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REGULATORY REQUIREMENTS FOR CONDUCTING CLINICAL TRIAL IN EUROPE

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ABSTRACT

The Clinical Trial Regulation EU No 536/2014 was developed in order to synchronize the evaluation and oversight procedures for clinical trials on medications intended for human use. This document provides further explanation of the concepts set forth in Directive 2001/20/EC and the Voluntary Harmonization Procedure (VHP) by the Heads of Medicines (HMA) Clinical Trials Facilitation Group (CTFG). Once implemented, it will encourage:

Standardizing the CT application procedure will increase efficiency throughout Europe. Greater transparency of data and processes in the medical industry increased medication effectiveness and safety

The rule aims to offer a single, consistent gateway and database to regulatory organizations and trial sponsors in each member state. The portal will act as the main method for sponsors to submit notices and applications while also allowing authorities to monitor the trial and make assessments. The new regulation has had a significant impact on the following things:

- Streamlining the clinical trial application procedure for the entire EU

- protocols to assess and approve clinical trials, avoid duplication, and speed up the process Introducing the concept of a single decision on a clinical trial,
- Streamlining reporting procedures to save researchers from delivering nearly identical data on the conduct of the study to different bodies

The European Medicines Agency (EMA) provided their broad perspective in March 2017. On the transition from the directive to the rule and the road to the portal and database's implementation

Keywords: CTIS, EMA, MSc, RMS.

Objective: To understand the submission Initial clinical trials application as per EU CTR

INTRODUCTION:

The Clinical Trials Directive 2001/20/ EC (the Directive) is superseded by the new Clinical Trials Regulation 536/2014, bringing about a significant regulatory change for clinical drug trials (the BCDTs) in Europe. (the Regulation), which was enacted in 2014 **[1]**. The new Regulation was anticipated to lower current bureaucratic hurdles and boost Europe's competitiveness in the area of developing pharmaceutical products. However, the academic literature has surprisingly devoted little attention to the possible difficulties of the new regulatory regime, notably with regard to the rights and safety of study participants.

These two issues will be examined. First, by excluding the evaluation and balancing of benefits and risks from the purview of ethical review, ethics committees (ECs) are marginalised; second, the qualifications of investigators are left up in the air, making it possible for a junior physician to serve as the principal investigator of a phase I or II CDT **[2]**. The study emphasises the urgent need to promote awareness and encourage conversation regarding these and other potential application issues of the new Regulation **[3]**.

The entire clinical trial procedure is covered by the new EU CTR, which consists of four essential business functions. Prior to long-term enterprise design revolutionization in crucial healthcare process areas, business must first temporarily modify its current patterns of operation **[2]**.

Figure 1: workflow of the CTR

Industry and member states will have to make sure that data and paperwork are supplied in accordance with the regulation's deadlines and adhere to strict corporate practices **[4]**. If these requirements are not met, there can be delays, more costs, and more effort needed. Missing significant checkpoints may result in applications being either expired or validated by default, depending on the application's state and what party a crucial activity belongs to.

The CTR 536/2014 and Directive 2001/20/EC's key points.

Directive 2001/20/EC

- Directive implemented in 2004
- Multiple application submission for respective National Competency Agencies and Ethics Committee for each MSC for single trial
- Individual assessment conclusion and decision for each MSC with no collaboration tool
- Limited information available to the public

Clinical Trial Regulation 536/2014

- CTR published in 2014
- Harmonized process across EU-Single application submission to all MScs
- Introduction of a single platform for submission of clinical trial application across the EU
- Collaborated assessment conclusion and decision using the CT Portal and Database
  - All information (except agreed Personally Protected Data and Commercially Confidential Information) available to the public

Initial Application

- The sponsor's initial application for a new clinical study in the EU

Substantial Modification Application

- An application to submit a request for significant changes to a clinical trial that has been approved

Non-Substantial Modification Application

- An application to submit non substantive changes to a clinical trial that has been .

Additional MSC Application

- A request to enroll an additional member state in a clinical trial that has been approved.

DISCUSSION:

The regulation requires a more comprehensive set of application information. Part I of an application, which includes data specific to the member states where the trial will be conducted, will be created centrally through the new CT Portal. Part II of the application will include data specific to the member states where the trial will be conducted **[5]**.

There are four application types: **[5]**

Application evaluation:

Evaluation of applications are evaluated according to rigorous deadlines that are outlined in the regulation by the relevant regulators from each member state. The RMS evaluates Part I with assistance from other MSC, and the MSC evaluates Part II **[4]** .

