

EU Clinical Trial Regulation
Building a successful programme

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Forward

The Clinical Trial Regulation (CTR) is set to revolutionise the way clinical trial processes are run across Europe impacting all EU member states and companies who wish to run clinical trials in the EU. Diligent member states, ethics committees and Pharmaceutical Companies are already preparing for this unprecedented change and those who have not, should soon begin preparing to avoid facing significant challenges when the legislation comes into force.

To be ready for 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 scrutinised.

This paper provides a synopsis of the new regulation, including insights on timing, the advantages of preparedness and the impact that Brexit may have. It also provides guidance on how companies can set up a successful CTR programme.

Introduction

In 2014, the European Medicines Agency (EMA) released Clinical Trial Regulation EU No 536/2014 [1] to harmonise the assessment and supervision processes for clinical trials on medicinal products for human use. It builds on Directive 2001/20/EC[2] and the ideals represented in the Voluntary Harmonisation Procedure (VHP)[3] by the Heads of Medicines (HMA) Clinical Trials Facilitation Group (CTFG).

Once effective, it will drive:

- efficiency through harmonisation of CT application process across Europe
- greater transparency in clinical processes and data
- enhanced safety and efficacy of drugs.

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 authorising clinical trials, removing duplication and reducing delays in the process
- introducing a lighter regulatory regime for trials conducted with medicines that are already authorised 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 recognising co-sponsorship, which acknowledges that a trial can be led by more than one organisation
- introducing the concept of a single decision on a clinical trial, which will replace the previous separate approvals given by the National Competent Authorities and Ethics (NCAE) committees. This also reduces the administrative burden on the Member States Concerned (MSC), particularly the elected Reference Member State (RMS)

Highlights of Directive 2001/20/EC & CTR 536/2014

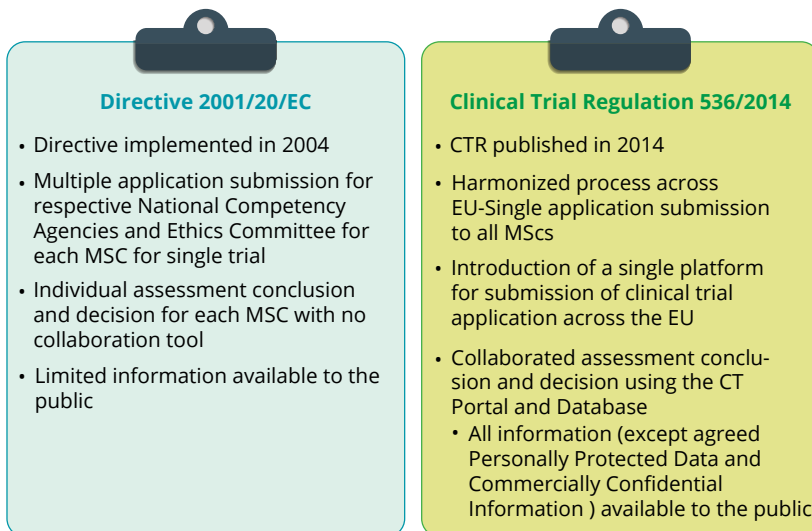


Figure 1: Highlights of Directive 2001/20/EC & CTR 536/2014

In March 2017, the European Medicines Agency (EMA) presented their high level view [4] on the move from

the directive to the regulation and the pathway to implementation of the portal and database.

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 revolutionise the whole enterprise architecture in key areas of the clinical process in the long term.

