WHITEPAPER

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Summary of new EU Clinical Trial Regulation

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Summary of new EU Clinical Trial Regulation

The changes the regulation brings companies need to already be reviewing their current processes, systems and supporting infrastructure for clinical trial applications and operations. They need to do so in every changing regulatory environment where Clinical Trial and related data is being ever more scrutinized.

This paper provides a synopsis of the new regulation

1. **Insights on timing**
2. **The advantages of preparedness.**
3. **The impact that Brexit**
4. **How companies can set up a successful CTR programme.**

The new regulation is applicable for Investigational Medicinal Products (IMP) for human use and does not apply to non interventional trials or trials without medicinal products such as devices or surgery etc. The regulation seeks to provide a single, unified portal and database for both trial sponsors and regulatory agencies in each member state. For sponsors the portal will be the main platform to submit applications and notifications and it allows regulators to perform their assessments and supervise the trial.

High level changes brought in by the new regulation include:
Streamlining the process for clinical trial application across EU.
Procedures for assessing and authorizing clinical trials, removing duplication and reducing delays in the process
Introducing a lighter regulatory regime for trials conducted with medicines that are already authorized and which pose minimal risk compared to normal clinical practice
Simplifying reporting requirements, sparing researchers from submitting largely identical information on the conduct of the study to various bodies.
Formally recognizing co-sponsorship, this acknowledges that a trial can be led by more than one organization

A. Demystifying the Clinical Trial Regulation:

The new EU CTR encompasses four main business processes within the end to end clinical trial process. It mandates industry to change their existing ways of working in the short term and revolutionize the whole enterprise architecture in key areas of the clinical process in the long term.

Industry and member states will need to ensure that data and documentation is submitted within the timelines defined by the regulation and adhere to strict business rules. Such requirements, if not met, may result in delays, higher costs and increased effort. Missing critical milestones may lead to applications being considered either lapsed or validated by default, dependent on the stage of application and with which party a critical activity lies.

B. Introduction to the CT Portal and Database:

The European Medicines Agency (EMA) will release and host the CT Portal and Database which aims to support the new CTR. The CT Portal and Database will be used by both sponsors and member state

authorities throughout the application, assessment and supervision processes.

The CT Portal and Database offers features that will help users in the end to end processes such as document management, task management, notices and alerts and reporting functionalities.

Overview of business functionality:

Sponsor workspace	
Submission of Initial application	
Submission of Substantial or Nonsubstantial Modification application	
Submission of Additional Member State Concerned application	
Respond to Request for information	
Submission of trial and subject milestone(s)	
Submission of Serious Breach(es), Serious Adverse Event(s) or Non Safety Measure(s)	
Request to defer publication information	
Management of user roles and permissions	
Authority workspace	**Public workspace**
Assessment of application dossier (Part I and/or Part II)	Overview of clinical trial statistics
Submission of application decision	Download of data and documents
Assessment of additional information	
Submission of corrective measure(s)	
Inspection planning and report	
Deferral of publication of assessment information	
Manage user roles and permission	

C. Timeline for CTR Compliance - Delivery time frame for the EU portal and EU database:

2019				2020				2023			
Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Preparation and Audit Phase								**Transition and Implementation Phase**			
Preparation and Audit Phase											
EMA will manage the development of the CT Portal and Database based on the regulation.											
A series of agile User Acceptance Testing (UAT) is being performed on the Clinical Trial portal and Database with consultation and feedback from Member State and industry representatives (UAT 6 was recently completed).											
After this phase- The portal will be prepared for independent audit once its development is completed. Post go-live, an official notice will be published by the European Commission (EC).											
Transition and Implementation Phase											
When Regulation 536/2014 becomes applicable, there is a three year transition period.											

In the first year of the transition period, new CT applications can be either be submitted under the old directive or the new regulation (via the portal).

In the second and third year of the transition period, all new CT applications (initial application) must be created via the CT Portal and Database.

It is expected that all clinical trials that were authorized through the Directive will remain, at least during the transition period, within EudraCT. After three years, all clinical trial applications will have to switch to the new regulation.

D. What does Brexit mean for clinical trial applications? Brexit agreement

Kingdom triggered Article 50 which started the process of leaving the European Union. Based on the regulation, regardless of where a company wishes to run clinical trials in the EU region, it will need to adhere to Regulation 536/2014.Depending on the outcome of the Brexit agreement and the possibility that after exit the UK's regulation could diverge from that of the EU, running clinical trials in the UK may result in additional compliance with UK based regulation.

EMA has also made it clear, as things currently stand, prior to any formal agreement, that when the UK leaves the European Union they will be considered a third country.

1. Part way through an initial clinical trial application: This is relatively unlikely as most CT applicants know the UK. It is probable that an organization would therefore wait to:

A. Submit any UK based trial as a mono-national trial under the directive with the aim to proceed to a Nationally Authorized Procedure (NAP) equivalent marketing authorization with the MHRA

B. Submit any multi-national trials (excluding the UK) under the directive or CTR with the aim to proceed to a Centrally Authorized Procedure (CAP) marketing authorization with the RMS and MSC(s) being from the remaining 27 member states

For new clinical trial applications post Brexit the regulation covers what is required from studies conducted in third countries as the UK would then be considered.

