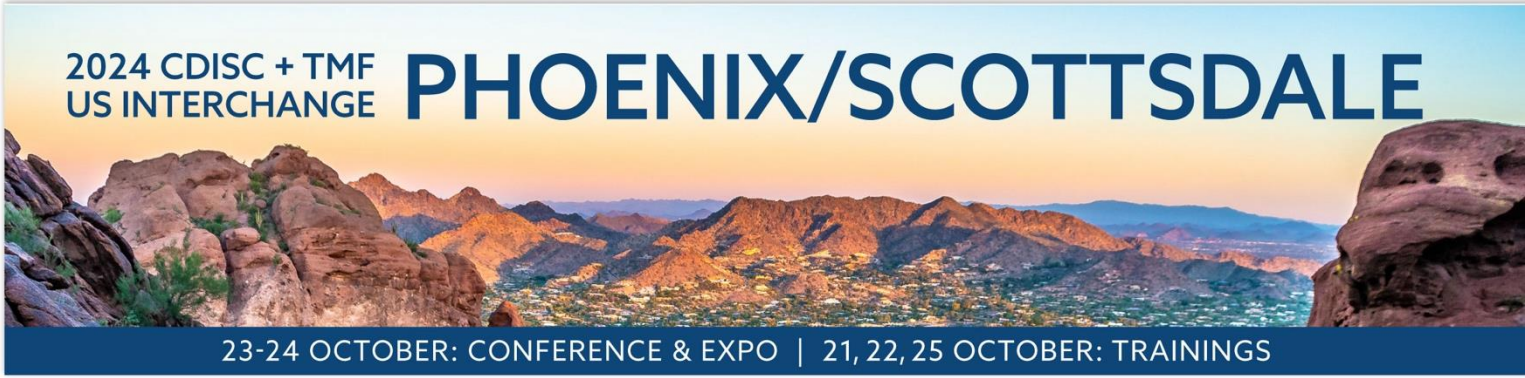


The EU CTR and Its Impact on the TMF

Presented by Karla Navera-Andersen, Clinical Trial Manager,
Clinical Operations, Ascendis Pharma

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

Meet the Speaker

Karla Navera-Andersen

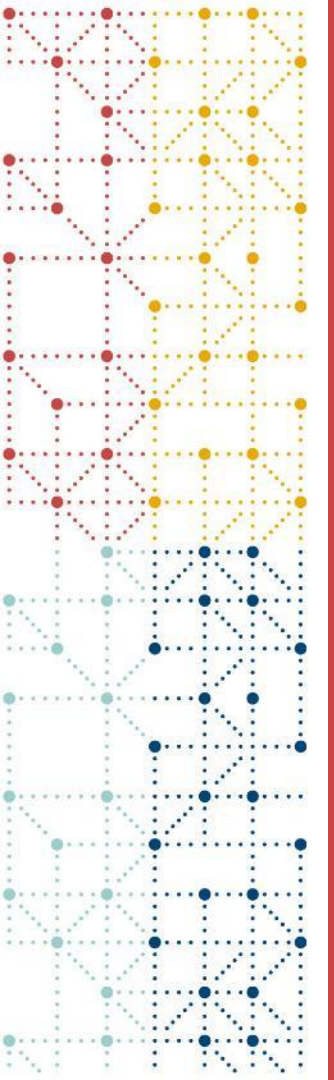
Title: Clinical Trial Manager

Organization: Ascendis Pharma A/S

Karla Navera-Andersen is an eTMF Manager turned Clinical Trial Manager at Ascendis Pharma A/S.

Karla holds a Master of Arts in English and a Pharma Consultant Diploma. She has spent over 15 years working with TMFs, starting her TMF career as a student in the paper TMF archive in a large pharmaceutical company.

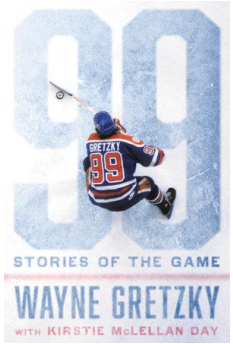
Since then, Karla has worked on both on the CRO and Sponsor side and whithin Clinical Operations and Regulatory Affairs. Currently, Karla is working as a Clinical Trial Manager, focusing on improving the quality and processes of TMF management within Clinical Operations and between Sponsor and CRO.