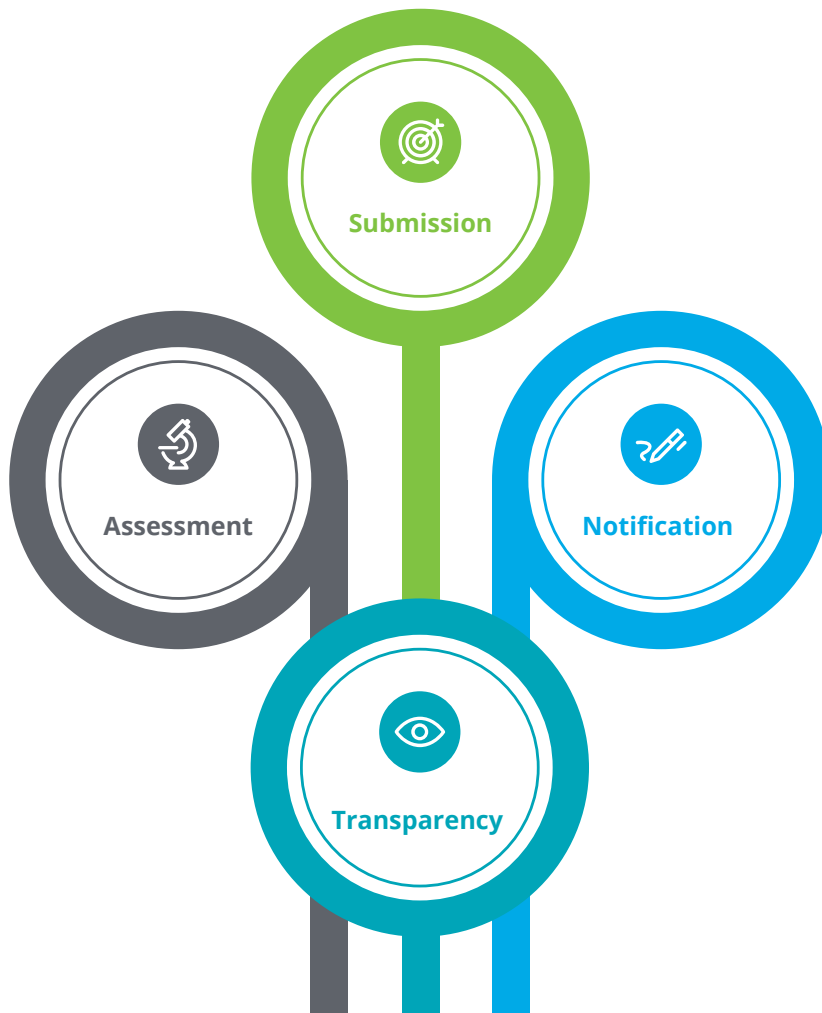


Figure 2: Demystifying the CTR

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.

The clinical trial application

The regulation requires a more comprehensive set of application information. An application consisting of Part I and/or Part II will be created centrally via the new CT Portal; Part I consists of information related to the trial, product and protocol whereas Part II consists of data specific to the member states where the trial will be run.

There are four application types:

- **initial application;** the first application to be submitted by the sponsor when applying for a new clinical trial in the EU
- **substantial modification application;** an application to submit a request for substantial changes to an authorized clinical trial.

- **non-substantial modification application;** an application to submit non-substantial changes to an authorised clinical trial.
- **additional MSC application;** An application to submit an additional member state to an authorised clinical trial.

Application assessment

Applications are assessed by the appropriate regulators from individual member states and based on strict timelines as defined in the regulation. The assessment of Part I is carried out by the RMS with the support of other MSC and the assessment of Part II is carried out by the MSC.

The initial application assessment:

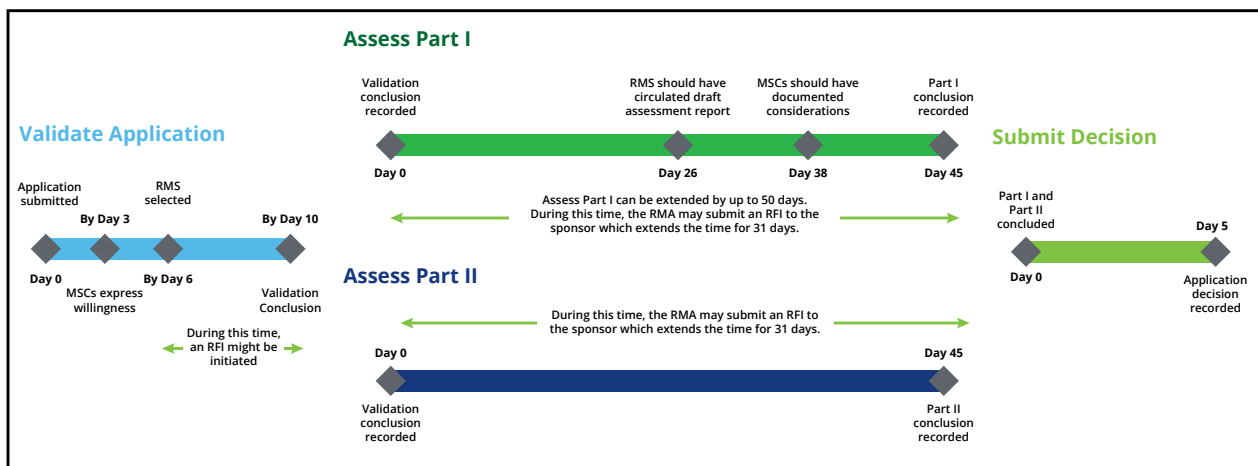


Figure 3: Initial Application Assessment Timeline

*For the purpose of consulting with experts, a trial involving an advanced therapy investigational medicinal product (ATMP) or a product defined in the Annex of Regulation (EC) No 726/2004 [5], an additional 50 days may be taken by the reporting Member State beyond that of the 45 days since the validation date, for the submission of the final Part I assessment including its conclusion.

Throughout the assessments, sponsor organisations are expected to respond to information requests raised by regulators.

Clinical trial notification and submission

During the course of running clinical trials, sponsors are required to submit various notifications via the CT Portal and Database, such as key trial milestones and important safety information. At the end of the trial, sponsors are expected to submit the necessary reports approval purposes.

Clinical trial publication

Through the CTR, EMA promotes transparency in the end to end process. With the exception of sensitive and commercially confidential information, information stored

in the database is published based on strict rules. Sponsors are allowed to manage the deferral of the publication via the portal.

EMA Policy 0070 [6] was published in 2014 and is the official policy for EU clinical data publication and the promotion of transparency of clinical data for the benefit of public safety and expedition of products to market. This paper does not discuss in depth Policy 0070 which is a considerable topic in its own right, however by considering some high-level components of Policy 0070 and CTR publication, the scope covered by both for the transparency of data for clinical trials becomes clearer.

	Policy 0070	Clinical Trial Regulation
Medicinal product clinical studies covered	Centrally authorised products only	Investigational medicinal products, regardless of whether they have a marketing authorisation
	Clinical studies submitted to the Agency in the context of a MAA, Art 58 procedure, line extension or new indication, regardless of where the study was conducted	Clinical trials conducted in the EU and paediatric trials conducted outside the EU that are part of paediatric investigation plans
Documents covered	Clinical data (clinical overview, clinical summaries and clinical study reports) and the anonymisation report	All clinical trial-related information generated during the life cycle of a clinical trial (e.g. protocol, assessment and decision on trial conduct, summary of trial results including a lay summary, study reports, inspections, etc.)
Publication channel Date it applies	EMA clinical data publication website	Future EU portal and database
	1 January 2015 (MAA or Art 58 procedure) or 1 July 2015 (line extension or new indication)	Expected in 2020
Publication from	October 2016	Expected in 2020

Figure 4: Policy 0070 vs CTR

Source: EMA website [7], Appendix, on disclosure rules, to the “Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014” [8]

The new CTR hopes to not only to attract sponsors to run research and development activities in the region but also to foster a patient centric and innovative environment. It will encourage increased transparency throughout the entire end to end process; from application submission to market authorisation.

The regulation strongly promotes transparency of trial data with it being publically accessible by default. There are a few exceptions as explained in the regulation [1] Article 81 paragraph 4:

The EU database shall be publicly accessible unless, for all or part of the data and information contained therein, confidentiality is justified on any of the following grounds:

- a. protecting personal data in accordance with Regulation (EC) No 45/2001;
- b. protecting commercially confidential information, in particular through taking into account the status of the marketing authorisation 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.

In February 2018, the European General Court ruled in favour of the EMA's approach to transparency on three

separate cases, in particular Policy 0043 – policy on access to documents [9]:

- Case T-235/15 - Pari Pharma v EMA [10]
- Case T-718/15 - PTC Therapeutics International v EMA [11]
- Case T-729/15 - MSD Animal Health Innovation and Intervet International [12].

As a result, rather than fighting the direction of travel for increased transparency, organisations are likely better investing their resources in their internal processes to recognise, minimize and allow appropriate redaction of Commercially Confidential Information (CCI) and Protected Personal Data (PPD) prior to a CT application.

