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Latest Updates on the EU Clinical Trials Regulation 536/2014

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Today’s Agenda

- Background on Clinical Trials Regulation
- The new Delivery Model
- Next Steps
- Conclusion
Background on Clinical Trials Regulation
Clinical Trials Regulation No 536/2014

- Major changes for clinical trials conducted in the EU
  - The Regulation harmonises the Assessment and Supervision process for clinical trials throughout the EU
  - The Clinical Trials Information System (CTIS - formerly EU Portal and Database) is a key element for the implementation of the Regulation

- Goal of the Clinical Trials Regulation
  - Create an environment favourable to perform clinical trials in the EU, with highest standards of safety for participants and increased transparency of trial information
Clinical Trials Regulation No 536/2014 - Timelines

Adopted by:
European Parliament on 02 Apr 2014
Council of Ministers on 14 Apr 2014

Signed off on 16 Apr 2014
Published in Official Journal on 27 May 2014

Expected to come into effect:
Agile development of CTIS as of June 2019
Solutions to support the Implementation of the new Clinical Trials Regulation

- **Single EU entry point** for clinical trial applications
- **Collaboration** in the evaluation and supervision at EU level
- Provides **workspace collaboration** tools, workflow and document management capabilities
- Provides **publicly available** information

- Delivers a module for the **electronic reporting** of suspected unexpected serious adverse reactions (**SUSARs**)
- Delivers an **electronic reporting** system for **annual safety reports** (**ASRs**)

- Delivers **transition** between the current and new systems
CTIS – Overview activities each of the stakeholder groups will be able to perform in the system

**Sponsors**
- Submit CTA and dossier and address request for information
- Update CT information relating to non-substantial modifications
- Submit notifications:
  - withdrawal
  - start of trial
  - end of recruitment
  - end of trial (in each MS, All MS, Global)
  - temporary halt
  - restart of trial
  - early termination
  - serious Breaches
  - unexpected events which affect risk/benefit
- Submit clinical study result summary
- Submit third country authorities’ Inspection Reports

**General public**
- Search & view CT information

**Commission**
- Submit CSR
- Submit Union Control Reports

**Member States**
- Communicate implementation of corrective measures
- Notify willingness to be RMS (Part 1) and RMS decision
- Submit requests for information
- Notify final validation (initial, additional MS or Substantial Modification)
- Submit final AR part 1 and 2
- Notify final single decision
- Submit inspection information
- Communicate disagreement with part 1 assessment

Source: EMA, EU TMB meeting, 08 Nov. 2018, Fergus Sweeney
CT Application - Examples (Sponsor)

Clinical trials

Source: EMA, EU TMB meeting, 08 Nov. 2018, Fergus Sweeney
CT Application - Examples (Sponsor)

A phase III, randomized, open-label, multicenter study comparing GW572016 a...

**Trial specific information (Part 1)**

<table>
<thead>
<tr>
<th>Trial details</th>
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<tbody>
<tr>
<td>Trial identifiers</td>
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<tr>
<td>Trial information</td>
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<tr>
<td>Protocol information</td>
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<tr>
<td>Scientific advice and Paediatric Investigation Plan (PIP)</td>
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<tr>
<td>Associated clinical trials</td>
</tr>
<tr>
<td>References</td>
</tr>
<tr>
<td>Countries outside the European Economic Area</td>
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</table>

**Sponsors**

<table>
<thead>
<tr>
<th>Name</th>
<th>Organisation type</th>
<th>Country</th>
<th>Type</th>
<th>Status</th>
<th>Legal representative</th>
<th>Scientific contact point</th>
<th>Public contact point</th>
<th>Third parties</th>
</tr>
</thead>
<tbody>
<tr>
<td>GlaxoSmithKline</td>
<td>Pharmaceutical company</td>
<td>United Kingdom</td>
<td>Commercial</td>
<td>Active</td>
<td></td>
<td></td>
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</table>