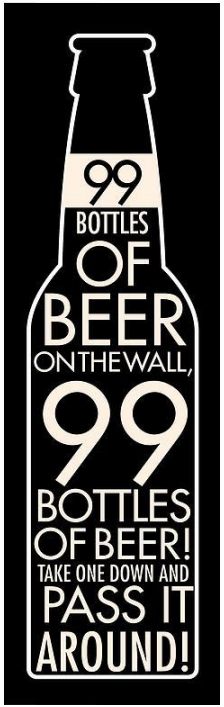


99

Articles in the EU Clinical Trials Regulation

Significance of 99





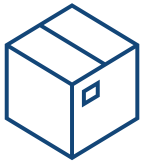
The EU Clinical Trials Regulation

- Effective January 2022, replacing the EU Clinical Trials Directive
- Implementation of the Clinical Trials Information System - CTIS
- TMF only mentioned in two articles of the EU CTR
- Streamlining, efficiency, reducing administrative requisites

Ascendis Pharma

- Ascendis Pharma founded in 2006
- eTMF System implemented in the Summer of 2020
- First eTMF Managers hired in the Fall of 2021
- eTMF previously housed in multiple systems and locations
- Challenging change management

The EU CTR Effect



Document Storage

New Documents

Redactions

Data Fields

Approvals

TMF Documents in Ascendis

- TMF housed in multiple systems and locations
- Many different CRO collaborators
- The ~~mess~~ challenge mostly rooted in the CTA process

The Game Changer: CTIS

- CTIS: One Submission
- Work Instruction: Documents cannot be a part of the EU submission if not filed in eTMF
- Submission documents to be **filed or cross-linked** to Clinical Vault/eTMF
- CRO to get direct access to our eTMF for country and site documents
- Short timlines for Request for Information as motivator
- Updates to our TMF Index

New Required Documents

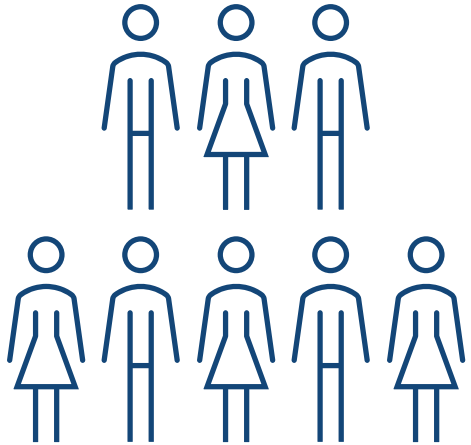
- Template statement on compliance Regulation (EU) 2016/679
- Compensation for trial participants
- Declaration of interest
- Site suitability form
- Informed consent and patient recruitment procedure
- Compliance with applicable rules for biological samples

New Required Documents

- Template statement on compliance Regulation (EU) 679
- Compensation for trial participants
- Declaration of interest
- Site suitability
- Informed consent and patient recruitment procedure
- Compliance with applicable rules for biological samples

The Danish TMF Network to the Rescue

- Network comprising 12-15 Danish pharmaceutical companies
- F2F meetings held every 6 months
- Mailing lists and LinkedIn group for random TMF questions and challenges
- Sharing knowledge from inspections, authorities and TMF Reference Model



Implications

Move misfiled documents

Reupdate TMF index

Retrain stakeholders

Redacted Documents

SPONSOR CONTACT

Medical Monitors

[redacted]
Ascendis Pharma
Tuborg Boulevard 12, DK-2900
Hellerup, Denmark
[redacted]

[redacted]
Ascendis Pharma
Tuborg Boulevard 12, DK-2900,
Hellerup, Denmark
[redacted]

Safety Reporting

Safety reporting should be primarily via the electronic safety adverse event (eSAE) reporting process directly through the Electronic Data Capture system (EDC) along with all relevant information within 24 hours of awareness.

