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„The Key Differences of the New Clinical Trials Regulation No.536/2014 Compared to the Clinical Trials Directive 2001/20/EC?"

verfasst von / submitted by

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Abstract

The Clinical Trials Directive 2001/20/EC was implemented in 2001 and was the first attempt to harmonize the guidelines and rules for clinical trial applications and approvals in the European Union and the European Economic Area. Although the purpose was to simplify procedures, the opposite has been observed as the number of clinical trial applications has decreased in recent years and bureaucracy has increased.

To counteract the resulting decrease in clinical trial applications and approvals, the new Clinical Trials Regulation (EU) No. 536/2014 was introduced in January 2022 and will replace the current essential document after a predefined transition period. The new Clinical Trials Regulation has three main objectives: simplifying clinical trial applications, increasing transparency, and protecting patients through simplified safety reporting.

The implementation of the new Clinical Trials Regulation will introduce an overwhelming number of changes and new procedures, and there is lack of a comprised document summarizing those changes. Therefore, this master thesis is set out to answer the following research question: What are the key differences and consequences of the new Clinical Trials Regulation No.536/2014 compared to the Clinical Trials Directive 2001/20/EC?

This thesis analyzes thoroughly the Clinical Trials Directive and the Clinical Trials Regulation and finally compares the two legislations, highlighting their main differences and impact on the clinical trial situation in Europe. In addition, a research framework on clinical trials, the European Union, their committees, and groups related to this regulation and an interview with an expert working in the field of clinical trials, will outline to answer the research question.

Zusammenfassung

Die Richtlinie 2001/20/EG über klinische Prüfungen wurde im Jahr 2001 eingeführt und war der erste Versuch, die Leitlinien und Vorschriften für klinische Prüfungen sowie deren Beantragung und Genehmigung in der Europäischen Union zu harmonisieren. Obwohl der Zweck darin bestand, die Verfahren zu vereinfachen, wurde das Gegenteil beobachtet, da die Zahl der Anträge auf klinische Prüfungen in den letzten Jahren zurückgegangen ist und der bürokratische Aufwand zugenommen hat.

Um dem daraus resultierenden Rückgang der Anträge und Genehmigungen für klinische Prüfungen entgegenzuwirken, wurde im Januar 2022 die neue Verordnung (EU) Nr. 536/2014 über klinische Prüfungen eingeführt, die das derzeitige grundlegende Dokument nach einer festgelegten Übergangszeit ersetzen wird. Die neue Verordnung über klinische Prüfungen verfolgt drei Hauptziele: die Vereinfachung der Anträge auf klinische Prüfungen, die Erhöhung der Transparenz und den Schutz der Patienten durch eine vereinfachte Sicherheitsberichterstattung.

Die Umsetzung der neuen Verordnung über klinische Prüfungen wird eine überwältigende Anzahl von Änderungen und neuen Verfahren mit sich bringen, und es fehlt ein zusammenfassendes Dokument, das diese Änderungen abdeckt. Daher soll diese Masterarbeit die folgende Forschungsfrage beantworten: Was sind die wichtigsten Unterschiede und Konsequenzen der neuen Verordnung (EU) Nr. 536/2014 über klinische Prüfungen im Vergleich zur Richtlinie 2001/20/EG über klinische Prüfungen?

In dieser Arbeit wird die Richtlinie über klinische Prüfungen und die Verordnung über klinische Prüfungen sorgfältig analysiert und schließlich die beiden Rechtsvorschriften miteinander verglichen, wobei die wichtigsten Unterschiede und die Auswirkungen auf die Situation der klinischen Prüfungen in Europa herausgehoben werden. Darüber hinaus werden weitere Themen vertieft, wie die Europäische Union, ihre Ausschüsse und Gruppen im Zusammenhang mit dieser Verordnung und ein Interview mit einer Expertin, die im Bereich der klinischen Prüfungen arbeitet, um die Forschungsfrage zu beantworten.