**Contact point for union**

<table>
<thead>
<tr>
<th>Organisation name</th>
<th>Address</th>
<th>Address line 1*</th>
<th>Address line 2*</th>
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</table>
Clinical Trials Regulation – Go Live Prerequisites

- Two main events condition the final go-live
  - EMA relocation in Amsterdam
  - Audit of CTIS outcome
    - Independent Audit on the Portal will start after EMA has relocated to Amsterdam and after UAT7
    - Audit will last 3-4 months
    - Audit report reviewed by EMA Management Board
The New Delivery System
Revised Project Plan for the CTIS

- Revision of the Clinical Trials Information System project plan by the EMA to
  - Improve the delivery
  - Ensure stakeholders can give \textit{feedback more regularly} so that their expectations can be taken into account
  - Ensure Regulation comes into application as early as possible, but retaining the possibility to extend functionalities in the future

- Restructuration of the contract for the system's delivery
  - The code for safety reporting will be merged with EU Clinical Trial Portal and Database system modules
  - To allow key bug fixing can be carried out
  - System to enter a phase of iterative, \textit{agile development as of June 2019}

- New approach will support the further enhancement of the system, in close interaction with the user community
  - Through the audit and
  - Until after the system has gone live and the Clinical Trials Regulation has entered into application

- EMA will make further announcements before \textit{user acceptance testing} commences

- EMA and Member States fully committed to ensuring the success of project and its delivery
The conclusion of the UAT Champions after pre-UAT7 in November 2018 was that the system required additional bug-fixes and improvements to be ready for a full UAT7.

The SAT testing of Release 0.7 was completed on 19 December 2018, with most significant SAT bugs resolved, but many of the bugs found in pre-UAT7 unresolved.

EMA has reviewed and accepted the SAT report and is now closing the CT1 contract (Unisystems, Greece).

Preparation of a UAT7-ready version based on pre-UAT findings will be carried out by an extended CT2 team (Everis, Spain).

Ongoing Release 0.9 development by the CT2 team (Everis, Spain) remains on track.
Critical pre-UAT7 Bugs will be fixed in parallel with R0.9 completion, before starting iterative development ahead of UAT7.
The delivery of the Clinical Trials Information System (CTIS) has moved from UniSystems (Greece) to Everis (Spain) within the IT4U Consortium. Everis is since 2016 the Consortium lead and the supplier for the delivery of the safety reporting functionalities. This supplier is therefore well familiar with the system, the requirements and the working environment. The change entails also the move to a new, iterative and more agile project, changing the team structure, dedication and communication model.
The New Delivery Model - Key Principles

**Five key principles of the new Delivery Model**

1. **Higher & structured user involvement**
   - Higher involvement of users at the right decision-making level (3 levels), with the MS and Sponsor Champions taking ownership of the final product.

2. **Goal-driven releases**
   - Future releases will pursue a specific goal, in line with a top-down agreed vision for the final product.

3. **Short & predictable delivery cycles**
   - Bringing incremental business value through predictable and shorter releases to enable regular feedback collection and alignment with users’ expectations.

4. **Direct interaction with IT supplier**
   - Involving IT supplier in continuous and direct interactions with MS and Sponsor Champions for better feedback take up.

5. **Continuous communication & training**
   - Updating regularly all users on the CTIS system progress and facilitating the transition to the new model and system.

The model will be continuously improved and fine-tuned in the light of lessons learnt and feedback.
The new Delivery Model fosters **ownership of the product** by the CTIS Expert Group & the MS and Sponsor Champions. EMA will play a project management and technical oversight role, with IT4U in charge of the delivery.

**Roles and Interactions: CT Governance in the new Delivery Model**

- **EMA Management Board**
- **CTR Coordination Group**
- **Monitoring sub-group**
- **CTIS Expert Group**
  - **Champions**
    - MS Champions
    - Sponsor Champions
- **IT4U**
- **EMA**

**Oversight of Governance, key decision making** on the outcome of the audit

**Ownership** of the final product

**Delivery** of the final product and **direct interaction** with users

**Project & contract management** and **technical oversight**

Source: CTIS Stakeholders meeting 20 February 2019
Sponsor Champions will become “Product Owners” in the new Delivery Model and will participate in the operational level of decision-making, by providing input regarding existing and expected functionalities of the system in the Sponsor workspace.