If the EDC is unavailable, a completed safety report form / pregnancy report form should be uploaded to the Sponsor Safety Reporting Portal (safety.ascendispharma.com) within 24 hours of awareness, or for sites that cannot upload to the portal, the safety report form can be sent via Fax to: 1-844-307-5997.

The Sponsor may suggest an alternate route for reporting SAEs, adverse events of special interest (AESI)s and Special situation reports as applicable. Such alternate mechanisms will be clearly communicated to the sites with applicable guidance from the Sponsor.

D4_Patient facing documents SF-10_IE_Acute_UK_REDACTED

English · Protocol (for publication) · **System version 1.00**
Submission date 22/12/2023
· **Version 1.0** · 13/01/2016

D4_Patient facing documents SF-10_IE_Acute_UK

English · Protocol (not for publication) · **System version 1.00**
Submission date 22/12/2023
· **Version 1.0** · 13/01/2016

Thoughts on Redacted Documents

- Will the redacted versions crowd our eTMFs?
- Are these at all eTMF documents?
- Duplicates?
- De facto submission document
- Can we refer to CTIS for these versions?

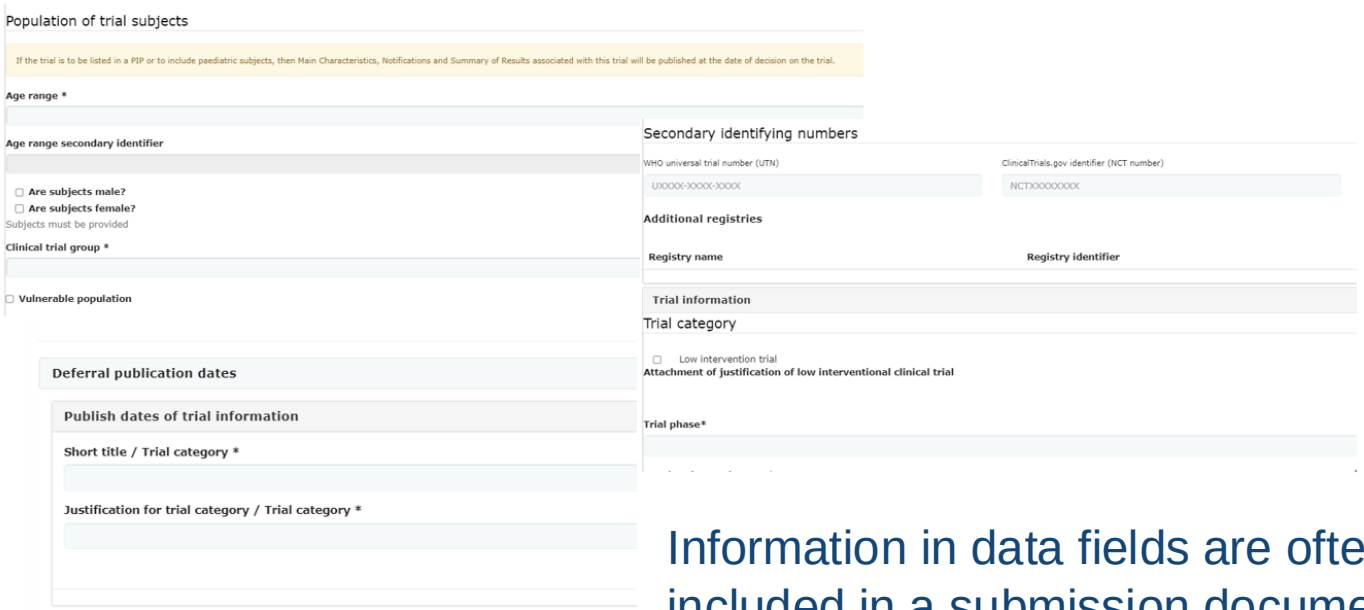
“Nothing in the Regulation states that the redacted versions need to be stored in the TMF”