Safety reporting

The regulation aims to also simplify the rules on safety reporting so that:

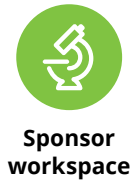
- not all adverse events (AE) and serious adverse events are recorded and reported
- for clinical trials that involve more than one investigational medicinal product (IMP) a single safety report can be submitted via the Eudravigilance system
- suspected unexpected serious adverse reactions (SUSARs) will be reported via the new Eudravigilance system
- annual Safety Reports (ASR) can be submitted via the CT Portal and Database by the sponsor of the clinical trial.

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 portal also enables the publication of relevant information stored in the database into the public domain.

Overview of business functionality



- Submission of Initial application
- Submission of Substantial or Non-substantial 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

- Assessment of application dossier (Part I and/or Part II)
- Submission of application decision
- Assessment of additional information
- Submission of corrective measure(s)
- Inspection planning and report
- Deferral of publication of assessment information
- Manage user roles and permission



Authority workspace

- Overview of clinical trial statistics
- Download of data and documents



Public workspace

Figure 5: Overview of Business Functionality

Source: EMA - Functional specifications for The EU Portal and Database, EMA, March 2015 [13]

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.

Timeline for CTR compliance

EMA originally published the timeline for CTR and the CT Portal and Database in 2015 [14]. However, due to delays for technical reasons EMA have been required to revise the schedule. The EU CTR is currently estimated to become applicable mid 2020 instead of October 2018 as originally planned.

In an update in March 2018 EMA stated: "The plan shows that the auditable version should be available for audit in **early 2019**, as required by the Clinical Trial Regulation.

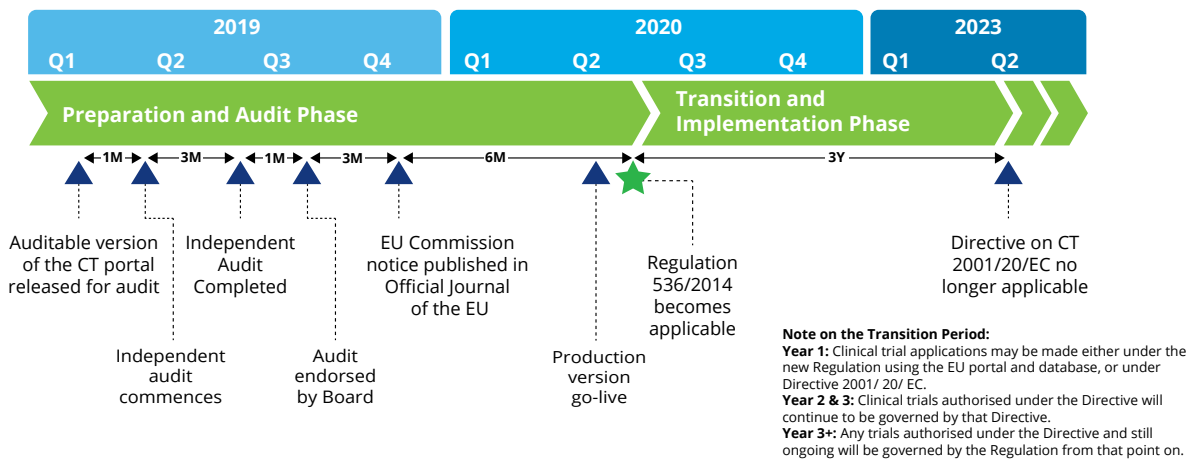


Figure 6: Timeline for CTR Compliance

The timelines shown are determined by starting with the updated audit commencement as expressed in EMA's notification of delay and applying the durations between milestones that EMA originally defined in December 2015 within document EMA/760345/2015 – Delivery time frame for the EU portal and EU database [14].

1. Preparation and audit phase

During this 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).

2. Transition and implementation phase

When Regulation 536/2014 becomes applicable, there is a three year transition period where Directive 2001/20/

EC will be applicable concurrently with the CTR. 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 authorised 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.

What does Brexit mean for clinical trial applications?

In 2016, the United 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. There is also the question of how existing trials that are currently run in the UK and the EU will be managed moving forward after Brexit. This will impact all pharmaceutical companies and regulators in member states, as well as existing patients.