The Product Owners are business users highly involved in all phases of the Delivery Model. They provide direct input regarding existing and expected CTIS functionality. They are the main source for business requirements and participate in all business validation sessions.

Source: CTIS Stakeholders meeting 20 February 2019
In the new delivery model the MS and Sponsors Champions will become the **Product Owners**, evolving from a previous ad hoc involvement in feature validation to a **continuous participation** in the delivery model.

From pre-UAT and R0.9 Champions…

- **Ad hoc participation**
- **Punctual interaction** with IT supplier
- **Involvement in feature validation** activities mainly

… to Product Owners

- **Structured and regular participation**
- **Continuous interaction** with IT supplier and development team
- **Involvement in all the phases** of the delivery model

- **Create requirements in Jira and give them business value**
- **Support in Analysis & Design by clarifying** business requirements and validating UI/UX outputs
- **Provide feedback on the functional requirements** of each Sprint
- **Provide** clarifications to the team of developers as needed
- **Validate** the features developed in user testing

A **Lead Product Owner (LPO)** is proposed to coordinate the work of Sponsors and assume the ultimate responsibility in case of disagreement.

Source: CTIS Stakeholders meeting 25 April 2019
The diagram below provides an overview of the different phases of the new Delivery Model. POs will be involved throughout the phases except for Release Planning (strategic & tactic decisions).

4. Organisation of work: Main activities

Source: CTIS Stakeholders meeting 25 April 2019
<table>
<thead>
<tr>
<th>Organisation of work - Planning until September 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>March</strong></td>
</tr>
<tr>
<td>W1</td>
</tr>
<tr>
<td>R07 bug fixing</td>
</tr>
<tr>
<td>Backlog consol.</td>
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<tr>
<td>Product Vision</td>
</tr>
<tr>
<td>Analysis &amp; Design</td>
</tr>
<tr>
<td>Sprint 1</td>
</tr>
<tr>
<td>Sprint 2</td>
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<tr>
<td>Sprint 3</td>
</tr>
<tr>
<td>Sprint 4</td>
</tr>
<tr>
<td>Validation</td>
</tr>
</tbody>
</table>

**Source:** CTIS Stakeholders meeting 25 April 2019

- Participation of Product Owners envisaged on a continuous basis
- Some peaks of work to be expected
### Key concepts: A Sprint in its context

Each Sprint will be preceded by a set of Preparatory Activities and followed by Testing and Validation activities. The participation of Product Owners is envisaged in all steps except for the development and testing phase.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Preparatory activities</th>
<th>Sprint</th>
<th>Testing</th>
<th>Validation (user testing)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analysis &amp; Design</strong></td>
<td><strong>Sprint Preparation</strong></td>
<td><strong>Development</strong></td>
<td><strong>SAT</strong></td>
<td><strong>Sprint Validation</strong></td>
<td>This phase will take the selected backlog items and transform them into artefacts suitable/“ready” for development (mock-ups, user stories, estimations and test scripts). Product Owners will provide clarification and validation and a “mock-up demo” will be shown to Expert Group. Based on the release plan, a number of “ready” backlog items will be proposed for the upcoming Sprint and after a review process, finalising Sprint Plan. Based on the Sprint Plan, the development team will execute the agreed backlog items. Product Owners will provide clarifications, if needed. The IT supplier will perform the SAT (Site Acceptance Testing), testing the developed items in the EMA environment. The items developed during that Sprint will be presented to the Product Owner and, if willing the CTIS Expert Group Members, will test and validate the full content of the release, based on the test scripts defined.</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td><strong>4 weeks</strong></td>
<td><strong>3 weeks</strong></td>
<td><strong>1 week</strong></td>
<td><strong>1 day</strong></td>
<td>1 weekly meeting 2 meetings Clarifications as needed - 1 day 5 days</td>
</tr>
</tbody>
</table>
| **Champions’ regular interactions** | | | | | | Non-sequential activities Source: CTIS Stakeholders meeting 20 February 2019
## Required Product Owner Resources in a Year

