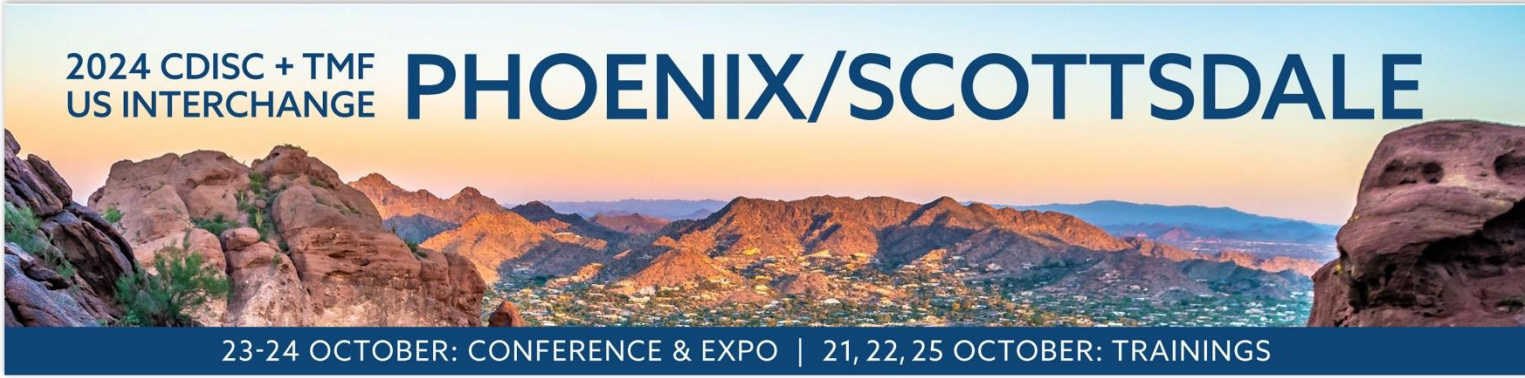

Navigating Regulatory Compliance: Complexities around the EU Clinical Trials Regulation (EUCTR)

Presented by: Anuj Thapar, Senior Product Manager, TransPerfect

Meet the Speaker

Anuj Thapar

Title: Senior Product Manager, Trial Interactive

Organization: TransPerfect Life Sciences

Anuj Thapar works as a Senior Product Manager with TransPerfect Life Sciences, where he heads the product teams for Site Feasibility and Site Activation Products. Anuj is MBA and MSc degree holder with over 25 years of work experience out of which last 8 years have been in Clinical Trials industry. He is passionate about automating the processes associated with Clinical Trial and specifically navigating the diverse regulatory frameworks around the world.

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.*

- *The author works in Trial Interactive division of TransPerfect Life Sciences, offering solutions for Clinical Trials*

Learning Outcomes

- Understanding of the EU Clinical Trial Regulatory Environment
- Clinical Trial Regulation (CTR) Main Features
- Impact on Stakeholders
- Top Complexities for EUCTR
- Considerations for Managing the Complexities

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Agenda

1. EUCTR Overview
2. EUCTR Key Features and Impact
3. Managing Complexities
   a) CTIS Considerations
   b) Transparency Considerations
   c) Modifications Submission
   d) Reporting Member State Considerations

What is EU CTR?

- **European Union Clinical Trials Regulation** (EU) 536/2014

- Entered into application on **31 January 2022,** replacing EU Clinical Trial Directive 2001/20/EC

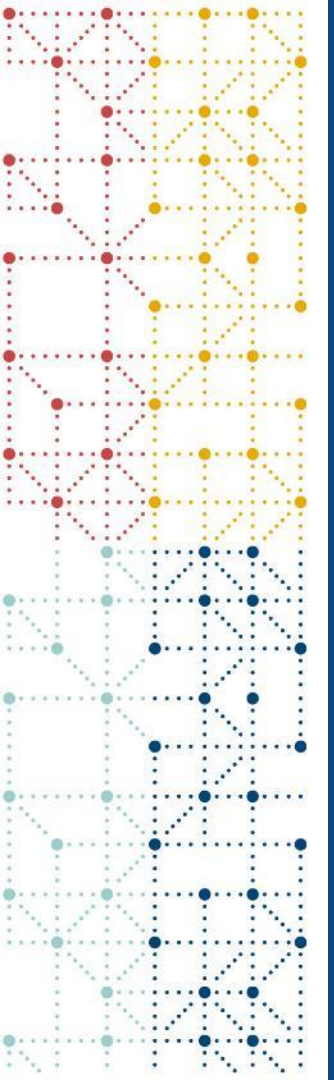
- EU pharmaceutical **legislation governing clinical trials in the EU/EEA** (European Economic Area): **27+3 countries** (excluding the UK and Switzerland).