Data Fields, Modifications and other Notifications

APPLICATION AND NON-SUBSTANTIAL MODIFICATION

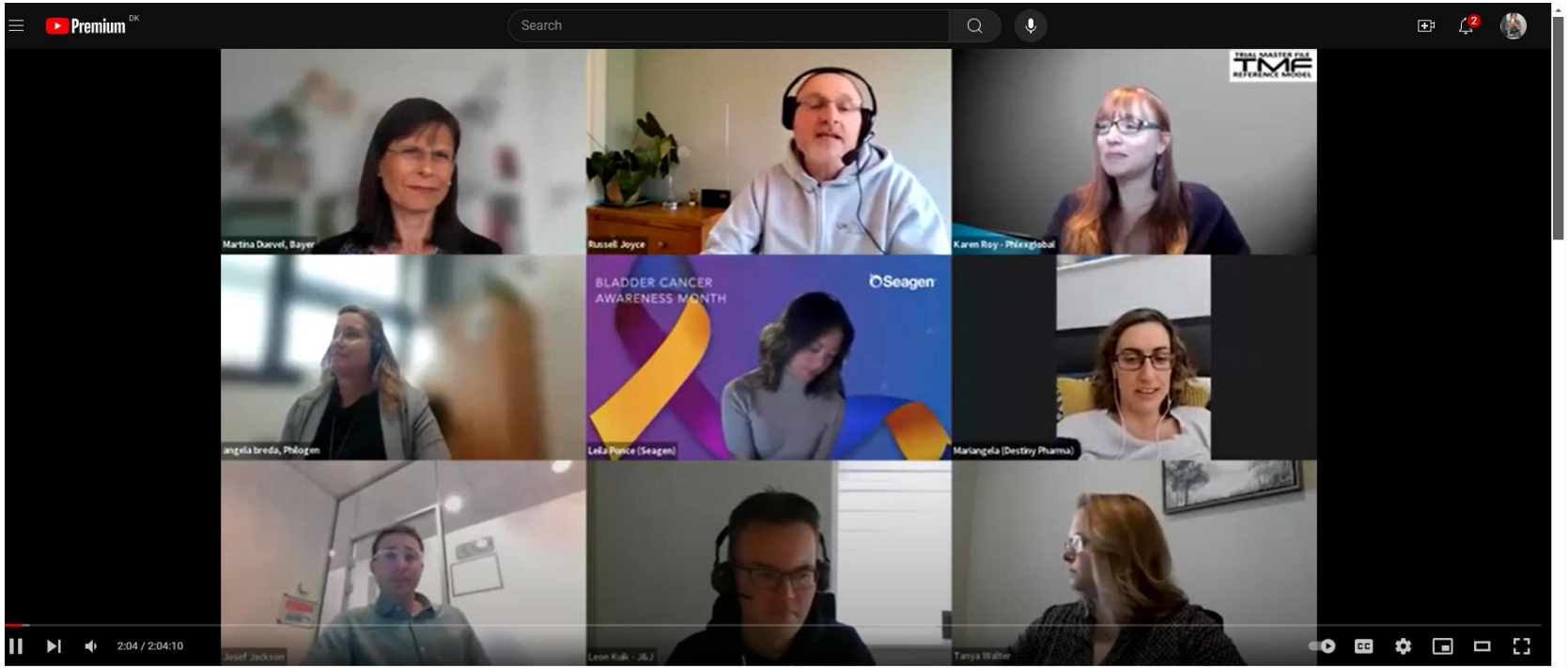
Type	ID	Parts	MSCs	Submission date	Decision date	Reason	Scope	Link	
Substantial modification	SM-1	Part I Part I Part I Part I Part I	IE(Under evaluation) DE(Under evaluation) PT(Under evaluation) DK(Under evaluation) AT(Under evaluation)	08/09/2023		+	+		+ INFO
Non-substantial modification	NSM-3	Part I Part I Part I Part I Part I	IE(Authorised) DE(Authorised) PT(Authorised) DK(Authorised) AT(Authorised)	05/09/2023	05/09/2023	-	-	-	
Additional MSC	AM-3	Part I (Translations) & Part II	PT(Authorised with condition)	08/06/2023	21/08/2023	-	-	-	+ INFO
Additional MSC	AM-2	Part I (Translations) & Part II	DE(Authorised with condition)	08/06/2023	21/08/2023	-	-	-	+ INFO
Additional MSC	AM-1	Part I (Translations) & Part II	AT(Authorised)	08/06/2023	04/09/2023	-	-	-	+ INFO
Non-substantial modification	NSM-2	Part I Part I	IE(Authorised) DK(Authorised)	07/06/2023	07/06/2023	-	-	-	
Non-substantial modification	NSM-1	Part I Part I	IE(Authorised) DK(Authorised)	31/05/2023	31/05/2023	-	-	-	
Initial	IN	Part I & Part II Part I & Part II	DK(Authorised with condition) IE(Authorised with condition)	08/02/2023	22/05/2023	-	-	-	+ INFO