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List of Abbreviations

ACT EU *Acceleration of Clinical Trials in the EU*

AMG *Austrian Medicines Act*

AMP *Auxiliary Medicinal Products*

BASG *Austrian Federal Office for Safety in Health Care*

CA *Competent Authorities*

CHMP *Committee for Medicinal Products for Human Use*

CMDh *Coordination Group for Mutual Recognition and Decentralized Procedures Human*

CMS *Concerned Member States*

CP *Centralized Procedure*

CRA *Clinical Research Associates*

CTA *Clinical Trial Application*

CTAG *Clinical Trial Coordination and Advisory Group*

CTCG *Clinical Trial Coordination Group*

CTD *Clinical Trials Directive*

CTEG *Clinical Trial Commission Expert Group*

CTIS *Clinical Trials Information System*

CTR *Clinical Trials Regulation*

DCP *Decentralized Procedure*

DSUR *Development Safety Update Report*

EC *Ethics Committees*

ECSC *European Coals and Steel Community*

EDQM *European Directorate for Quality of Medicines and Healthcare*

EEA European Economic Area

EEC *European Economic Community*

EMA European Medicines Agency

EMRN *European Medicines Regulatory Network*

EU *European Union*

EudraCT *European Union Drug Regulating Authorities Clinical Trials Database*

EUPD *EU Portal and Database*

EV *EudraVigilance*

FDA Food and Drug Administration

GCP *Good Clinical Practices*

GCP IWG *Good Clinical Practice Inspectors Working Group*

GCTO Global Clinical Trials Operations

GMP *Good Manufacturing Practice*

HMA *Heads of Medicines Agencies*

IB *Investigational Brochure*

ICH *International Council for Harmonisation*

ICH-GCP *International Conference for Harmonisation Good Clinical Practice*

IMPD *Investigational Medicinal Product Dossier*

KPI *Key Performance Indicators*

MA *Marketing Authorization*

MAA *Market Authorization Application*

MAH *Marketing Authorization Holder*

MRC *Medical Research Council*

MRP *Mutual Recognition Procedure*

MS *Member States*

NCAs *National Competent Authorities*

NP *National Procedure*

RACI *Regulatory Network Responsibility Assignment*

RMS *Reference Member State*

SUSARs S*uspected Unexpected Serious Adverse Reactions*

USA *United States of America*

Table of Figures

1 Introduction

Clinical trials are central to the development of pharmaceuticals as they assess safety, establish a benefit-risk ratio, determine their efficacy, and continuously improve medical care. Consequently, clinical trials must be conducted in the European Union (EU) for drug innovation to support and promote progress in research and development.(1) To adequately contribute to the evidence-based sector, clear infrastructures must be in place to support research and innovation.(2)

Research in the medical field is crucial to remain competitive in the scientific sector and to provide the best possible healthcare to the public. Therefore, a decrease in number of clinical trials not only negatively affects the pharmaceutical and research sectors, but also affects everyone else, as it impacts all patients, health professionals and society in general.(3)

1.1 History of Clinical Trials

In modern medicine, clinical trials are the gold standard for evaluating the safety, dosage, efficacy and risk-benefit ratio of novel therapeutic treatments or other interventions. They are the predominant form of determining the validity of various factors of a new therapy and are also commonly used to demonstrate a benefit of the new therapy over the current standard treatment. They are well controlled and conducted in a strict regulatory environment.(4)

The history and development of clinical trials goes back many centuries. The first recorded study with legumes, which served only to compare therapeutic treatments, was already described in biblical times. In 1747, James Ling conducted a very famous scurvy study, which was innovative at the time because it already contained many elements of a controlled study.(5,6) The appearance and use of placebos began in the 18th century, and the very first controlled double-blind study was conducted a few years later, in 1943, by the British Medical Research Council (MRC).(7)

The British MCR then also conducted the first randomized control trial for streptomycin in pulmonary tuberculosis in 1946. These studies are still considered groundbreaking and pioneering, as they were the first study to have inclusion criteria, a carefully crafted study design and conduct.(8,9)