- The aim is to create an attractive and favourable environment for conducting clinical research, ensuring high standards of public transparency and participant safety in clinical trials.

Key CTR Features

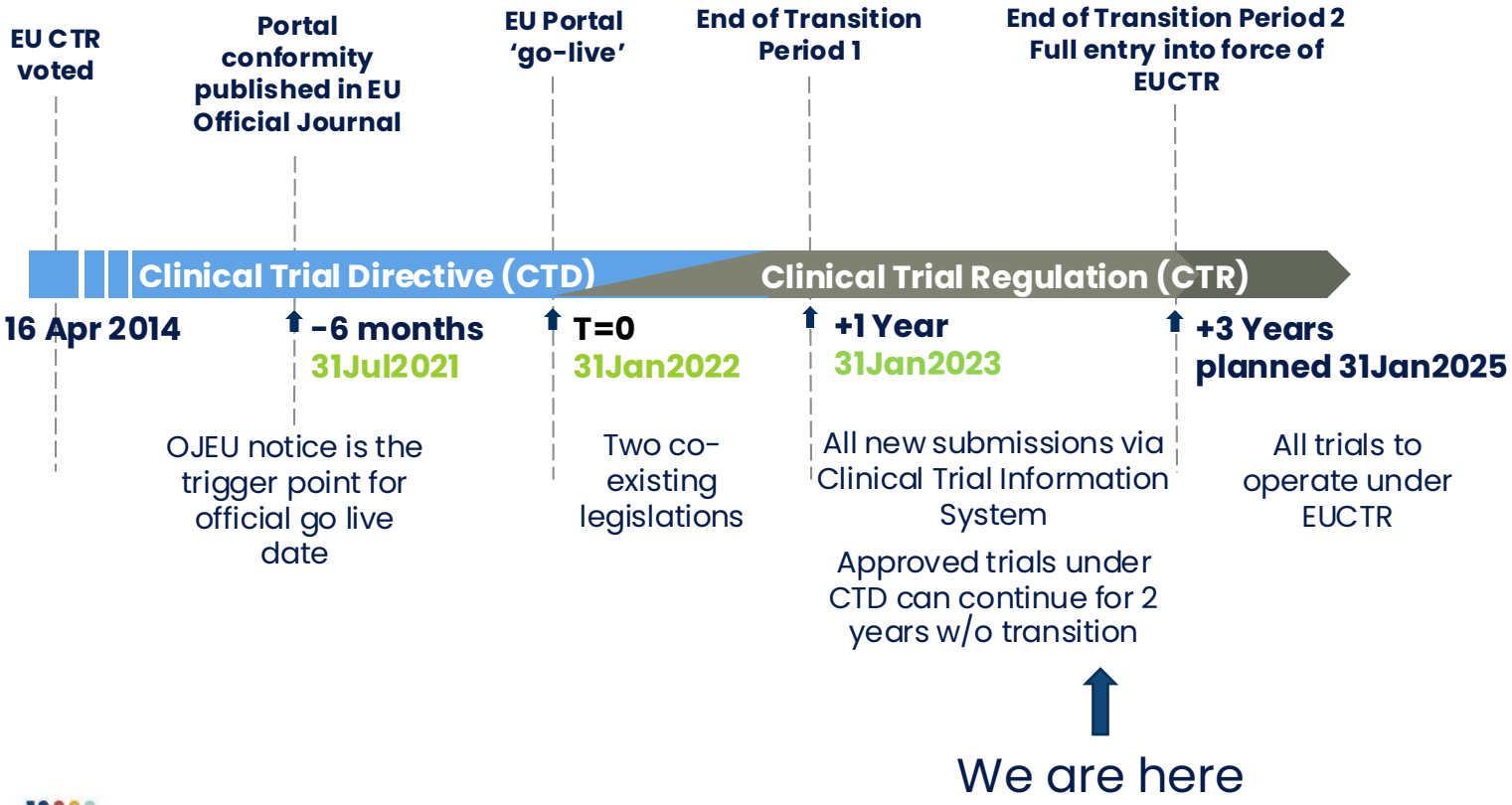
New EU Clinical Trial Ecosystem

- **Stakeholders Impacted:** Authorities, Ethics Committees, Sponsors, Sites, Third-Party Vendors
- **3-Year Transition Period:** Ongoing projects can operate under CTD; transition to new framework required later (dual regulatory frameworks).
- **Single Entry Point:** Clinical Trial Information System (CTIS)(Country-level approvals still required)
- **Extended Response Times:** Up to 12 calendar days for RA/EC queries (including document updates: protocols, ICFs)
- **Enhanced Transparency:** Stricter scrutiny on CCI, PPD in applications, results, and clinical study reports (post-MAA)
- **New Requirement:** Layperson summary results publication



Complexities - EUCTR

EU CTR Implementation Timelines



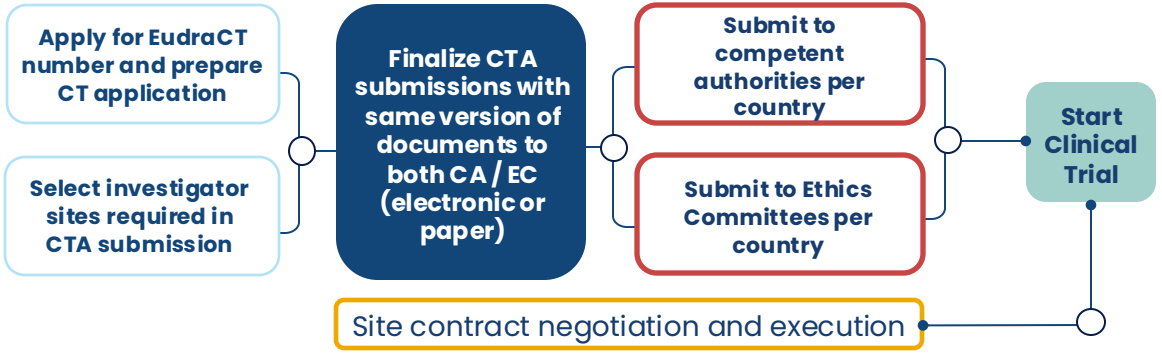
CTD – CTR Comparison

Topic	CTD	CTR