Data Fields in CTIS



Information in data fields are often already included in a submission documents

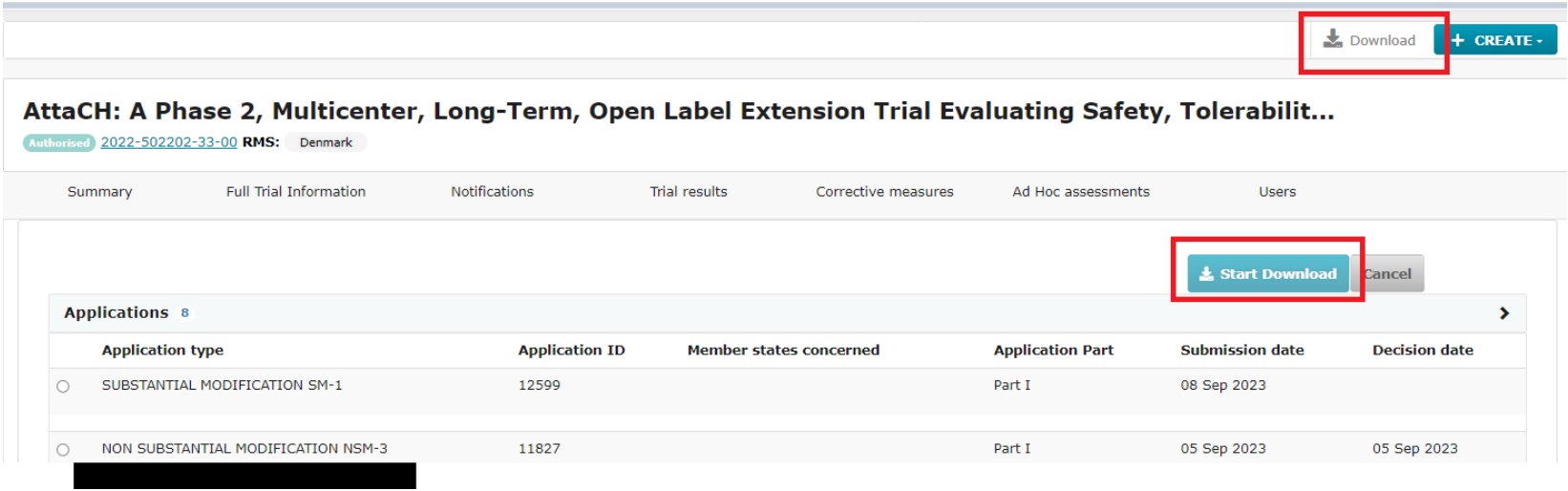
TMF Reference Model to the Rescue



Workshop - EU Clinical Trial Regulation and Impact on TMF Content and Process (07-Apr-2022)

Downloading Information from the CTIS

- Full submission / notification / modification packages
- Dates and structured data
- Assessment reports



Approvals and List of Approved Documents

2022-502202-33-00

Please note that a committee member may have been absent from the meeting due to scheduling conflicts. Furthermore, if a committee member had a conflict of interest, they would thus not have participated in the discussion and assessment of the application.

If a sponsor requires a specific list of members who participated in the application, they may contact MREC for this information (kontakt@dvmk.dk).