The initial application assessment:

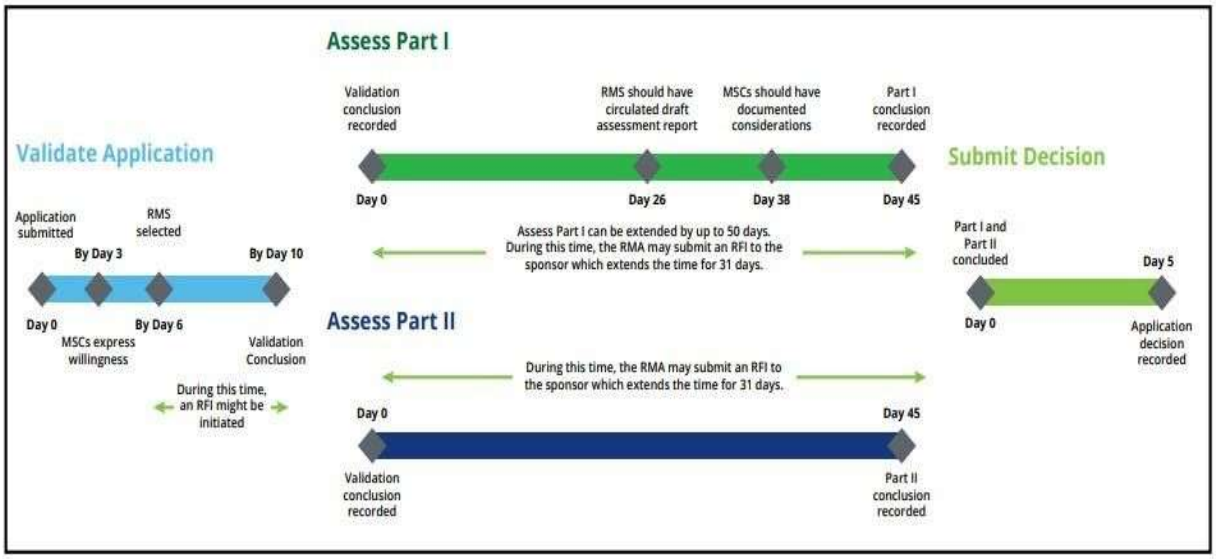

Figure 2: Initial Application Assessment Timeline

Announcement and submission of clinical trials

While conducting clinical trials, sponsors are expected to disseminate a number of warnings, such as significant trial milestones and essential safety information, via the CT Portal and Database. Sponsors are required to submit the required reports for approval at the conclusion of the study **[6]**.

publishing clinical trial results

By using the CTR, EMA promotes transparency throughout the entire process. Sensitive and commercially sensitive material is excluded from the database's publication of information, which is done in strict accordance with the rules. The publication's delay can be managed by sponsors using the portal. EMA In 2014, as a part of Policy 0070[7], the official EU clinical data disclosure and promotion policy was released. It is easier to understand what both Policies 0070 and CTR publishing entail when they refer to the disclosure of clinical trial data by contrasting a few high-level features of each **[6]** .

Pharmaceutical clinical research is included.	**Policy 0070**	**Clinical Trial Regulation**
	Products that are centrally approved exclusively	**Medical items that are still in development but do not yet have a marketing authorization**
	Clinical studies, regardless of the study's location, submitted to the agency in connection with an MAA, Art 58 procedure, line extension, or new indication	**Clinical trials conducted in the EU and paediatric studies conducted outside the EU that are a part of plans for paediatric research**
Documents Required	**Clinical information, including the anonymization report and clinical trial summaries and reports.**	**Every document created in connection with a clinical trial during its course (Examples include the protocol, evaluation and determination of the trial's conduct, a lay description of the trial's findings, research reports, inspections, etc.)**

Safety updates

As a result of the regulation's efforts to clarify the requirements for safety reporting,

- The recording and reporting of adverse events (AE) and serious adverse events (SAE) is not always done.
- A single safety report may be provided via the Eudravigilance system for clinical trials involving more than one investigational medical product (IMP).
- The new Eudravigilance system will be used to report suspected unexpected significant adverse reactions (SUSARS).
- The clinical trial sponsor may submit Annual Safety Reports (ASR) through the CT Portal and Database **[8]**.

In order to support the new CTR, the European Medicines Agency (EMA) will launch and host the CT Portal and Database. During the application, review, and oversight processes, sponsors and member state agencies will use the CT Portal and Database. Furthermore, the portal permits the public dissemination of important data that is stored in the database **[9]**.