<table>
<thead>
<tr>
<th>Role</th>
<th>Main tasks</th>
<th>Total FTEs</th>
<th>Average FTEs needed assuming total group of POs involved</th>
<th>Type of involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MS Product Owners</strong></td>
<td>Provide feedback, as planned, in all phases of the E2E model (excl. internal testing), based on the Release Plan defined by the CTIS Expert Group, and Coord. Group and coordinate among themselves</td>
<td>3.4</td>
<td>(Assuming 8 MS POs) 0.43 FTEs, ≈ 2 days/week</td>
<td>Continuous, as the majority of the issues are expected to concern them (i.e. 80%)</td>
</tr>
<tr>
<td><strong>Sponsors Product Owners</strong></td>
<td>Provide feedback, as planned, in all phases of the E2E model (excl. internal testing)</td>
<td>0.9</td>
<td>(Assuming 4 Sponsor POs actively involved out of the 9 Champions) 0.25 FTEs, ≈ 1 days/week</td>
<td>Continuous, but irregularly distributed over the weeks as the participation will be concentrated on specific periods to address issues that are only relevant for them (i.e. about 20%)</td>
</tr>
<tr>
<td><strong>Lead Sponsor Product Owner</strong></td>
<td>Coordinate the feedback of Sponsor Product Owners and participating in some meetings on their behalf</td>
<td>0.6</td>
<td>≈ 3 days/week</td>
<td>Continuous, but irregularly distributed over the weeks</td>
</tr>
<tr>
<td><strong>Rapporteurs</strong></td>
<td>Participate in the Analysis &amp; Design demo sessions and in the Release Validation on behalf of CTIS Exp.Gr.</td>
<td>0.5</td>
<td>(Assuming 4 per each release/assignment)</td>
<td>Periodic, but concentrated on specific validation activities:</td>
</tr>
<tr>
<td></td>
<td>Validation on behalf of CTIS Exp.Gr.</td>
<td>0.13</td>
<td>0.13 FTEs/week ≈ 0.6 days/week</td>
<td>• at the end of each A&amp;D phase, on a monthly basis  • at the end of each release, every 3 months</td>
</tr>
<tr>
<td><strong>CTIS Expert Group</strong></td>
<td>Provide input to the Product Vision and to the Release Plan &amp; join meetings</td>
<td>0.1</td>
<td>-</td>
<td>Only during the Release Planning phase (including 4 meetings per year and preparatory activities)</td>
</tr>
</tbody>
</table>

Source: CTIS Stakeholders meeting 25 April 2019
Sponsors Product Owners – Status June 2019

- 1 Lead Product Owner (0.6FTE): Pierre Omnes, ACRO (Syneos, France)
- 4 PO (0.25 FTE)
  - Ingeborg Boddeke, EUCROF (ICON, NL)
  - Ruediger Pankow, ACRO (Parexel, Germany)
  - Stephanie Kromar, EORTC
  - Milagros Blazquez, EFPIA
- 5 PO BACK UPs:
  - Gaby Di Matteo, EFPIA (Pfizer)
  - Lydia Dominguez, EUCROF (Sermes, Spain)
  - Tuula Ikonen, EORTC
  - Chris Price, EuropaBio
  - Marianne Andersson, EFPIA
  - (Cheryll Nattress (EFPIA) )
- Commitment requested by EMA: Until CTIS is in place and for maintenance (few years)
Success Factors

- Need to work as **One Team**, all together they are the End-to-End Delivery Model team to implement the system

- Need constant contribution from everyone involved when needed, specially from **the Product Owners**, which requires **availability** and commitment

- The new Delivery Model will **transform** the current way of working. For this, certain **flexibility** will be required at the beginning, as well as **change management** actions to support the transition

- After the transition phase will start a **steady routine** for the long term
Summary EU CTIs Platform
THANK YOU FOR YOUR ATTENTION

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