The approval is valid for the following trial sites and investigators

Trial Site: Rigshospitalet, Principal investigator: [redacted]

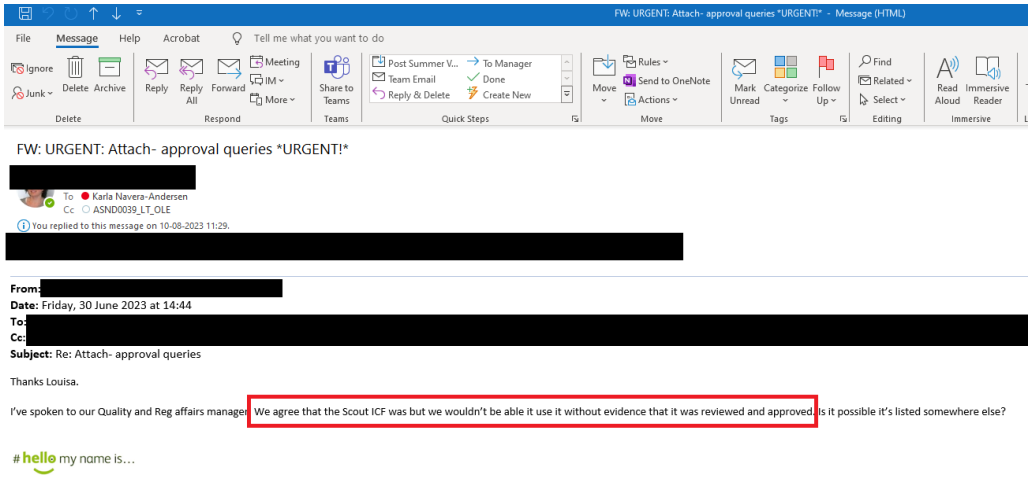
List of documents on the basis of which the decision was made

List of submitted documents can be accessed via Full Trial Information in CTIS.

Challenges of Assessment Reports

- “Submitted” not “Approved”
- Review of approved documents in eTMF against an approval letter
- Stakeholders lack reference for finding latest approved document
- Added workload and increase of mistakes in manual tracking
- Sites are accustomed to good ol’ fashioned approval letters listing date and version of patient facing documents and have no access to CTIS

Story About an Irish Site

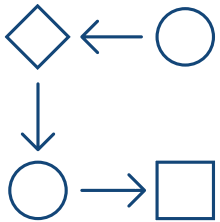


We agree that the Scout ICF was but we wouldn't be able it use it without evidence that it was reviewed and approved.

Input to the Authority to the Rescue

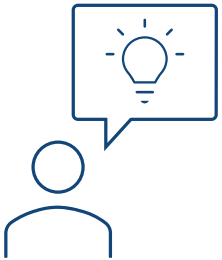
- CRO contacted NREC directly
- TMF Network discussion with the Danish HA regarding the issue
- Danish HA crowdsourced questionnaires for CTIS input

In Conclusion

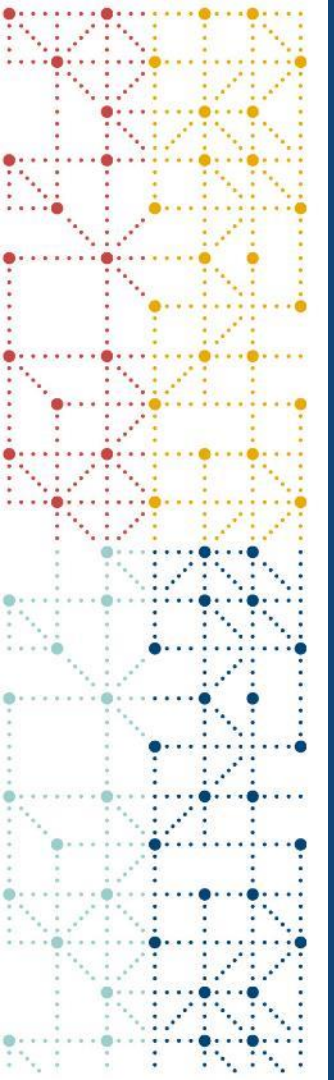


Challenges brings upon change for the better

Resources and networking



Constantly provide input to authorities



I’ve got 99 problems but TMF ain’t one

- Jay Z (not really)

Thank You!