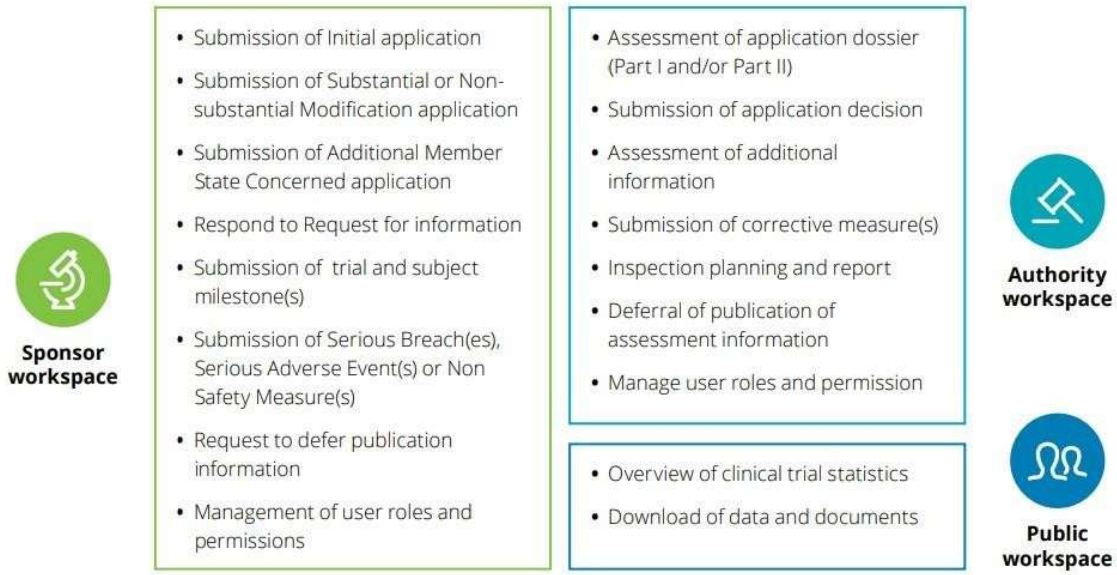

Figure 3: Business Functionality Overview

In order to help users with end-to-end processes, the CT Portal and Database offers features including document management, task management, notifications and alerts, and reporting functionalities.

Timeline for CTR compliance

The CTR and CT Portal and Database Timeline was first provided by EMA in 2015. However, EMA was forced to alter the schedule due to delays brought on by technical issues. As of right now, the EU CTR is anticipated to go into effect around the middle of 2020 rather than the previously anticipated October 2018 **[10]**.

As required by the Clinical Trial Regulation, the plan implies that the auditable version should be accessible for audit in early 2019, according to an update from EMA in March 2018.