Clinical research has evolved from simply trying to compare therapeutic treatments to a large number of different methods and tools for clinical trials. Today, clinical trials include randomization, blinding and the use of placebos, and among the many different types, a randomized controlled clinical trial is one of the most powerful scientific assessment tools for interventions. There are also multiple challenges associated with this evolution, ranging from scientific, ethical and legal aspects.(10)

With the progress of science, ultimately ethical questions arose and therefore the medical and research sector were forced to establish ethical progress, especially for the protection of human beings. The idea of an ethical framework goes back to the Hippocratic Oath, which obliges doctors to follow certain professional standards and to preserve life. Throughout history, however, this oath has often been broken by putting scientific progress and curiosity above human protection, even leading to abuse, e.g. during the Second World War.(4)

The result was the introduction of several guidelines for the protection of human subjects to complement medical and scientific developments. The Nuremberg Code of 1947, e.g., was the first international ethics guide for medical and scientific research involving human subjects. This was followed by the Declaration of Helsinki in 1964, which focused on guidelines specifically for human subjects, constantly changing and treated as a living document to keep pace with scientific advances and modern research techniques. Finally, in 1996, the International Conference for Harmonization Good Clinical Practice (ICH-GCP) were published and have been universally adopted as the standard for all ethical principles related to clinical trials.(11)

As ethics and medical research developed, regulations for clinical trials were established in parallel, often based on some of the aforementioned documents. The goal was to have more government agencies to monitor clinical trials and enforce regulations and laws more closely. This resulted in the Food and Drug Administration (FDA) in the United States of America (USA) in 1862 and the European Medicines Agency (EMA) in the EU and European Economic Area (EEA) in 1995.(12)

Clinical trials are divided into different phases, with each phase having a specific objective as shown in Figure 1 Often, the new therapy in question can only move on to the next phase of the clinical trial once one phase has been successfully completed. Patients and all other participants, such as sponsors, investigators, and clinical research associates (CRA), have to be carefully selected and must meet certain requirements to be eligible for the clinical trial. These criteria therefore exclude some groups of patients who may have other diseases

or who are already taking other medications, as these factors could affect the outcome of the trial. To ensure that the validity and robustness of the data is guaranteed, strict regulations apply in the EU and the EEA countries Liechtenstein, Norway and Iceland.(13)

1.2 Clinical Trial Phases

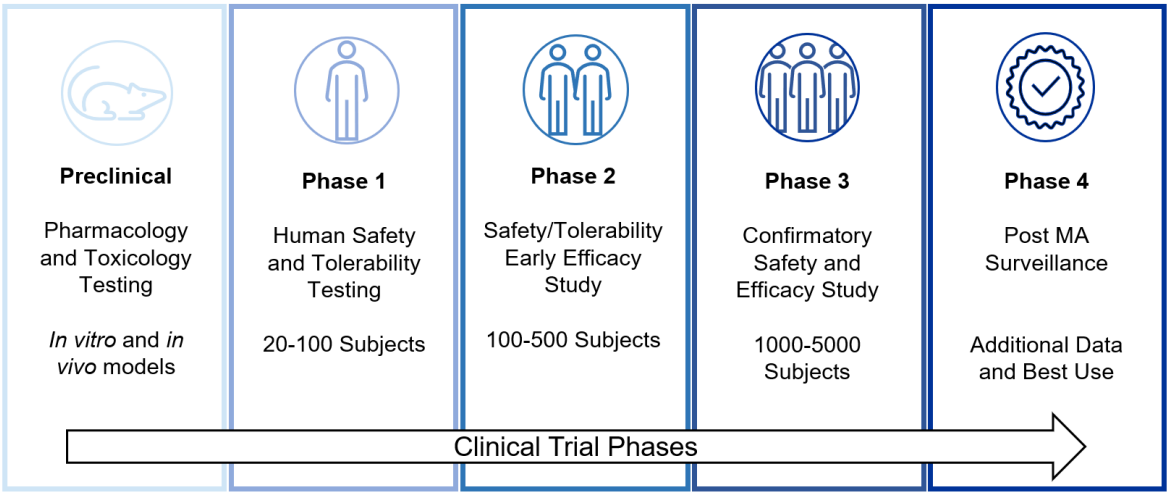

Figure 1 Clinical Trial Phases

Shows the different phases of clinical trials. The preclinical phase is used to conduct pharmacological and toxicological tests in in vitro and in vivo models. Phases 1, 2 and 3 of the clinical trial are used to determine safety, tolerability, and efficacy. The fourth phase of the clinical trial is conducted after approval and serves to collect additional data and information on best use.

