Clinical Trial Regulation EU 536/2014, Opportunities and incentive for innovation. Evolution of the Sponsor/CRO Relationship

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Agenda

1. ACRO Introduction
2. Stakeholder Engagement
3. Portal and Database
4. User Management
5. Concerns?
6. EU Legal Representative

ACRO

- ACRO member companies manage over 9,000 clinical studies involving nearly 2 million participants annually
- ACRO member companies conduct clinical studies in 142 countries across 6 continents
- ACRO member companies currently employ over 110,000 people worldwide, of whom 30,000 work in the EU/EEA
- ACRO members contributed to the development of all of the top 50 selling drugs

The Top 10 CROs Are Members of ACRO

- BioClinica
- Chiltern
- Covance
- ICON
- Medidata
- PAREXEL
- PPD
- PRA
- IQVIA
- Syneous Health Clinical

EMA Stakeholder Meetings

- EMA is holding various stakeholder meetings to consult on process under the new EU Regulation
- PPD has representation via ACRO at these stakeholder meetings
- Topics include:
  - Sponsor-driven activities
  - Safety reporting
  - Public-driven activities
- ACRO is actively involved in user acceptance testing as the portal and database are developed – 69 of 305 (23%) testers who responded in UAT 1 were from ACRO member companies and we have representatives participating in F2F testing for UAT6 and planned UAT7

Regulation Requirement

Article 80 **EU portal**

The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a portal at Union level as a single entry point for the submission of data and information relating to clinical trials in accordance with this Regulation. The EU portal shall be technically advanced and user-friendly so as to avoid unnecessary work. Data and information submitted through the EU portal shall be stored in the EU database.

Portal Access

+ Sponsors can manage trials via two options:

+ Trial-centric Approach

- Available only to the “sponsor”
- Only CT Administrator is required
- User becomes CT Admin by creating CTA
- Management of the users by the CT Admin is at trial level
- Users to are not affiliated with a sponsor organisation

+ Organisation-centric Approach

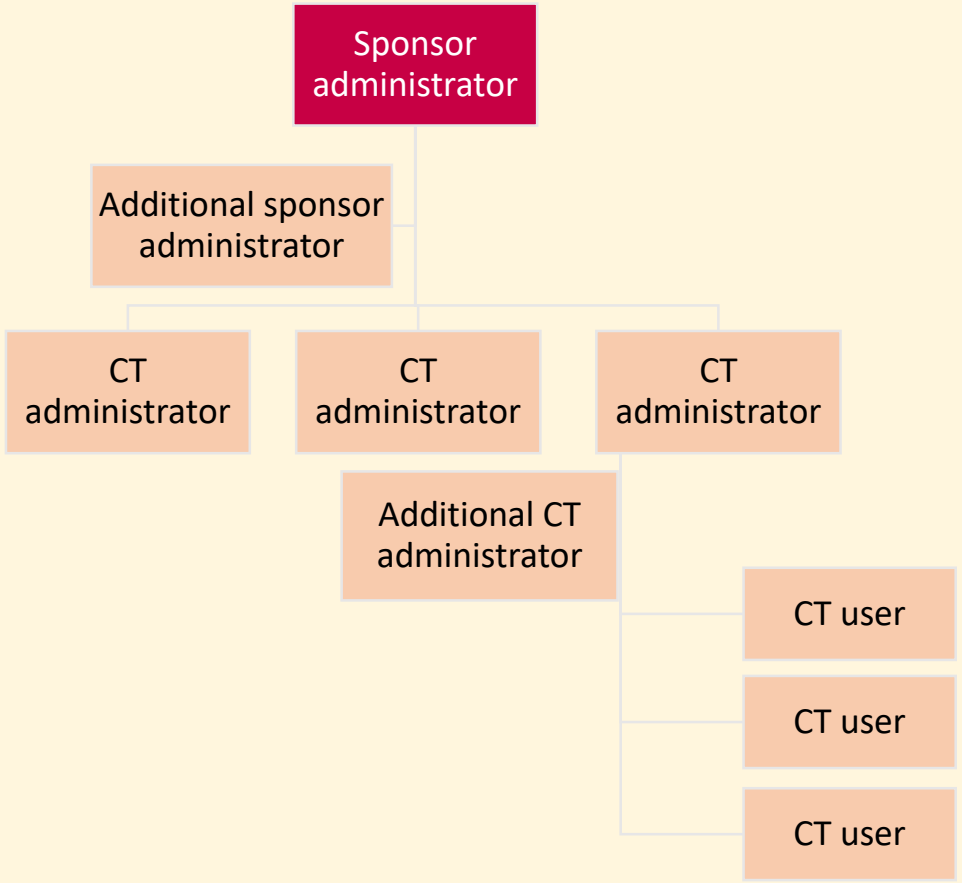
- Available to all (sponsor, MSs, EC, MAH)
- A high level administrator required (sponsor admin, MS admin, EC admin, MAH admin)
- Users become affiliated with the organisation of the high level administrator