Process	Not harmonized between MSs One dossier for CA and one dossier for EC(s), parallel or sequential	Part I (scientific dossier) / Part II (national parts) all submitted via the **Clinical Trial Information System.** Together, or I then II
Content	Alignment on core documents but significant disparities in local country document requirements	Submission requirements defined in CTR Annex I **Increased harmonization** with alignment on core documents (limited changes) and more defined country requirements (to a degree)
Evaluating bodies	Not harmonized between MSs in terms of national contact points (CA/EC) or (eventual) involvement of local ECs	CA assessment for **Part I coordinated** between MSs by RMS, **Part II nationally assessed** (CTR mandates timelines, not the process) then **unique trial decision (part I+II)** per country
Timelines	Not fully harmonized between MSs (particularly around eventual clock stops)	Harmonized procedure enforced by CTR. Timelines enforced by tacit approval principle on Part II assessment. Note the 12 days to answer RFIs and a default winter clock stop

EU Study Start Up Principles No Changes

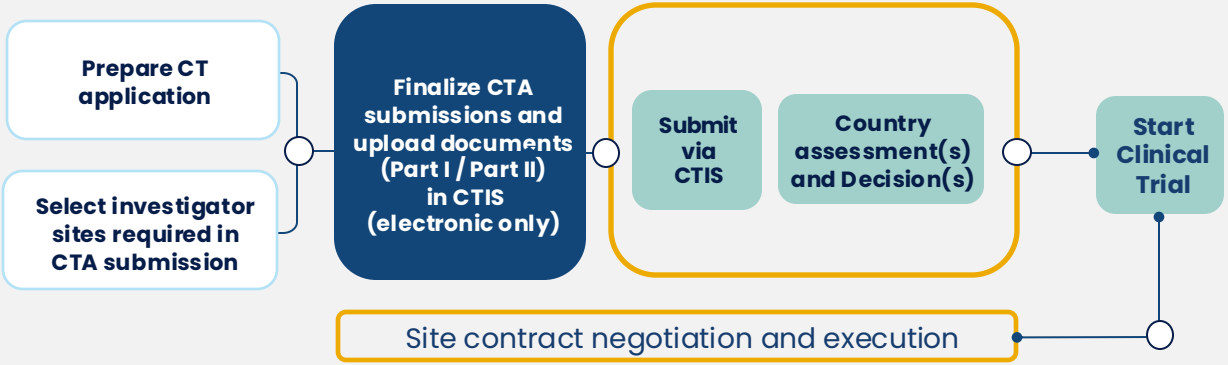
CTD

Until 31Jan2023 (for initial CTAs)

