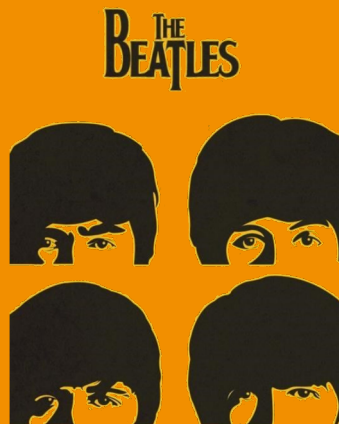




Let CDISC be !

PHUSE Virtual EU Connect 2020
November 9-13, 2020

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Agenda

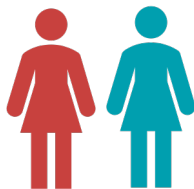
- **CDISC and Medical Devices**
- **Terumo Business Case**
- **LivaNova Business Case**
- **Conclusion**

CDISC and Medical Devices

CDISC and Medical Devices – Subject Matter Expert

Our backgrounds

CRO/Pharma where clinical trials have standard structures, mandatory use of CDISC, clear roles of biostatisticians and statistical programmers in the full process.



Medical device company

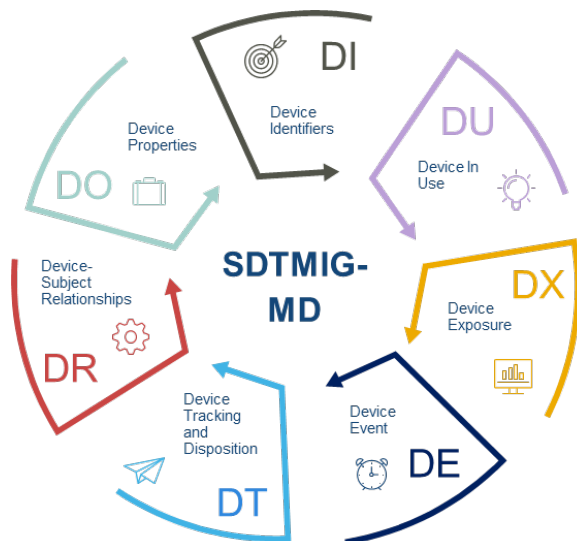
Database structure **not** standardized, CDISC standards **not** mandatory only optional, but standardization is needed.



We work in two medical device companies

Our CDISC knowledge can enhance internal processes related to database structures and statistical analyses.

CDISC and Medical Devices – SDTMIG-MD Example



DOMAIN	SPDEVID	DIPARMCD	DIPARM	DIVAL
DI	ABC1234	DEVTYPE	Device Type	Valve
DI	ABC1234	MANUF	Manufacturer	LivaNova PLC
DI	ABC1234	MODEL	Model Identifier	Perceval
DI	ABC1234	SERIAL	Serial Number	ABC1234
DI	ABC1234	VALVENUM	Valve Number	2
DI	ABC1234	MANSITE	Manufacturer Site	Vancouver

DOMAIN	USUBJID	SPDEVID	DXTRT	DXMETHOD	DXSTDTC	DXENDTC
DX	ITA1001	ABC1234	VALVE	SURGICAL	2018-09-27	
DX	USA6001	DEF5678	VALVE	SURGICAL	2018-03-16	2018-10-16

DOMAIN	USUBJID	SPDEVID	DETERM	DECAT	DEACNDEV	DESTDTC
DE	ITA1001	XYZ9999	Sizing, positioning or deployment difficulties	VALVE NOT IMPLANTED	Another Valve Used	2018-09-27
DE	USA6001	DEF5678	Material Deformation	DEFICIENCY	Explant	2018-10-16