ALL CTs stream: access to all trials under the umbrella of the organisation of the administrator

CT -specific stream: allows access to a subset of trials under the umbrella of the organisation of the administrator

Administrator Burden

- Sponsor Administrator
  - Creates additional administrator users
    - **High-level administrators** (Sponsors, Member States, EU Commission, MAHs)
    - **Medium-level administrators** (Sponsor Clinical trial and MS national organisation administrators)
    - **Regular Users** – Role specific
  - Administration of all users linked to sponsor (either All CTs or CT specific)
  - CT administration for all sponsor trials
    - Create additional CT admin users
    - Delegating the appropriate permissions to already registered CT users
    - Administration of CT users



User Management

- Industry generally (including ACRO) and academic researchers have been concerned that a lack of flexibility in how users can be assigned may create confidentiality issues

- Clinical trials are conducted according to various models (e.g., in-house by sponsor, fully outsourced to CRO partner, sponsor/CRO partnership, sponsor/academia partnerships, sponsor/other biopharma partnerships)

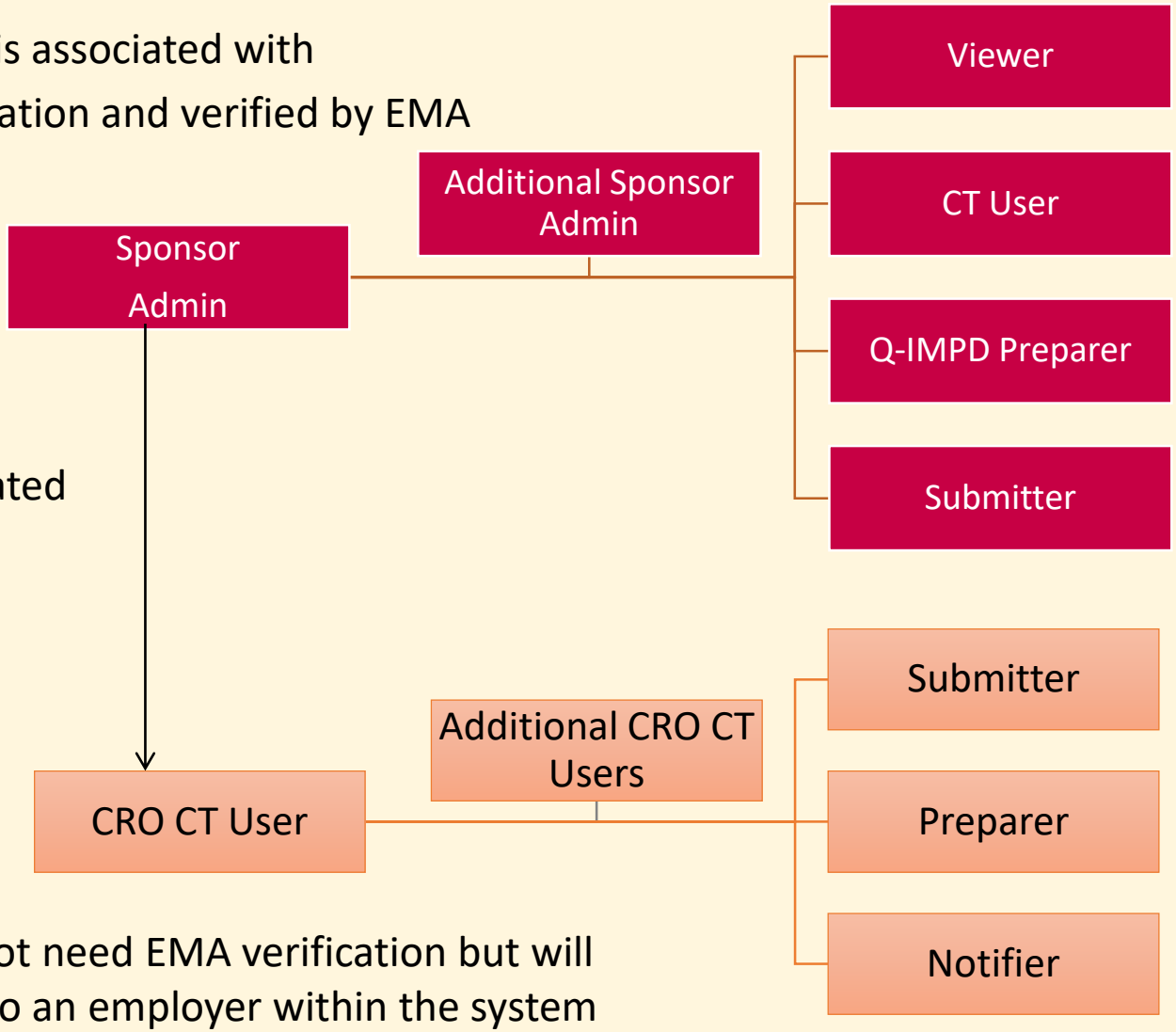
- Granularity in the system is needed to ensure information is not shared inappropriately with the various partners involved in a trial