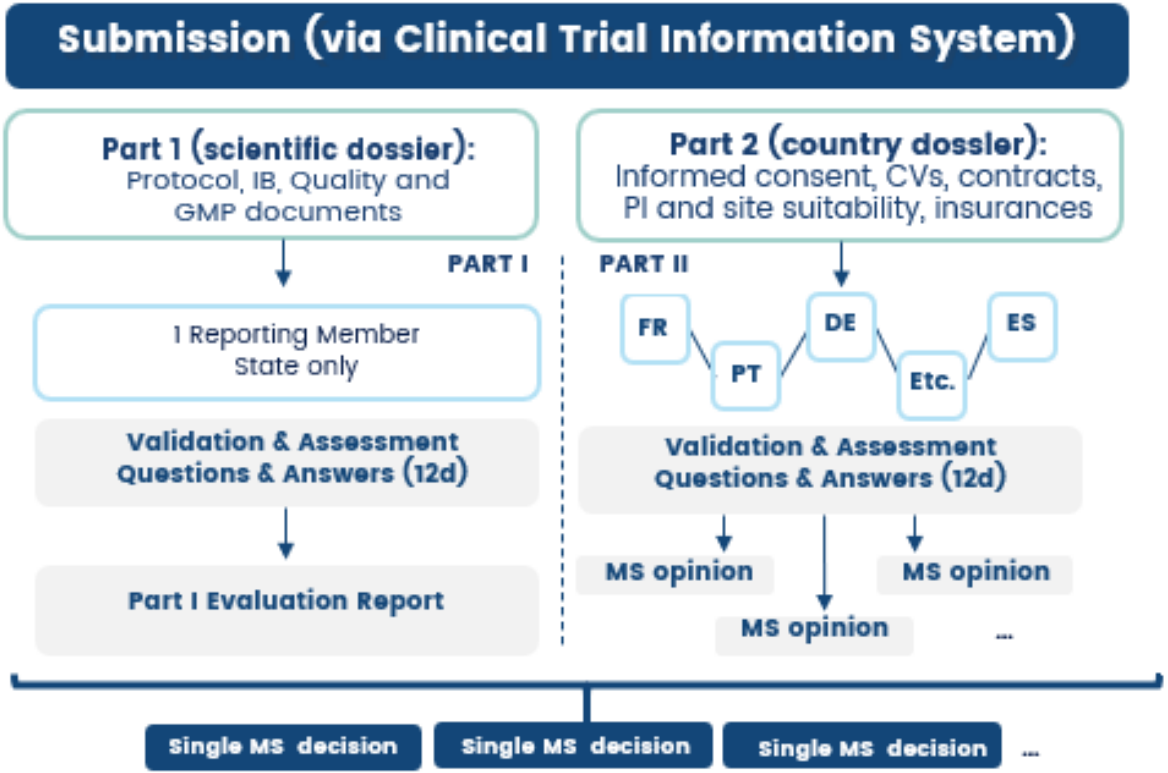


CTR

Since 31Jan2022



Clinical Trial Application (Under CTR)



Initial Approval
60-106 days (Art. 5-8)
[max 156 days for ATMPs*]
12 days for query response

Substantial Modification
49-95 days (Art. 16-22)
[max 145 days for ATMPs*]
12 days for query response

Addition of a New Country
52-83 days (Art. 14)
12 days for query response

Tacit approval system once timelines have passed

**ATMP - Advanced Therapy Medicinal Product*

More on timelines **here** (EMA)

Impact on Stakeholders

Regulators:

- Streamlined regulatory process reduces redundancy and improves efficiency
- Regulators also have enhanced tools for monitoring and supervising clinical trials.

Patients:

- Have improved access to information about clinical trials, including safety data and trial outcomes.
- Leads to increased trust and participation in clinical research.