2. Trial ongoing where the UK is the RMS or a MSC:

It is not fully clear at this stage as to the overall impact and the processes that will need to be followed where the UK is an RMS or MSC and when at the time of Brexit the UK ceases to be a member state.

Also stated is: "A change of RMS cannot take place during a pending procedure. Before accepting a change of RMS, the MAH should in cooperation with the RMS close all the procedures

During a Marketing Authorization Application (MAA) where the UK is the RMS or a MSC: The current MAA would likely have to be closed and possibly two new applications made in its place:

A. Nationally Authorized Procedure (NAP) equivalent marketing authorization with the MHRA.

B. Centrally Authorized Procedure (CAP) marketing authorization with the RMS and MSC(s) being from the remaining 27 member states.

E. CTR touch points within the industry

1. **At the start of the study**, some key sponsor operational processes such as site selection, product registration and application submission will be impacted. Sponsors are required to enhance the existing processes and organization to meet the data and documents requirements for submission.

2. **During study conduct,** project notification milestones must be submitted intermittently for each member state concerned. It is expected that this touch point will be tracked effectively to ensure all key milestones, including start of trial dates, subject recruitment dates and temporary halt dates, are submitted in a timely and validated fashion. Not submitting the Subject recruitment date within the required timeline may have negative impact to the approval of trial.

3. The new regulation has put greater emphasis on patient safety within various procedures. As such, sponsors have to ensure that issues, such as unexpected events, breaches and safety measures are submitted within the timeframe set in the regulation. These notifications are submitted via the portal and assessed by the respective member states.

F. Smart steps to develop your CTR implementation approach:

1. Identify the regulatory impact to the enterprise

Processes – The impact of CTR to the various processes within an organization should be assessed, such as feasibility/site selection processes and protocol planning processes when initiating an application. Focus must also be directed to existing third party services and their detailed processes such as arrangements with Contract Research Organizations (CRO) and external vendors.

Organization (People) – The impact of CTR to the Organizational structure and people should be assessed. This includes the geographic presence of the organization in the region and whether it has the resources and capabilities to implement the regulatory change whilst supporting Business-As-Usual (BAU) processes.

Data – The impact of CTR on the completeness, quality and provision of existing data and documents should be assessed. This includes identifying new data elements and documents to be implemented as a result of the regulations.

Technology – The impact of CTR to the technology landscape such as the Clinical Trial Management System (CTMS) and Document Management System (DMS); both Internally and externally should be assessed. With the introduction of the CT Portal and Database, organizations may need to assess how to integrate and support this.

Time – The CTR defines detailed deadlines for different processes during the course of trial. Although the majority of these impacts the authority assessment process, there are time limits that concern sponsor organizations such as Request for Information (RFI) during assessment.

2. Assess CTR gap and readiness

Vision: Overall regulatory vision and strategy

Clinical trial governance: Data and process governance and stewardship

Availability: Data and document availability and accessibility

Quality: Data quality and validation is needed. Based on these individual areas, key criteria should be assessed and measured.

Integration: Enterprise data integration architecture

Lifecycle: Data and Process workflow; data capture, and Management

Logical and physical model: Data structure and model, catalogue management and unstructured content management

3. Defining the CTR strategy and roadmap

Logical and physical model: Data structure and model, catalogue management and unstructured content management

The CTR timeline - The initiation of the CTR will be decided based on the development of the CT Portal and Database, and the outcome of the audit report. This will start the three year transition period, which is very important for sponsor organizations. Since this is a compulsory exercise that is defined by EMA, sponsor organizations must incorporate this undertaking in the overall roadmap

Harmonise regulatory strategy - With a significant number of new regulations and standards being introduced (e.g. identification of medicinal products (IDMP), CDISC CTR2, General Data Protection Regulation (GDPR), Policy 0070 on Transparency, Medical devices) at a time of dramatic technical change (Block Chain, Artificial Intelligence, Robotic Processing Automation, Natural Language Processing to name but a few) and political (Brexit) changes, sponsors should consider the best strategy to move forward.

It is important that the strategy and roadmap is agreed and continuously communicated across the enterprise. Providing a comprehensive plan to implement CTR is not enough. In organizational environments which seem to be ever more silo-ed and complex, it is highly beneficial to organizations to have foundational programmers for Enterprise Programmes Governance, Change Management and Communications and other governance structures in place.

4. Setup a CTR programme

Organisations who embark on implementing CTR - must realise that it is not solely driven by Information Technology. As such, business involvement is imperative in supporting the delivery of the programme and ensuring that the process transition and change is smooth.

The first step to establishing an effective programme is to identify key stakeholders. This includes identifying the sponsorship, business and technical stakeholders. Depending on how a sponsor business operates, other third parties involved in the running of trials such as **Clinical research organizations and suppliers must also be included**. Stakeholders will need to have the ability to provide stewardship of the programme and to influence important process and cultural changes in the organization.