User Roles nad Permissions

- Functionality available to a given user can be customised through the combination of one or more roles (e.g., a user can be assigned a validator role-submitter and an assessor role-prepare etc.)
  - Create permission: allows the user to edit, upload documents, save, update saved drafts. It also allows users to copy from an existing CTA to create a new one.
  - View permission: allows user to view structured data, documents, and includes download of documents.
  - Update permission: allows updating submitted information
  - Delete permission: delete refers to eliminate/cancel draft items
  - Withdrawal permission: refers to only submitted items
  - Share permission: allows the user to share the respective data/documents within their workspace per the use cases
  - Submit permission: allows the user to submit data/documents from their respective workspace to the EUPD
  - Other more specific i.e., assign task, extend task

Assigning Users

Sponsor admin is associated with sponsor organisation and verified by EMA



Permissions allocated within the system

Other users will not need EMA verification but will have association to an employer within the system

User Interface – API Discussions

- Submitters want to be able to use their infrastructure and backend systems to build datasets based on specs from EMA and then send to CT EUPD
- The full management, through a system interface/API, of the lifecycle of a clinical trial is seen as a strategic objective

Top Prioritised Areas by Stakeholder

Member States

1. Task Management
2. Workflow Changes
3. Oversight of Activities Screen

Sponsors

1. Access Management (Roles and Permissions)
2. Oversight of Activities

A manual upload into the CT EUPD from submitters system seems to be optimal approach for short to medium term!

Complexity of Outsourcing

- A sponsor may work with a number of different CROs to manage its clinical trials across Europe. For a particular clinical trial, it is not uncommon for the tasks regarding Part I and Part II to be assigned to different CROs
- Currently, a company may work with one CRO to prepare the CTA, with different CROs submitting the CTA in different Member States, managing the assessment process and making the necessary notifications as the trial proceeds
- This may not be possible in the future, when a single application dossier covering Parts I and II will be submitted; although future enhancements may allow different submitters for different country Part II sections

ACRO Concerns

- Unlikely that (at least initially) a CRO will be able to interrogate the database for reports detailing all activities on clinical trials performed by that CRO
  - CROs will therefore need to continue to maintain their own activity databases, creating potential for inconsistency with EMA database
- In the case of a non-EU sponsor that is required to appoint a legal representative in the EU in accordance with article 74, no special access arrangements are planned for the legal representative
  - CROs will therefore need to continue to maintain their own activity databases, creating potential for inconsistency with EMA database

Legal Representative Requirement

- A CRO acting as legal representative under Regulation (EU) No. 536/2014 will
  - Be subject to enforcement action under EU law for sponsor non-compliance with the Regulation, even in relation to tasks not contracted by the sponsor to the CRO. Therefore …
  - CROs will need to perform due diligence with regard to sponsor activities to ensure compliance with the Regulation

- ACRO has discussed this issue with the European Commission Pharmaceuticals Unit and requested guidance on the appropriate nature and extent of such due diligence activities

Next Steps

- Audit of the portal and database is delayed to 2019 with expectation to complete in Q4 2019
- UAT 7 delayed to Q1 2019
- Audit start Q2 2019. Expect 4 to 6 months for audit and report, 2-3 months EC decision time
- Commission adoption of portal planned Q1 2020 (Six months to implementation = June to Oct 2020 possible)
- *The Board heard that the development of the auditable release of the portal and database (release 0.7) is complete. The release is now in an intensive phase of pre-testing before formal user acceptance testing (UAT7) can start in early 2019. Taking into account the rate of progress with testing and bug fixing, and the relocation of the Agency, the audit field work will take place once the Agency has settled in Amsterdam, after March 2019. Dependent on successful completion of the audit and review by the Management Board around the end of 2019, the system could be ready to go live later in 2020.*

Clarity for Future

- Industry stakeholders need a clear commitment from EMA to let industry understand what will be included in the auditable version and in the production version so that industry can start putting business processes in place
- Access to a testing sandbox as soon as possible is requested to enable better system understanding and consider connection from existing internal systems with the portal
- It is critical for industry that developed business processes do not need to be replaced or significantly modified for future system iterations – MSs urge industry to prepare now as the submission portal should not dictate upstream processes
- Sponsor and CRO need close collaboration to ensure appropriate access to the portal in line with contracted responsibilities i.e., EU legal rep, notifying milestone dates, etc.