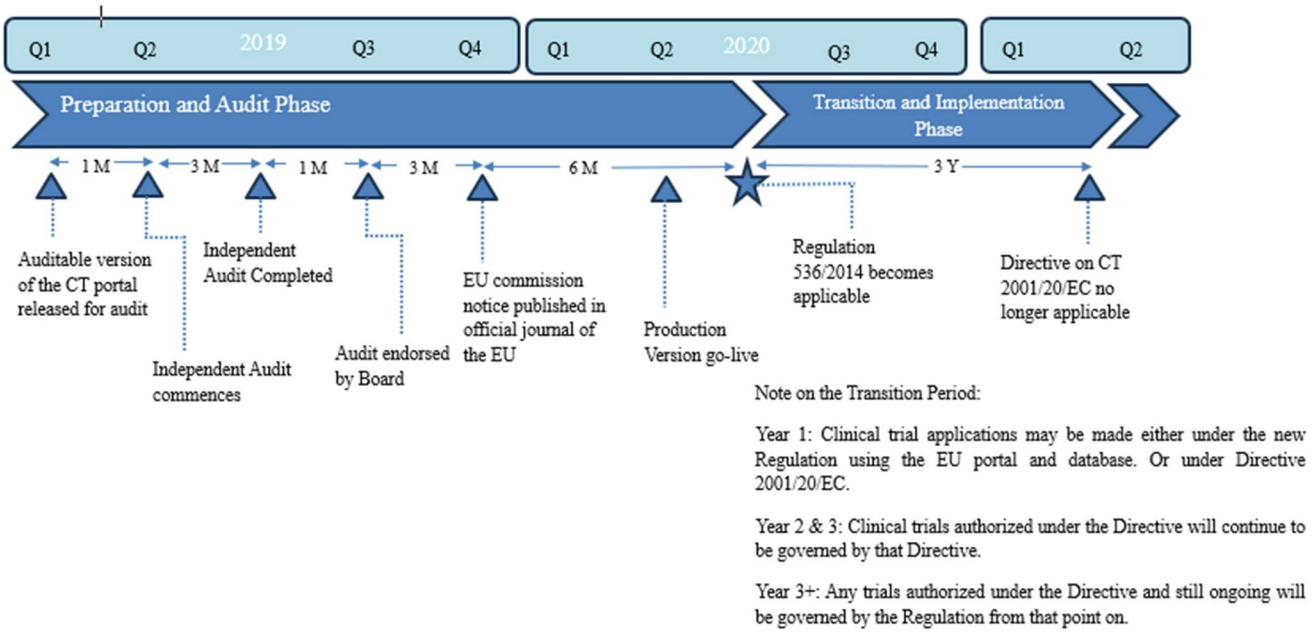

Figure 4: The CTR Compliance Schedule

The timelines are calculated using the intervals between milestones that EMA originally specified in its document EMA/760345/2015 - Delivery time frame for the EU portal and EU database, which was published in December 2015, starting from the start date of the amended audit as specified in EMA's notification of delay **[10]**.

Steps to develop a CTR implementation approach

1. Determine how regulations will affect the business.
2. Assess CTR gap and readiness
3. Defining the CTR strategy and roadmap
4. Setup a CTR programme
5. Implement enterprise-wide transformation

1. **Determine how regulations will affect the business.**

The CTR is involved in every stage of running clinical trials, from study start-up to conduct, safety & monitoring, and close-out. To ensure that the CTR transformation is more targeted and less disruptive, a detailed impact assessment that takes into account every part of the firm is required **[10]**.

Figure 5: Identifying Regulatory Impact to the Enterprise

Processes –

When submitting an application, it is important to consider how CTR may affect several organizational procedures, such as those involved in feasibility, site selection, and protocol planning. Focus must also be placed on currently offered third-party services and their specific procedures, including as agreements with Contract Research Organizations (CRO) and outside vendors.

Organization-

It is important to assess how CTR may affect the workforce and organisational structure. This involves the organization's physical presence in the region and if it has the resources and skills necessary to implement the rule change while maintaining business as usual (BAU) operations.

Data –

It is important to evaluate how CTR may affect the accuracy, reliability, and availability of the current data and documents. This includes identifying new informational components and paperwork that will be used as a result of the rules.

Technology-

to assess the impact of CTR on both external and internal technology systems, such as the Document Management System (DMS) and Clinical Trial Management System (CTMS). When the CT Portal and Database are launched, organizations might need to think about how to support and integrate them.

Time-

The CTR establishes deadlines for several tasks that must be completed within the trial. Though there are certain time restrictions that concern sponsor organizations, including Request for Information (RFI) during review, most of them have an effect on the authority assessment process.

2.Analyse the CTR gap and readiness.

In sequence for a thorough assessment of the present situation is required to comprehend the sponsor organization's readiness and gap. Key criteria should be evaluated and quantified based on each of these areas **[11]**.

- Vision: Overarching plan and vision for regulation
- Clinical trial governance: management and governance of data and processes
- Accessibility - The availability and accessibility of data and documents
- Quality- Data quality and validation
- Data Integration: Architecture for enterprise data integration
- Lifecycle: Workflow for data and processes, including data acquisition and management
- Logical and physical model - Data structure and model, unstructured content management, and catalogue administration

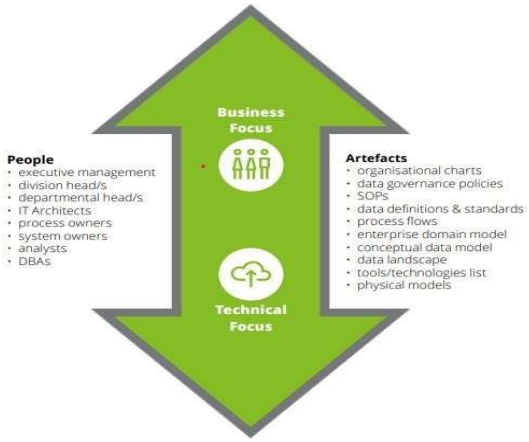

Figure 6: Assessing CTR gap and readiness

3.

Defining CTR strategy and roadmap

If sponsor organization’s want to properly apply the rule, they should consider creating a workable plan and coordinating it with the broader strategy and goal.

For the purpose of developing a strategy and roadmap, an organization may be able to draw upon other business, technical priorities, initiatives, or projects **[12]**.

This Includes:

- Activity Grouping and Prioritization

- Analysis of Resources
- Analytical reasoning.

4.Establish a CTR initiative

When implementing CTR, organization's need to know that technology is not the sole factor driving it. Corporate involvement is therefore crucial to facilitating the program's execution and guaranteeing the seamless transition and transformation of the process.

