To compare the efficacy on glycaemic control of Drug A against placebo in subjects with T2D.			
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.			
6	INTMODEL	Intervention Model	Parallel Group		CDISC	
7	TBLIND	Trial Blinding Schema	Single Blind		CDISC	
8	NARMS	Planned Number of Arms	9			

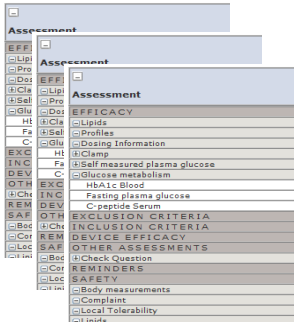
Detailed flowchart | Trial Design | Visit | Compound | Dosage | Profile | CDISC TS

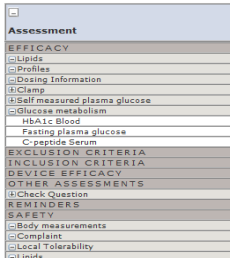
Project Standards

Lifecycle of Trial

Trial Planning | **Trial Conduct** | **Analysis & Reporting**

Project Standards Team (PST)





Protocol

Protocol Amendments

Protocol information used to create CRF

Schedule of activities

Study Group

CRF

Data captured in CRF

Data

Clinical System

Output

aCRF

aCRF explains where in the SDTM the data is located

SDTM

ADaM prepared from SDTM

ADaM

Protocol metadata | **Conduct metadata** | **Analysis metadata**

Global metadata repository

Trial metadata repository

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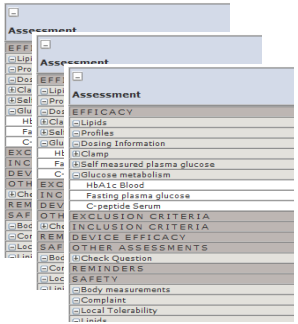

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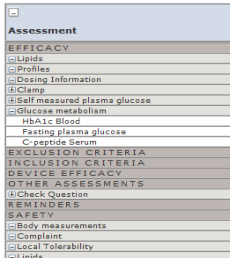

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ADaM

Global metadata repository

Protocol metadata

v1

v2

Conduct metadata

v3

Trial metadata repository

v4

Analysis metadata

v5

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Project Standards

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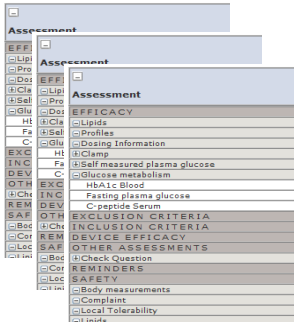

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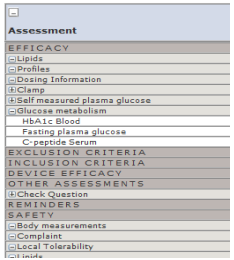

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ADaM

Global metadata repository

Protocol metadata

Conduct metadata

Analysis metadata

v1 **v2** **v3** **v4** **v5**

Trial metadata repository

Version Compare program

Version Compare

Enable transparency/traceability during the lifecycle of trial

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Detailed Flowchart compare between base trial NN1234-5678 (CTR)(v2) and compare trial NN1234-5678 (CTR)(v1)

			Base				Compare				
Change Type	Change Description	Flowchart Group	Assessment Group	Assessment Subgrou	Primary	Flowchart Group	Assessment Group	Assessment Subgrou	Primary	Assessment Details
Assessment added	HDL Cholesterol Serum (HDL_CHOL_SERUM) added	EFFICACY	Lipids		Y					HDL Cholesterol Serum (HDL_CHOL_SERUM)
Assessment deleted	Body Weight (BODY_WEIGHT) deleted					SUBJECT RELATED INFORMATION AND ASSESSMENTS	Body measurements		Y	Body Weight (BODY_WEIGHT)

Cover | High level assessments | Detailed assessments | Visit | Collection | Footnote

Visit compare between base trial NN1234-5678 (CTR)(v2) and compare trial NN1234-5678 (CTR)(v1)

Change Type	Change Description	Display Visit (Base)
Planned trial time changed	0D is changed to 14D at visit V1	Y
Planned trial time changed	0W is changed to 182D at visit V110	Y
Planned trial time changed	0W is changed to 56D at visit V40	Y
Planned visit time window changed	±0 is changed to ±14D at visit V1	Y
Planned visit time window changed	±0 is changed to ±7D at visit V110	Y
Planned visit time window changed	±0 is changed to ±14D at visit V40	Y
Visit added	Visit V100 added	Y
Visit added	Visit V120 added	Y

Cover | High level assessments | Detailed assessments | Visit | Collection | Footnote

Comparision of Assessment Collection between base trial NN1234-5678 (CTR)(v2) and compare trial NN1234-5678 (CTR)(v1)

Change Type	Assessment (Topic Code)	Visit ID (MMA)	Visit Short Label
Deleted	Adverse event (ADVERSE EVENT)	10	V1
Added	Adverse event (ADVERSE EVENT)	40	V40
Added	Adverse event (ADVERSE EVENT)	110	V110

Cover | High level assessments | Detailed assessments | Visit | Collection | Footnote

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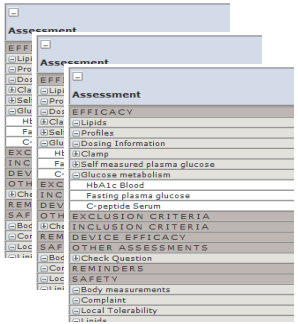

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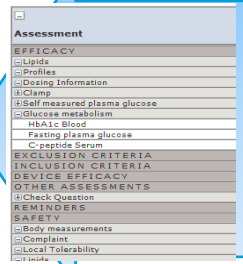
Schedule of activities

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

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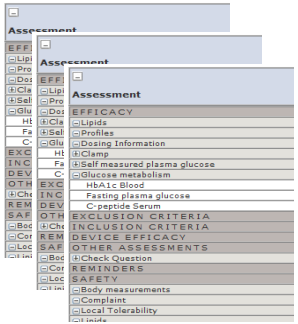
Project Standards

Lifecycle of Trial

Trial Planning | Trial Conduct | Analysis & Reporting

Project Standards Team (PST)



Protocol

Protocol Amendments

Protocol information used to create CRF

CRF

Data captured in CRF

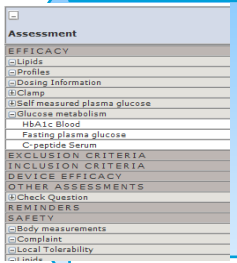
Data

Clinical System

Output

Schedule of activities

Study Group



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Traceability program

Traceability report

Traceability report during the lifecycle of trial

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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 Labe	Statu	Standard	Definition Completed	Linked to CT	Primary Assessment	Mand	Linked to domai	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

MDR: Metadata Repository, CT: Controlled Terminology

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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

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