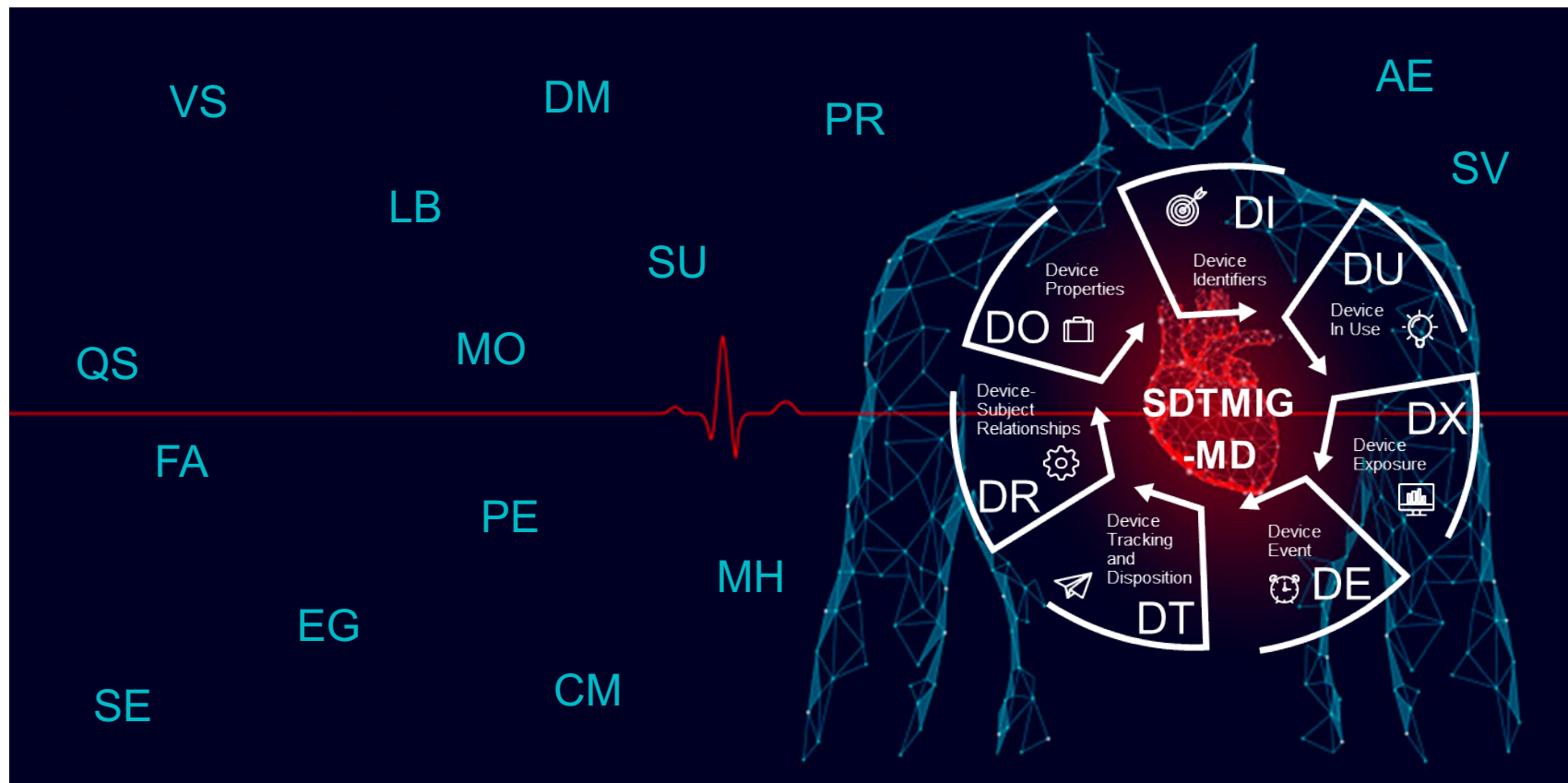
DOMAIN	SPDEVID	DTTERM	DTPARTY	DTPRTYID	DTSTDTC
DT	XYZ9999	NOT IMPLANTED	SITE	ITA1	2018-09-27
DT	ABC1234	IMPLANTED	SUBJECT	ITA1001	2018-09-27
DT	DEF5678	IMPLANTED	SUBJECT	USA6001	2018-03-16
DT	DEF5678	EXPLANTED	SPONSOR	LIVANOVA	2018-10-16