Source 1 Author´s Chart

Before a clinical trial can be conducted in humans, a preclinical investigation, which is part of drug research, is carried out to test the toxicity and pharmacology of the drug in question. This is usually done on microorganisms in the form of *in vitro* tests and then later rodents and small animals in *in vivo* tests. After preclinical research and investigations have revealed no or acceptable toxicity and pharmacology, the drug can move on to the various phases of clinical trials.(10) (Figure 1)

At this stage of the process, the sponsors, i.e., the organization or individual overseeing multiple sites where the clinical trial in question is being conducted, have to be involved in the process from this point on. Investigators are medical professionals, who plan and conduct clinical trials. The main link between these two important roles are the CRAs. They are responsible for monitoring written procedures, pre-screening clinical trial sites, reviewing regulatory information, reviewing subject records, and regularly visiting trial sites and logging site visits.

The Clinical trial process is divided into four phases as depicted in Figure 1Generally, the first three phases must be successfully completed for the drug to be considered for marketing authorization (MA) and thus for subsequent supply and sale. Sometimes these phases overlap and take place at staggered times, but generally each phase is successfully completed, and the clinical trial then moves on to the next step.

As shown in Figure 1 in the first phase of clinical trials, the experimental medicinal product and the treatment are tested on a small group of about 20 to 100 people, mainly to assess the safety and tolerability of the drug in humans and to identify possible side effects. The volunteers participating in the first phase of the clinical trial are healthy volunteers to obtain data on the drug without interference with other medicinal products that the volunteers are taking due to their predisposition to another disease.

The second phase of the clinical trial already includes a larger group of patients and is primarily intended to again determine the safety and tolerability of the tested drug. In addition, the efficacy of the drug has to be proven and the safe dosage has to be determined. This particular phase involves 100-500 subjects and can take up to several years to collect all the necessary data and information.

Phase three is the part of a clinical trial in which the drug in question is compared to the gold standard of current treatment and/or to a placebo. This phase is conducted in a patient population of 1000-5000 and has to be multicentered, i.e., involve more than one hospital, clinic or research institution. The purpose is to see how the drug compares to existing treatments and to confirm safety and efficacy. The fourth and final phase of the clinical trial is conducted when the drug is already on the market and is designed to gather even more data and additional information on how best to use the drug.

1.3 European Union and its Committees

At various times throughout history, attempts have been made to unite several areas of the world and create a center of power, alliances, and ideologies. However, many of these attempts failed due to power struggles that eventually led to two World Wars. The economy suffered the consequences of the World Wars and European ideology was lost in the remnants of Europe. After this period, European leaders joined together and pursued the goal of uniting the region with the right methods to end international strife and promote economic stability and social harmony.(14)

In order to ensure these goals in the 1950s, a number of new institutions were established, including the European Commission, the Court of Justice, the Council, and the Assembly, which later became known as the European Parliament. All these institutions formed the foundation for today's EU. After the sudden end of Second World War six countries: Germany, Belgium, France, Netherlands, Italy and Luxembourg came together to from an area of free trade for multiple key resources including coal and steel. With that the European Coals and Steel Community (ECSC) was formed in 1952.(15) Due to the success of this body more alliances and treaties were formed and among them the, European Atomic Energy Community, European Economic Community (EEC) and Economic Monetary Union. These committees became the founding institutions for the international Treaty of Maastricht, where the existing committee consisting of six countries were extended by six additional ones.