At the time of writing, EMA has prepared some Brexit procedural guidance [15] and [16] and within its Brexit preparedness plan [17] the Agency has stated that the continuation of the CT project to provide a Clinical Trial Portal and Database is a category one priority (the highest priority) "Some projects with legal deadlines (**clinical trials**, EudraVigilance) as well as other projects (SPOR)" Substance, Product, Organisation and Referential master data. 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. "EMA is working on the assumption that the UK will become a third country as of 30 March 2019." [18]. While this message from EMA goes beyond the CTR, when related to the Portal and Database, it means Brexit should not impact the timeline for the remaining 27 member States to become compliant to CTR.

For existing Marketing Authorisations, The EMA guidance discusses the requirement to transfer UK MAs and that it is possible to do so during ongoing regulatory procedures [15]-4a. The EMA guidance suggests that "Marketing Authorization Holders should consider the timelines of the respective procedures and plan in order to avoid a situation where decision making processes of the procedures will overlap." For an application/trial where the UK is an RMS or MSC, excluding products which are pre-CTA there are three possible states that a trial could be in when Brexit occurs:

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 organisation 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 Authorised Procedure (NAP) equivalent marketing authorisation 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 Authorised Procedure (CAP) marketing authorisation 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. However in March 2017 the CMDh (Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human) agreed an update to the CMDh position on changing the RMS [19]-3.1.2 to allow the invocation of Article 50 to be considered an "justified reason" to change the RMS. 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 in the current RMS even if they have not yet started and confirm to the new RMS that no procedure is being examined in the current RMS." [20]

3. During a Marketing Authorisation 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 Authorised Procedure (NAP) equivalent marketing authorisation with the MHRA
- b. Centrally Authorised Procedure (CAP) marketing authorisation with the RMS and MSC(s) being from the remaining 27 member states.

The MHRA also reflects some of EMAs concerns, although they are somewhat more cautious in their wording. “MHRA is aware that companies who market pharmaceuticals in the EU and UK will need to plan and make decisions in advance of the UK’s departure from the EU in March 2019”[21]. They state that in the event of a no-deal scenario that they “would be pragmatic in establishing UK regulatory requirements” and they “would ensure the minimum disruption and burden on companies as the UK exits the EU”. In March 2018 transitional arrangements were agreed in principle between the UK Government and the EU as part of the draft Withdrawal Agreement that will, if finalised and ratified, govern the terms of the UK’s exit. Assuming the draft Withdrawal Agreement becomes legally binding, and on similar terms to the current draft, the transition would maintain the status quo for 21 months post the March 2019 scheduled departure of the UK from the European Union. The implication is that should CT Portal and Database go-live in 2020, the regulation will remain applicable for trials where the UK is the RMS or an MSC for a number of months prior to a UK departing the EU.

Further to this, in the Life Sciences Industrial Strategy for the UK Government, authored by Professor Sir John Bell [22] he states “As the UK seeks to do more complex and innovative trials, MHRA needs to continue engaging with sponsors to assist with innovative protocol designs and should facilitate efficient approval of complex trials and amendments to such trials, for example, to add new arms.” and “There should be an ambition to develop the regulatory environment... This will require regulators, health systems and industry, as well as academic trialists, to work together in updating *ICH-GCP regulations.”

Numerous other parties have also argued that because of the rich R&D capability in the UK and the diverse patient population in the EU, this synergy should continue post

Brexit. This would ensure better safety and help speed up the marketing authorization process for the benefit of patients.

From 2009 to 2011 the EMA and FDA operated the EMA-FDA GCP Initiative [23] which required shared inspections of clinical trial sites and in November 2017 the EMA entered into a MRA (Mutual Recognition Agreement) with the FDA for GMP (Good Manufacturing Process) inspections [24]. A decision is expected on expansion of operational scope to include products manufactured for Clinical Trials. These initiatives demonstrate a willingness on the part of the EU to co-operate with other regional/national agencies and it is hoped that a similar initiative might be sought by the MHRA and EMA and supported by the UK Government and EU Commission.

ICH-GCP compliance will also clearly continue to be a fundamental pre-requisite for high quality, patient orientated trials, whether submitting an application and executing a trial in the UK under the CTR or any new UK regulatory regime, post Brexit. Ultimately though, whether there will be a mutual recognition type agreement that would allow the MHRA and organisations with trials being conducted in the UK to access and submit via the CT Portal and Database will need to be determined in the coming months. Regardless, the MHRA must already be considering what solution to create in a “maximum change” scenario. Equally as certain, is that organisations should not delay implementation of the regulation and should themselves be preparing to be in a position of compliance with CTR and be ready to exchange data between their own systems and the Portal and Database.