Sponsors:

- Adapt to new transparency obligations, including the need to publish trial results in the CTIS.
- Ensure compliance with GDPR and other data protection regulations

Top 3 Complexities

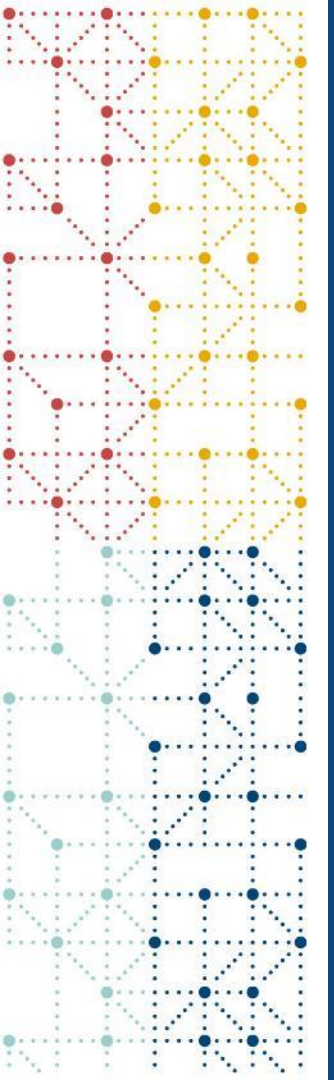
1. New Clinical Trial Information System (CTIS) (impact on all processes pertaining to submission preparation, management and archiving, new ways of working required)

2. Transparency: PPD&CCI management / redaction. Protocol and its synopsis, patient documents, study results and CSR made public

3. Modifications / Amendments (no parallel assessment possible)

Others:

Choosing your Reporting Member State (RMS) (RMS will have an important coordination role in clinical trial application assessments throughout the conduct of the trial)



Clinical Trial Information System

CTIS Considerations

Strategic Decisions:

- In-house, partial, or full delegation of CTIS management
- Direct impact on outsourcing strategy and CRO/vendor qualification
- Consider operational impacts of vendor changes

User Management:

- New responsibilities for delegating/managing users within your organization and vendors
- Delegation is **individual** (no company-wide delegation)
- Factor user management into your insourcing/outsourcing strategy
- Plan for scalability based on portfolio size

Organizational Setup:

- Organization details visible to all until Sponsor Admin is nominated
- Switch to organization-centric mode upon admin nomination

Limitations:

- No geographic assignment for Part II preparers, Q-IMPD
- User delegation limitations to consider in planning

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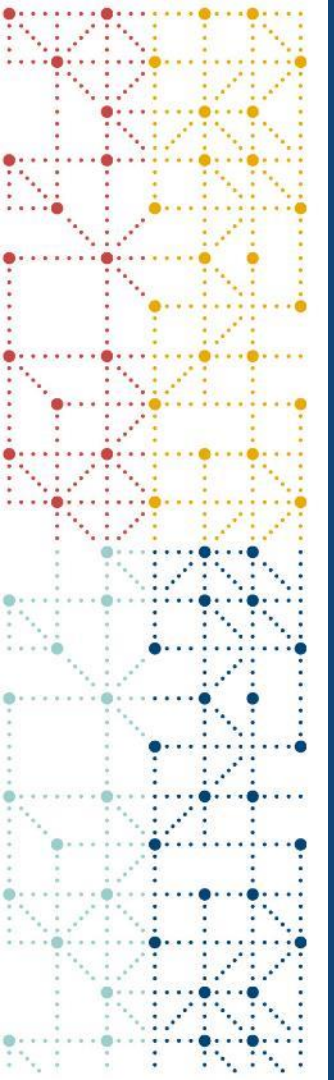
CTIS: Organization Centric vs Trial Centric

Organization centric	Trial centric
For sponsors with **larger number** of trials	For sponsors with **small number** of trials e.g., Academia
A **high-level sponsor administrator** validated by **EMA** is required	**No high-level** sponsor administrator validated by EMA is required
The high-level administrator at **organization level** manages users **in CTIS**	Users become the CT Admin of a trial **at the time of creating an initial CTA**
Users become **affiliated** to the **organization** of the **high-level administrator**	Management of business roles by the CT Admin is **at trial level only**
Users **need** to be assigned with the CT Admin **role** by the **high-level s**ponsor administrator to create an initial CTA	