DOMAIN	SPDEVID	DOTESTCD	DOTEST	DOORRES
DO	XYZ9999	LVLVSIZE	Labeled Valve Size	S (21 mm)
DO	ABC1234	LVLVSIZE	Labeled Valve Size	M (23 mm)
DO	DEF5678	LVLVSIZE	Labeled Valve Size	L (25 mm)

DOMAIN	USUBJID	SPDEVID
DR	ITA1001	XYZ9999
DR	ITA1001	ABC1234
DR	USA6001	DEF5678

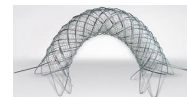
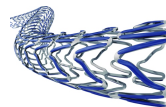
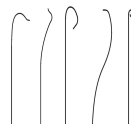
"PP05 - Medical Device SDTM Domains: A Real Case",
A.Sacco, R.Teli, LivaNova, PHUSE EU Connect 2019

CDISC and Medical Devices – Not only SDTMIG-MD



CDISC and Medical Devices – Implementation

- Not mandatory
- But full process and compliance to CDISC are preferable
- Specific waivers can be justified:
 - **Process waiver**, it can be decided not implement part of the process based on internal knowledge, available resources, budget, timelines;
 - **Compliance waiver**, due to eDC data limit or sponsor decision.



Terumo Business Case

A first CDISC initiative

Active in Multiple Fields

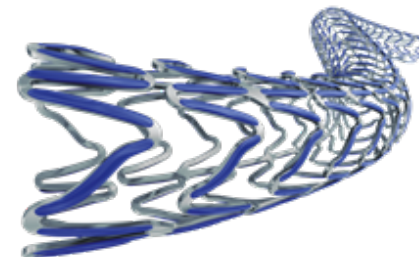
Interventional Cardiology
Interventional Oncology
Peripheral Interventions
Cardiovascular Surgery



Main characteristics:

More information available at : <https://www.terumo-europe.com/en-emea/clinicaldata/e-ultimaster-trial>

- Clinical Field: Cardiovascular Intervention
- Product : Coronary Stent
- Study Design: Observational study (Registry), single arm, open label, 5 majors timepoints : SCR, BASELINE, PROC, 3MFU, 1YFU
- Primary endpoint:
Validate Efficacy and Safety: Composite Endpoint of different SAE up to 1 year after procedure (i.e. Cardiac Death, TV related to MI and CD-TLR).
- Secondary endpoint: exploratory analysis
Status: FPI in 2015, DBL 2019, N = 37.198, 378 sites, 50 countries



1 vessel diseased, 1 coronary lesion identified and treated by using 1 stent

➔ Data easily mapped : DM, MH, CM, AE, EG, LB, etc.

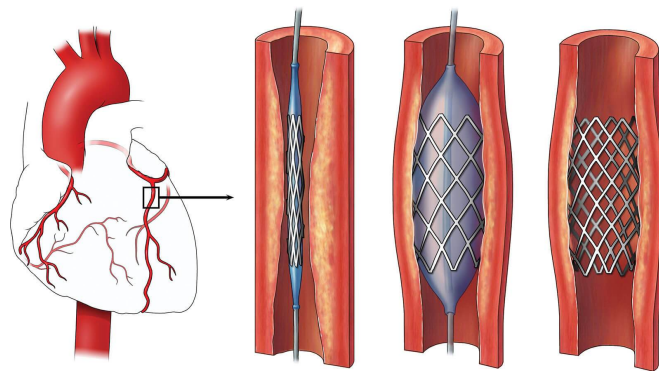
➔ All devices information goes to specific MD domains : DU, DI, DE

■ Where goes the **lesions description** data ?

Segment description,
lesion location and complexity,
lesion type, vessel lumen, etc.

■ Where goes the **procedure data** ?

Arterial access site, side, guided by use
of additional imaging, action taken based
on imaging results, etc.