The international Treaty of Maastricht, officially known as the Treaty on European Union, was ratified by the heads of the European Community in Maastricht in 1992. The Maastricht Treaty was then implemented in 1993, from which point on the EU was formed. Nevertheless, the EU was not established all at once, but is the result of gradual integration and was then seen as a framework of members for unified security, politics and justice.(16)

The EU has undergone many refinements and expansions, but today the EU consists of twenty-seven member states (MS) and spans the geographical region of Europe. It has increased more than four times compared to its number of starting MS. The main force behind the creation of such an influential union was cooperation and joint management of problems, with political strategies driving this union forward.(16)

The EU is steadily expanding its power by hosting a number of new institutions. Although these have changed from the founding committees established in the 1950s, the main principles aimed at aligning and monitoring economic and political integration have remained the same. The Treaty on European Union provides for seven main institutions: The European Parliament, the European Council, the Council of the European Union, the European Commission, the Court of Justice of the European Union, the European Central Bank, and the Court of Auditors. In general, the number of EU institutions has increased significantly over time, as has the number of EU agencies and advisory bodies.(17)

From the historical development of regulations and guidelines it is obvious that no committee or union can prevent all incidents. Therefore, the focus is on corrective actions, measures and conclusions that can be drawn from the incidents that have occurred. These

incidents are taken as the basis for many legislative reforms and the introduction of laws, policies and regulations. Institutions that help with these matters and whose aim is to harmonize products and standards are, for example, the European Directorate for Quality of Medicines and Healthcare (EDQM). It is responsible for setting common quality standards to control the quality of medicines.

The EU has been at the forefront of every major crisis in the last decade, including the health crisis that required medical and pharmaceutical supplies for therapeutic treatments. On these unique occasions, the EU institutions and their MS seize the opportunity to work together, facilitate care, and leverage their infrastructure of regulatory networks and especially the EMA.(17)

1.4 The European Medicines Agency

One of the most important and influential committees, especially for the health and pharmaceutical industry, is the EMA. It was established in 1995 and its main purpose is to harmonize the existing national regulatory authorities responsible for medicinal and pharmaceutical products for the protection of human and animal health in the EU and the EEA. The EMA seeks to accomplish this objective by ensuring the scientific evaluation, supervision, and control of medicinal and pharmaceutical products for human and veterinary use in the EU.(18)

The EMA is responsible for granting MA in the EU and EEA, which companies can apply for. It is an invaluable part of the drug and therapeutic development process in the EU, as it is involved in several steps throughout the life cycle of a pharmaceutical. The EMA facilitates the development of different types of medicines and ensures access to them for different MS and countries. Finally, it is responsible for informing the public, patients and health professionals.(18)

This authority is important for research and development of medicines, and not only pharmaceutical companies depend on it, but also scientists, patients, everyone working in or involved in healthcare, and healthcare decision-makers need to work closely with the EMA in one way or another. The EMA organization has seven scientific committees and more than 30 working groups, each specializing in a particular area. Their committees and working parties are composed by highly qualified personnel of the different European national authorities.

The committees and working groups are responsible for scientific contributions related to the development of medicinal products and their regulations. They support the agency by

providing scientific advice to companies and institutions, developing guidelines and guidance for the MA of medicinal products, and advocating regulatory harmonization at an international level. The scientific evaluation of medicinal products for human use is carried out by a separate committee, the Committee for Medicinal Products for Human Use (CHMP), which is specifically responsible for this purpose.(19,20)

1.5 The Different Marketing Authorization Application Procedures in the EU

In Europe, it is important that every pharmaceutical product, whether for human or veterinary use, has a valid MA. A valid MA is a prerequisite that the product can be put on the market for sale and distribution. The marketing authorization holder (MAH), often a pharmaceutical company, is accountable for ensuring that the product is marketed in accordance with the regulations and guidelines of the respective MS and that the conditions of MA itself are complied with.(21)

In general, a valid MA must be available for each MS for the MAH to be able to market the drug. For some simplified procedures for the simultaneous granting of MA in several countries, there are community MA for pharmaceuticals which are then valid in all or several EU MS, depending on the market authorization application (MAA) procedure.