*International Conference on Harmonisation – Good Clinical Practice

CTR touchpoints within the industry

A recurring perception of the CTR is that it is predominantly about data, and therefore typically under the scope of Information Technology (IT). Although this is partly true, the new regulation is not limited to meeting the data requirements. In reality, the new CTR will affect multiple business touch points within the clinical operations and study management.

When organisations are looking to prepare for the implementation of CTR they would be wise to approach the task by not just focusing on their readiness from a data landscape, Clinical Operations and Regulatory Affairs perspective, but on how the correct approach could improve their operational efficiency.

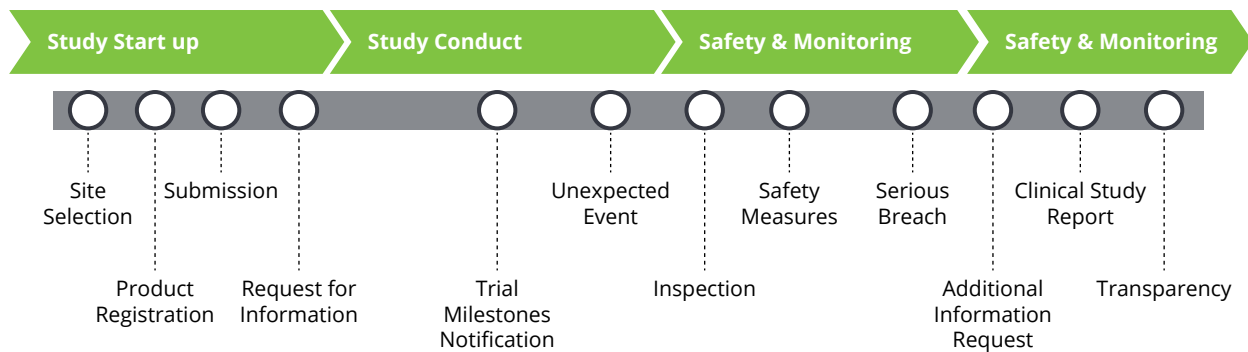


Figure 7: CTR Touchpoints with Industry

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 organisation to meet the data and documents requirements for submission.

During study conduct, project notification milestones must be submitted intermittently for each member state concerned. It is expected that this touchpoint 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.

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.

Industry pain points



Figure 8: Industry Pain Points

Smart steps to develop your CTR implementation approach

Between 2005 and 2015 there was a substantial acquisition and outsourcing trend [25] within the industry. This trend has resulted in a more diverse business model and operational landscape within most pharmaceutical companies; meaning any transition can be either straight forward or challenging. As a result, there is no 'one size-fits-all' approach in addressing the new CTR and an Enterprise Architecture assessment is fundamental to any transformation within a pharmaceutical organisation.

1. Identify the regulatory impact to the enterprise

As outlined in the previous section, the CTR touches the end to end process for running clinical trials; Study Start-up, Study Conduct, Safety & Monitoring and Study Close Out. In order to ensure that CTR transformation is more targeted and less disruptive, a comprehensive impact assessment that covers the whole spectrum of the enterprise is required.

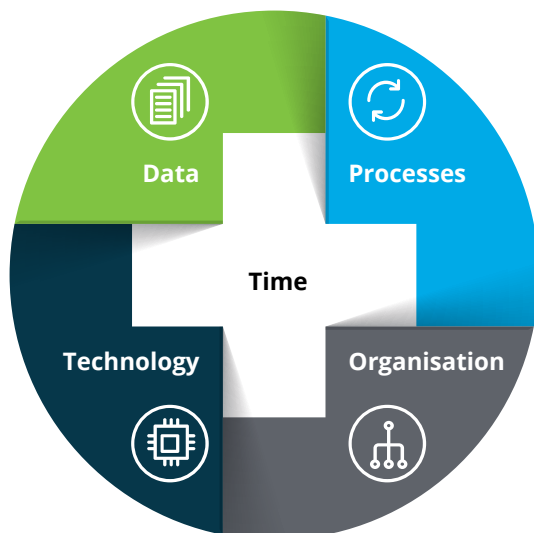


Figure 9: Identifying Regulatory Impact to the Enterprise

- **Processes** – The impact of CTR to the various processes within an organisation 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 Organisations (CRO) and external vendors.
- **Organisation (People)** – The impact of CTR to the organisational structure and people should be assessed. This includes the geographic presence of the organisation 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, organisations 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 impact the authority assessment process, there are time limits that concern sponsor organisations such as Request for Information (RFI) during assessment.