Transparency Considerations

Migration to CTIS: Consider Transparency

- Effective 1/31/23 all new applications to be made in CTIS
- Existing EDR data to be migrated to CTIS by 1/31/25
- Would not be applicable for CTD trials are ending before 1/31/25
- CTIS to be used for:
  - Submitting annual safety reports (one per study)
  - Adding new member states to ongoing trials.
  - Receiving agency feedback and assessment information (per country for Part II).
  - responding directly to agency requests for information.
  - uploading redacted and anonymized trial details for the public to view

Transparency: Key Definitions

- **Commercially Confidential Information (CCI)**
  Any information submitted to CTIS which is not in the public domain, or publicly available, and where disclosure may undermine the legitimate economic interest or competitive position of the owner of the information.

- **Personal Data (PD)**
  "Personal data' means any information relating to an identified or identifiable natural person ('data subject'); an identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person'. (Article 4(1) of Regulation (EU) 2016/679 and Article 3(1) of Regulation (EU) 2018/1725).

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EU CTR: Disclosure Considerations

The EU database "shall be publicly available unless one or more exceptions apply" (Art. 81)

These exceptions are:

*a) protecting **personal data (PD)** in accordance with Regulation (EC) No 45/2001;*

*b) protecting **commercially confidential information (CCI),** in particular through taking into account the status of the marketing authorization for the medicinal product, unless there is an **overriding public interest** in disclosure;*

*c) protecting **confidential communication between Member States** in relation to the preparation of the assessment report;*

*d) ensuring effective **supervision** of the conduct of a clinical trial by Member States*

Only data and information defined in the Regulation **as being submitted via the portal and/or stored in the database** shall be held in that database and **subject to the disclosure rules** set out in the Regulation.

New Transparency Rules endorsed in October 2023 by EMA and introduced in CTIS in June 2024

Clinical Trial Application Dossier

Part I (core dossier)	Part II (country dossiers)
• Cover letter • Protocol • Protocol synopsis • Endpoint related patient documents • Investigator's brochure • GMP documents • IMP Dossier (Quality and Safety-Efficacy) • AxMP Dossier (as needed) • Scientific Advice and PIP • IMP Labeling content	• Recruitment arrangements • Subject info, informed consent form and procedure • Suitability of the investigator • Suitability of the facilities • Proof of insurance • Financial and other arrangements • Proof that data will be processed in compliance with Union law on DP • Compliance with use of biological samples

New Transparency Rules (Oct2023) – Structured data

<table>
<tr><th rowspan="2">Structured data</th><th colspan="2">Category 1</th><th>Category 2 integrated p h1&2</th><th>Category 2 & 3 (excl. integr. ph1&2)</th></tr>
<tr><th>Paediatrics and/or PIP</th><th>Adults</th><th></th><th></th></tr>
<tr><td rowspan="2">CTIS application fields</td><td rowspan="2">First MSC decision</td><td>First MSC decision</td><td rowspan="2">First MSC decision</td><td rowspan="3">First MSC decision</td></tr>
<tr><td>30 months after EU/EEA End of Trial</td></tr>
<tr><td>CTIS application fields on dose and treatment duration[1]</td><td colspan="3">30 months after EU/EEA End of Trial</td></tr>
<tr><td>MSC(s) conclusions and decision outcomes</td><td colspan="4">That MSC decision</td></tr>
<tr><td>Notifications on trial status and recruitment</td><td colspan="4">As soon as submitted by sponsor</td></tr>
<tr><td>Notific. on serious breaches, urgent safety measures, unexpected events</td><td>After MSC assessment</td><td>30 months after EU/EEA EoT & MSC assessment</td><td colspan="2">After MSC assessment</td></tr>
<tr><td>Corrective measures (suspension, revocation, modification request)</td><td colspan="4">When applied by MSC(s)</td></tr>
</table>

[1]As a temporary measure, the publication of fields 'strength of product' and 'strength of active substance' has been suspended: further information will follow

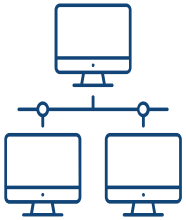
New Transparency Rules (Oct2023) – Documents