For a MAA to be approved, the application dossier must generally contain data suggesting better evidence of the safety, quality, and efficacy of the product. However, depending on the submitted a MAA may also be rejected due to missing or insufficient data. The aim of a MAA is to demonstrate that the benefits outweigh the risks before the product can be placed on the market and sold and dispensed to the public.(20)

A national MA is valid for five years. After this period, the authorization must be reassessed and renewed. The aim of this review is to ensure that the benefits still outweigh the risks and to determine whether additional information on the product has been obtained since the original authorization was granted. After this renewal of the MA, the MA may be valid indefinitely, or the MAH must renew it and repeat the procedure again in five years. (20)

In the EU and EEA there are four different routes to obtaining a MA. The four different MAA procedures are national procedure (NP), centralized procedure (CP), mutual recognition procedure (MRP) and decentralized procedure (DCP). If the product is a new registration and has no MA in any EU country then the MA has the option to choose from NP, CP and DCP, which are further described in Figure 2. If the drug already has a MA in one or more EU MS and wishes to apply for MA in other EU MS, the application procedure is the MRP.

Regardless of the individual MAA route applied for, the approval revolves around a dossier consisting of five modules divided into a common technical document part and a non-common technical document part. The non- common technical document part mainly contains information on regional administrative data and is therefore region specific. The common technical document part summarizes information on the overall quality summary, non-clinical summary, clinical summary, quality, non-clinical study reports and clinical study reports.(22)