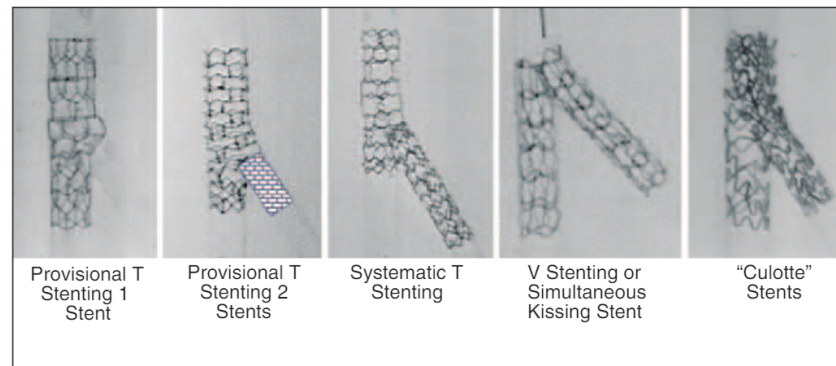
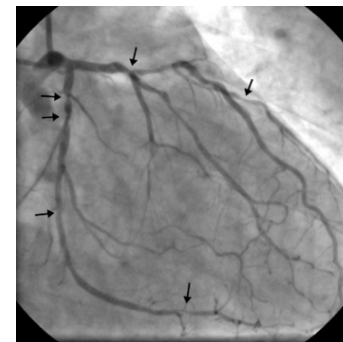
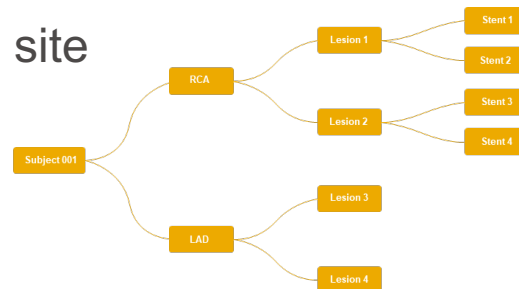
TERUMO - Let's complicate a bit ..

1 subject << 1+ vessels << 1+ lesions << 1+ stents

Multiple coronary lesions at the bifurcation site

Important parameters are :

- Lesion location (proximal vs distal)
- Lesion characteristics
- Vessel diameter (main/side branch)
- Lesion length
- Number of stent used
- Stent overlap
- ...



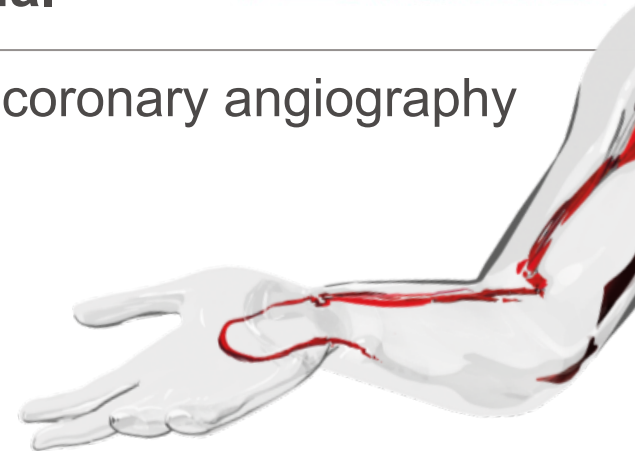
- **Adjudicated Adverse Event of Specific Interest** as main parameter for primary endpoint of the study :
 - eCRF data → AE vs Adjudicated Data → CE/FA.
 - Additional information than standard AE domain data collected and included in analysis: Relationship to device/procedure, Decision rationale
- Most of **device don't contain any drugs** .. but EX domain is mandatory
- Few device contains drug (e.g. Drug Eluting Stent), even if classified as device (one exposure, only local effect) should it still be recorded in EX ?
- In the CRF, AE and CM of specific interest are listed, are not recoded by using a standard methodology (MedDRA and WHODrug Dictionnary)

DIStal versus **CO**nventional **RADIAL** access for coronary angiography and intervention: a randomized multicenter trial

Main characteristics:

More information available at <https://clinicaltrials.gov/ct2/show/NCT04171570>

- Clinical Field: Peripheral Intervention
- No Investigational Device, Comparison of Access Technique
- Study Design: Interventional study (RCT), 2 arms, open label, FU only until discharge (Day 3)
3 majors timepoints : SCR, BASELINE, PROC.
- Primary Objective and Primary Endpoint :
Demonstrate the superiority of Distal Radial Access (DTRA) to Conventional Transradial Access (CTRA) regarding forearm Radial Artery Occlusion rate (RAO) at discharge
- Secondary endpoint: safety and efficacy exploratory analysis
- Status: FPI 2019, LPLV 2021, N ± 315/1300 (SEP-2020), 14 sites, 9 countries



DIStal versus **CO**nventional **RADIAL** access for coronary angiography and intervention: a randomized multicenter trial

Distal



Conventional



DIStal versus **CO**nventional **RADIAL** access for coronary angiography and intervention: a randomized multicenter trial

- How to derive Safety Population Flags?
Not from EX ! Not from DX ! But from PR ..
- How to integrate all procedural information into PR?
- How to standardize the information related to additional medical devices used during the procedure when they are not **the investigational device** (comparable as CM vs investigational drug)



MD domains are probably designed to fit pharmacological study where a device is used to deliver the study drug but is not yet ready to answer all needs of a Device only studies.

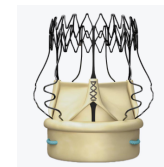
LivaNova Business Case

Pooled database project

Cardiovascular

Advanced Circulatory
Support

Cardiopulmonary
Heart Valves



Neuromodulation

Drug-resistant epilepsy

Difficult-to-treat depression

Obstructive Sleep Apnea

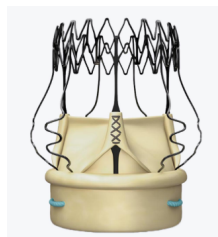


LivaNova

Health innovation that matters

Pooled Database Project

- From EU Virtual CDISC Interchange – status in April 2020



Perceval®

3 Purposes
Regulatory, Exploratory,
Confirmatory

9 Perceval® studies

Several analyses (MDR,
CE certification, National
Regulatory Agencies)

Solution Pooled
CDISC Database

Pooling Strategy

EDC/raw
datasets

iSDTM

iADaM

Pooled Database Project – A circular process

- **Successful aspects**

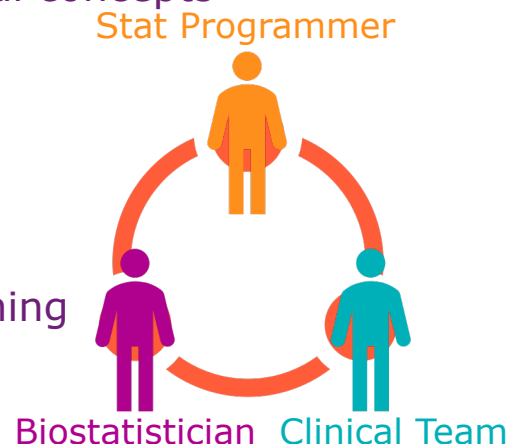
- Global overview of the upcoming analyses/submissions
- Sharing and clarifying needs and knowledge
- Better understanding of the role of some biomedical concepts

- **Unsuccessful aspects**

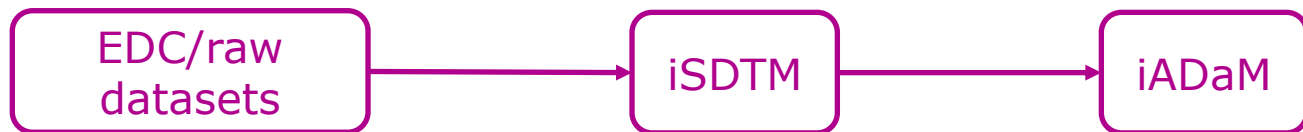
- Documents review as stand-alone files

- **Points of improvement**

- Have on board key opinion leaders from the beginning
- Be timely and together on the project needs



Pooled Database Project – Pooling strategy



- **Advantages and disadvantages**

- Expected = Actual

- **Advantages**

- iSDTM allows alignment and standardization of controlled terminology and dictionary versions, harmonization of coding strategy, creating a single source for ADaM
- iADaM starting from iSDTM allows to focus on derivations, alignment of algorithms, clear traceability to the predecessor