2. Assess CTR gap and readiness

In order to understand the sponsor organisation gap and readiness, a detailed assessment of the current state

- **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



Figure 10: Assessing CTR gap and readiness

A series of interviews and analysis of existing data and documents in line with the expectations and requirements of the CTR, should help answer some of the

key questions required to come up with a well-planned strategy and roadmap.

? Who is currently **responsible for regulatory submission and reporting** in the organisation?

? How is **data currently held** for the purpose of regulatory submission?

? What are the current **Service Level Agreements** with suppliers and third parties in relation in clinical trials?

? What **data and/or documents** related to clinical trials reside with **external supplier/third parties**? Does the organisation have timely access to the data?

? Is the CTR **communicated** to the respective operational team?

? What is the process of responding to a **Request for Information**?

? Who is **responsible for the implementation** of the CTR?

? What **clinical trial services** are currently being **outsourced** to third party organisations?

3. Defining the CTR strategy and roadmap

Whilst most sponsor organisations will normally opt for a more tactical solution to be CTR compliant, it is important to know that such transformations will be labour intensive. In order to effectively implement the regulation, sponsor organisations should look at defining a realistic roadmap and harmonising it with the overall strategy and vision.

An organisation may be able to leverage other business, technical priorities and programmes or projects when coming up with a strategy and roadmap. This includes:

- grouping and prioritization of activities
- resource analysis
- logical analysis.

Organisations need to also consider the timeline and how to harmonise the regulatory strategy:

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 organisations. Since this is a compulsory exercise that is defined by EMA, sponsor organisations 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. Some of these new regulations are indirectly or directly linked to CTR and should be considered as part of the transition and implementation. Understanding the touch points CTR has with these will

allow for a comprehensive implementation approach, reduction of the risk of duplicative efforts and increased cost, while at the same time provide significant benefit beyond 'just' compliance.

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 organisational environments which seem to be ever more silo-ed and complex, it is highly beneficial to organisations to have foundational programmes for Enterprise Programme 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 organisations 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 organisation.

Establish an adequate Regulatory Change Management Office

Often with any transformation programme, the importance of change management is often overlooked and does not operate as effectively as it should. It is therefore imperative that change management office is established.

Due to 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 workstreams 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 touchpoints 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 organisations 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 organisations to make necessary provisions to understand and interface with the system. This includes user management for the organisation, 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

In order to provide better support, one of 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

Throughout conducting Clinical Research a significant amount of time is spent on non-clinical activities such as authority submission, documentation and report creation. 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.

Conclusion

Not all organisations are taking the same approach or are at the same level of readiness for the new CTR. Cancellation or delays of previous regulatory initiatives have made it a challenge for owners of regulatory implementation programmes to maintain the required commitment from senior management and budget holders. With the recent changes of dates for CTR there is increasing concern that the go-live date will continue to be pushed out. This has resulted in some companies taking a wait-and-see approach while others see the risk of not preparing their organisations sooner rather than later as potentially more costly due to sustaining a longer implementation timetable. Regardless of the current approach, or even size of an organisation, there are a number of factors to consider when seeking a successful outcome.

Key success factors

- **Start now – Wait-and-see may not be the answer**

Whilst the timeline is still not locked down, it is clear the requirement 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 organise 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 organisations, a proper dashboard and reporting infrastructure should be in place. This will allow sponsor organisations 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 organisation. Companies should consider the spirit of the regulation, the benefits it will offer and its touchpoints with other regulations and take the opportunity to drive operational change beyond compliance.

Contacts



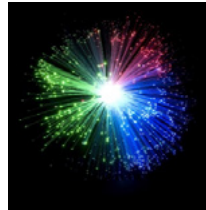
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