Establish an adequate Regulatory Change Management Office - The implications of not adhering to the regulation and strict timelines, the change management office must not only understand the CTR but also other related regulations such as IDMP, publication etc.Similarly, enterprise-wide awareness and understanding of the CTR and the CT Portal and Database is also critical and the change management and communication work streams should support that process. This will ensure a more effective adoption, transformation and support with processes, data and technology, directly or indirectly impacted by the regulation.

5. Implement enterprise - wide transformation

Enterprise wide governance: Once processes and procedures are in place, in order to ensure consistent adoption, a well-structured governance framework must be implemented for a change of this magnitude. The governance framework will encompass data/document ownership, enterprise definition, data quality/validation and mastering of key clinical trial data. Due to the impact to business and response turnaround time, it is equally important to ensure key process touch points are governed and monitored.

Procedural artefact changes: Aligning existing Processes and procedures One of the major impacts of the CTR is the required changes to existing business processes and procedures. This will mean that validated documents such as Standard Operating Procedures (SOPs) and Work Plans (WPs) will either need to be updated and/or created to align to the new regulation. New SOPs which describes how the EU CT Portal and Database will be managed and used by users, will also need to be developed.

Clinical trial transition/migration: The CTR timeline allows a three year transition period in which existing and new clinical applications needs to be managed intelligently between the old directive and new regulation. As such, sponsor organizations will need to put significant consideration as to how to plan this. Key activities that are considered laborious and resource intensive such as data migration and process transition will be inevitable as soon as the regulation becomes applicable, but really should be considered well in advance.

CT portal and database management and integration: The introduction of the CT Portal and Database requires sponsor organizations to make necessary Provisions to understand and interface with the system. This includes user management for the organization, user management for individual trials and system on-boarding and training. In addition, considering the amount of data and documents involved, a robust information management solution should be in place. Such a solution should involve the capabilities related to document management and end-to-end integration. This can be costly and time consuming depending on the internal enterprise landscape and the amount of external third party systems involved.

Regional and country level structuring - the key requirements of CTR is to ensure proper legal representation within the region; especially where trials are run. As a result, a degree of restructuring of roles and responsibilities means that sponsors may need to assess where they run trials and devise the right strategy to meet its operational needs moving forward. This will require particular thought from sponsors around who they should nominate as the RMS for their different trials and both the historical and current capacity of the involved MSCs to be best placed to be the RMS. Of course, due to the method of RMS selection this does not necessarily mean they will achieve the RMS they nominate.

Automation of regulatory notifications - Key regulatory processes within the business process can be potentially automated by implementing a workflow management solution. This will allow key tasks such as Validation RFIs, Part I RFIs and/or Part II RFIs to be routed to the designated stakeholder/s and to be notified in a timely manner. It can also automate the routing of tasks related to data issues and process issues.

G. Conclusion

Regardless of the current approach, or even size of an organization, there are a number of factors to consider when seeking a successful outcome.

Focus on Present practices

Business Focus	Technical Focus
People • Executive Management • Division Head/s • Departmental Head/s • IT Architects • Process Owners • System Owners • Analysts • DBAs	**Artefacts** • Organizational Charts • Data Governance Policies • SOPs • Data Definitions & Standards • Process Flows • Enterprise Domain Model • Conceptual Data Model • Data Landscape • Tools/technologies List • Physical Models

Key Success Factors

Start now – Wait-and-see may not be the answer - Whilst the timeline is still not locked down, it is clear there quirement to have a well built, functioning portal as soon as possible is critical and

there is considerable interest, willingness and pressure from key stakeholders to ensure that the portal is truly ready as soon as possible. There are a number of National Competent Authorities that have already updated their processes and systems to become compliant with the regulation. Stakeholders should take the opportunity now to organize and plan their transition because of the deep impact of the regulation on internal processes and operational activities.

It is not just an IT driven initiative - Data and documents required for the regulation may be sourced from different sources internally and/or externally. Consideration should be taken on any limitations identified in the technical processes in order to provision the information such as latency, frequency, validation, transformation and translation.

Think big but start small - Trying to boil the ocean is a recipe for failure. Reaping the full rewards that CTR promises may take many years to achieve. Trying to make too many changes at one time may be risky and will definitely impact a sponsor's business as usual processes. However, with the right structured iterative programme set on a strong foundation, compliance and fundamental enterprise wide change can be achieved.

Build insight for better oversight - Due to the importance of the process and the significant size of some sponsor organizations, a proper dashboard and reporting infrastructure should be in place. This will allow sponsor organizations to monitor key aspects of the regulations such as the application and RFI processes indicators, timer warnings, data quality and their overall status.

Move beyond compliance - Just being compliant with the regulation should not be considered enough for any forward looking organization. Companies should consider the spirit of the regulation, the benefits it will offer and its touch points with other regulations and take the opportunity to drive operational change beyond compliance.

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