Pooled Database Project – Pooling strategy

- **Disadvantages**

- more complex traceability for iSDTM, more complex specifications
- high number of datasets to create and validate → SDTM validation and some additional checks in SAS

- **Points of improvement**

- Use a strategic order for SDTM mapping to be more efficient in subsequent steps:
 - E.g. to complete as first all SDTM domains involving efficacy and safety endpoints for heart valves: DM, DI, DO, CV, PR, AE.
 - The most derivations to be programmed in ADaM have these domains as source, and these ADaM are the source of the key outputs to be produced.

Pooled Database Project – Advantages

■ Advantages on time

Task	Items	% hours
iSDTM documentation ¹	-	15%
iSDTM programming	23	50%
iADaM programming	16	10%
1° analysis TFL	97	25%

¹ specifications and define-xml.

- iSDTM 65% of whole programming time
- iADaM and TFL 35% of whole programming time

Pooled Database Project – Advantages

- **Advantages on time iADaM and TFL current project**
 - efficiency gained due to CDISC standard structure of the source
 - iSDTM source for iADaM
 - iADaM source for TFL
 - including “last minute” updates due to an amendment to SAP

Pooled Database Project – Advantages

■ Advantages on time

iSDTM in future projects 3 scenarios

- No ongoing study, no additional study, no update → +0 hours
- e.g. 2 ongoing studies, updates needed → +80 hours, around 7% of the time spent for SDTM tasks until now
- e.g. a new study on Perceval, updates needed → +120-160 hours, around 10-13% of the time spent for SDTM tasks until now

Pooled Database Project – Advantages

- **Advantages on time**

- iADaM and TFL for future projects**

- iADaM new variables, new datasets → +40 hours, around 33% of the time spent for iADaM task until now
 - TFL new outputs / updates needed → +160-200 hours, around 40-50% of the time spent for TFLs task until now

Pooled Database Project – Advantages

- **Advantages on time for future projects**
 - Comparison of %hours distribution of programming tasks for the 1st analysis and future analyses

Task	1° analysis % hours	Next analysis Best scenario % hours	Next analysis Worst scenario % hours
iSDTM	65%	0%	9%
iADaM	10%	3%	3%
TFL	25%	10%	12,5%
Total	100%	13%	24,5%

Pooled Database Project – What's Next?

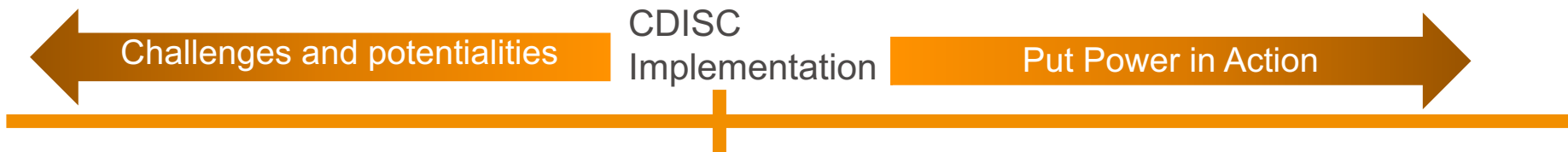
■ September 2020

- Perceval Pooled Database - already 2 new analyses required
- VNS Therapy® - kick-off meeting for a new pooling project
- LivaNova confirmed CDISC implementation for all new studies and for pooling of legacy data of certain products

Let CDSIC be!

Conclusion

From Power to Action



From Power to Action

- Enable **Reusability** of the data and facilitate Data Pooling
- Increase **Clarity and Accessibility** of the data, Improve **Transparency and Traceability** of the Data from eDC to CSR
- Improve **Cross-functional Collaboration** by sharing information and knowledge, Empower analysis and facilitate decision making
- **Foster Efficiency** Data manipulation and **Reduce Cost and Time**
- Enhance **Innovation** (e.g. Big Data, Data Visualization Dashboard)

Thank you

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