It also involves identifying the technical, business, and sponsorship stakeholders. Other third parties, such as clinical research organizations and suppliers, who are involved in the administration of trials must also be included, depending on how a sponsor firm operates. Stakeholders will need to be able to oversee the program and have a significant impact on crucial organizational process and cultural changes **[10]**.

5. Implement enterprise-wide transformation

In the Implement enterprise-wide transformation it includes various steps that are to be followed

• **Enterprise-wide governance**

To ensure consistent adoption of a change of this magnitude, a well-structured governance framework must be established after the establishment of the necessary processes and procedures. Data/document ownership, enterprise definition, data quality and validation, and important clinical trial data management will all be covered by the governance structure. It is essential that crucial process touchpoints be tracked and managed since they affect company operations and response times.

Modifications to procedural artefacts: coordinating current protocols

The requirement that presents corporate processes and procedures be modified is among the CTR's most significant ramifications. It will be necessary to create or modify validated documents, such as Standard Operating Procedures (SOPs) and Work Plans (WPs), in order to comply with the new laws. Additionally, new SOPs explaining how users are to administer and utilize the EU CT Portal and Database must be created **[8]**.

Transition/migration of clinical trials

During the three-year transition phase between the old directive and new rule, future and current clinical applications must be properly handled in accordance with the CTR timetable. Sponsor organization's need to take this into serious consideration when planning. Data migration and process transformation are two time-consuming but essential operations that must be scheduled well in advance of the law's implementation.

• Database management and interaction with the CT portal

The CT Portal and Database must be understood and used by sponsor organizations, thus they must make the required arrangements. This covers system onboarding, training, and user management for the organization as well as individual trials. In addition, considering the amount of data and documents involved, a robust information management system had to be implemented.

End-to-end integration and document management should be included in such a system. The amount of money and time required for this could vary depending on the internal enterprise environment and the quantity of external third-party systems involved **[4]**.

• Regional and country level structuring

To provide more support, one of the primary goals of CTR is to ensure that the area, particularly the areas where trials are held, has qualified legal representation. The extent of job and responsibility reorganization may need sponsors to assess trial locations and devise optimal operating strategies moving forward. When choosing the RMS for their various trials and how to most leverage the past and current capabilities of the participating MSCs, sponsors will need to carefully evaluate these factors. Naturally, given the methodology of RMS selection, this does not imply that they will implement the RMS that they suggest.

• Automation of regulatory notifications

It takes a lot of time to do non-clinical tasks including submitting authority requests, completing paperwork, and producing reports when conducting clinical research. Regulatory duties that are essential to the business process may be automated with the help of a workflow management solution. Important actions such as Part I, Part II, and/or Validation RFIs will be sent to the selected stakeholder(s) and they will be notified in a timely manner. It also has the ability to automatically handle problems and route jobs requiring data **[13]**.

CONCLUSION:

Not many organizations are approaching the new CTR in the same way or are at the same level of readiness. Previous regulatory measures that were canceled or delayed have made it is difficult for those in charge of regulatory implementation. Programs to retain the necessary dedication from holders of the budget and senior management. With the latest CTR date adjustments, there is growing concern that the go-live date will be postponed even further. Consequently, a number of businesses have chosen to hold off.

Others, however, are aware that waiting too long to get their companies ready could result in higher expenses and a longer timeline for implementation. and such, they recognize the danger. In any case, whether it's the present strategy or just the size of an organization.

SUMMARY:

In discussing a new clinical trial legislation in the European Union (EU), the article emphasizes the two-part application procedure that involves trial-specific data for member states. With Part I being evaluated by the RMS and Part II being evaluated by the MSC, it introduces four different application types and severe timelines for evaluation. On the basis of EMA Policy 0070 for the dissemination of clinical data, sponsors are required to submit alerts and data through the CT Portal and Database. Utilizing the Eudravigilance system for safety reports and SUSARs is one of the streamlined regulations for safety reporting. Clinical trial data is accessible to the public through the CT Portal and Database, which are hosted by the EMA. Technical problems caused the CTR implementation to be initially postponed until mid-2020. To understand how the rule will impact their processes, third-party services, data accuracy, and technological systems, organizations must complete impact assessments. The language focuses on sponsor preparedness and authority evaluation when outlining detailed deadlines for trial-related tasks. Sponsor organizations should develop a practical plan that is in line with their larger vision to implement the CTR successfully, taking into account corporate participation, governance, procedural changes, clinical trial transition, CT Portal and Database management, regional factors, and automated regulatory notifications.

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