Documents type	Category 1		Category 2 and 3 *including integrated ph1&2*
	Paediatrics and/or PIP	**Adults**	
Protocol, synopsis, patients facing documents	Upon results' submission	30 months after EU/EEA End of Trial	First MSC decision
SmPC, if available	Never		
Subject information and informed consent form			That MSC decision
Recruitment arrangements, *including procedures for inclusion and copy of advertising material*			
Final summary of results, Lay person summary of results	As soon as submitted	30 months after EU/EEA End of Trial	As soon as submitted
Clinical study report, *if available*	As soon as submitted *(requirement: 30 days from MA)*		
All other documents, including any MS document	Never		

Scope for Balancing Transparency and Disclosures

Clinical Trial Operational Data	Results and Reports
Initial application (structured data and documents: Protocols, synopsis, patient documents)	Interim and final results (6-12 months after trial end), including a Layperson version
Life Cycle maintenance (substantial modifications, additional member states, routine and ad hoc notifications)	Clinical study report (upon marketing application completion)

Maintaining Transparency



« TRANSPARENCY BY DESIGN » APPROACH

Review processes to minimize amount of PPD/CCI required to be processed downstream

ADAPTATIONS TO DOCUMENT AUTHORING

Adapt document creation to minimize amount of PPD/CCI to be included (including during answers to questions)

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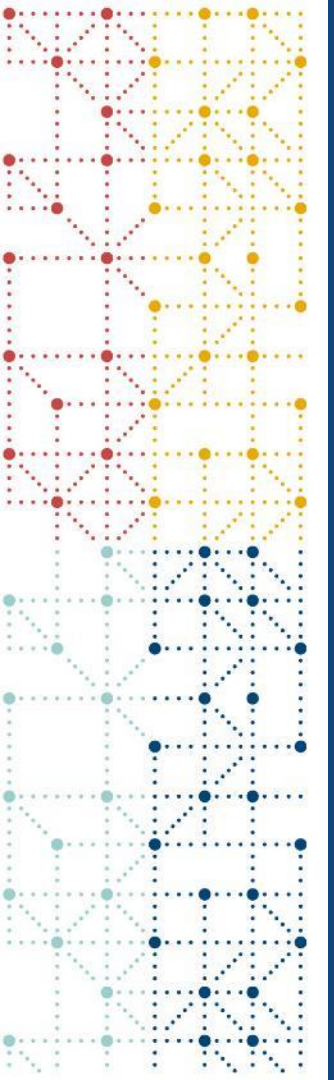
Transparency: Data Anonymization

- While clinical trial application documents may only require masking, results, and clinical study reports may require more advanced redaction techniques
- Select the right technique for CCI or PPD
- More than just redaction (anonymization, shuffling, offset, Generalization)
- Removing data that can lead to direct or indirect identification of Participant or Staff
- Anonymization technique should be based on the risk score calculated (statistically) based on the number of types of data points and sets.
- Examples: Sex, Age, Race, Ethnicity, Country, Subject Id



Modification Considerations

Modifications (Amendments under CTR)

Topic	EU CTR
Substantial Modification	• Change that has a substantial impact on the safety or rights of the subjects and/or the reliability and robustness of the data generated • Submission and authorization required before the change can be implemented • Categorization of a change as a SM is a responsibility of the sponsor
Non Substantial Modification Relevant For Supervision (Art. 81.9)	• New concept that does not exist under Directive 2001/20/EC • Any change which is not substantial, but is considered relevant for supervision of the trial by the MSCs • No authorization or refusal mechanism, immediately implementable but corrective actions by MSCs remain possible • Not the silver bullet to get all your notifications in (not a date stamp process)
Non Substantial Modification	• Notification of non substantial changes is not required (nor supported). Non substantial modifications should be recorded and contained in the trial documentation and subsequently submitted in the subsequent application of a substantial modification (if any). • Documentation of non substantial modifications should be available on request for inspection purposes as appropriate

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Submission Planning - Considerations

- Only one Substantial Modification allowed at any given time
- Up to 3 months to receive decision

Strategic Considerations

- Reduce the number of Substantial Modifications
- Filing Substantial Modifications along with non-substantial modifications
- Regroup submissions when possible to limit filing SMs in isolation

Reporting Member State

Reporting Member State

- Sponsors proposes RMS at the time of the initial application
- RMS to be confirmed in parallel to validation (proposed or other)
- Important role as leading the Part 1 assessment, moderate discussions & create draft assessment report
- Careful consideration when selecting the RMS based on feedback from Regulatory Teams and CROs.

Using EMA metrics on:

CTAs Submitted

CTAs Under Review

CTAs Approved

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Thank You!