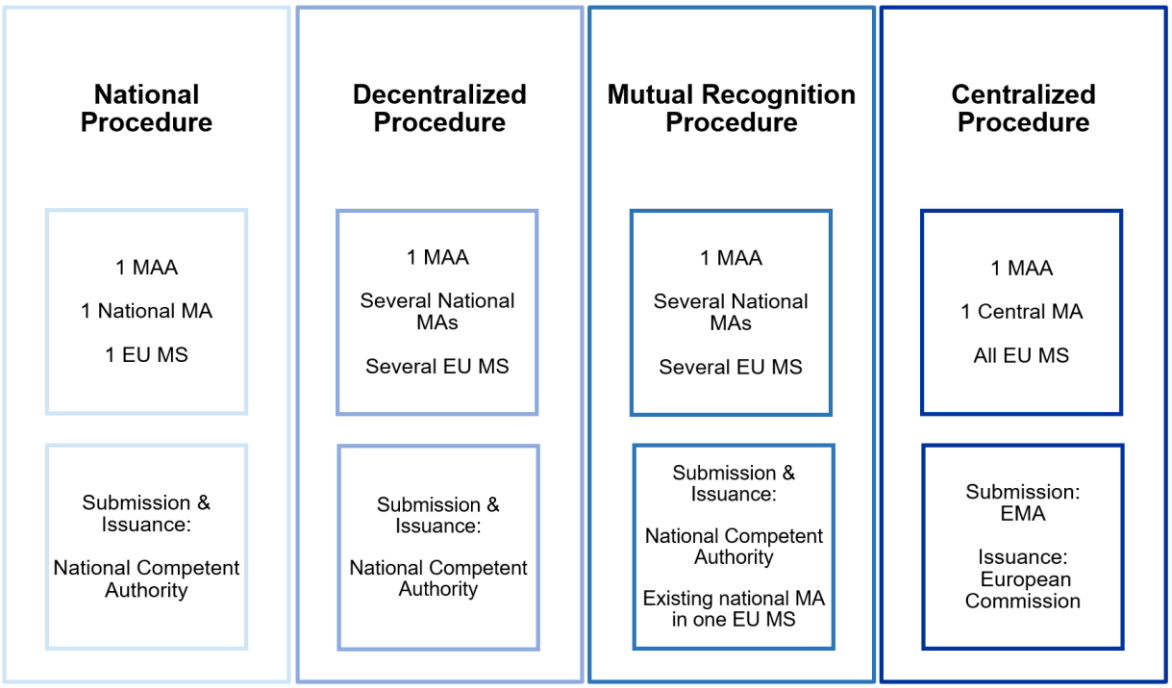

Figure 2 Different Market Authorization Application Procedures in the EU

This figure shows the different MAA procedures in the EU. There are four different routes: national procedure, decentralized procedure, mutual recognition procedure and centralized procedure. For each MAA procedure, it is listed how many MAAs have to be submitted, what kind of MA is issued at the end of the procedure and for how many EU MS it applies. At the end of the figure, the authority to which the MAA must be submitted, and which issues the final approval is listed.

Source 2 Author´s Chart

National Procedure

The NP is an application route chosen when an individual EU MS wants a MA for a specific drug and the MAA goes directly to the national competent authorities (NCAs) and must follow the specific national law of the MS concerned. (23) As an example, it is stated that when applying for a MA via a NP in Austria, the application documents would go to the NCA Austrian Federal Office for Safety in Health Care (BASG) and the legal basis for the application would be anchored in the Austrian Medicines Act (AMG) (24). This procedure is

no longer frequently used nowadays because the disadvantage is that the MA and thus the supply and sale of the drug are only valid and permitted in a single EU MS.

Decentralized Procedure

The DCP is an application procedure in which an MAA is submitted simultaneously in several EU MS. It is a joint procedure in which one country takes the lead as the reference member state (RMS) and the other countries are referred to as concerned member state (CMS). These procedures are concluded with the granting of several national MA by the respective NCA of the countries involved, i.e., the MAs are EU -wide harmonized, but still national authorizations, which are however not necessarily granted at the same time. With the advantage that only one application, i.e., one dossier for the specifically selected countries in which the pharmaceuticals is to be marketed, has to be submitted.(25)

As shown in Figure 2 the assessment of the application is carried out by the NCAs of the RMS and the CMS, with the RMS in fact carrying out the initial assessment of the drug and writing an assessment report. The CMS may then either agree with the assessment report or request further data and/or clarifications. In this case, the dossier must be submitted to the Coordination Group for Mutual Recognition and Decentralized Procedures Human (CMDh).(26)

The CMDh is a coordination group composed of one representative from each EU and EEA MS; the secretariat is provided by the EMA. The group's main task is to examine and coordinate all issues relating to MAAs for pharmaceuticals for human use in two or more MS. The legal basis for this procedure is anchored in Directive 2001/83/EC.(27)

Centralized Procedure

The CP is a MAA route with a centrally authorized final product with a single MA. It is another common procedure where two countries are selected to represent the interests of all MS. One of the countries is then rapporteur and the second country is co-rapporteur, both selected by the EMA.(28)

In this procedure, the pharmaceutical company submits one application to the EMA for MA valid in all EU MS. The scientific dossier is first examined by a joint European committee. This EMA Committee CHMP, then draws up a majority recommendation for or against granting a MA. This recommendation is called a positive or negative opinion.

The final granting of the central MA after a positive opinion is done by the European Commission, based in Brussels. The CP applies equally to all EU MS. This means that market access can take place in all EU MS at the same time. This application procedure is legally anchored in Regulation (EC) No 726/2004.(29).

The main advantage is that a single MAA can be submitted for the entire EU. Nevertheless, not all pharmaceuticals are eligible for the CP, they have to fulfil a number of criteria to be able to apply for a MA under the CP. They must either contain a new active substance not covered by Article 3(1), be a generic medicinal product whose reference product has already been authorized through the CP or be a pediatric medicinal product.(28)

Some MAA for certain pharmaceuticals must be submitted via the CP, as they are classified in categories where the EU has decided that every EU and EEA citizen should have the right and opportunity to access the drug. The categories are medicinal products produced by a biotechnological process, orphan drugs, medicinal products with a new active substance for the following therapeutic indications: cancer, acquired immunodeficiency syndrome, neurodegenerative diseases, diabetes, autoimmune diseases and other immunodeficiencies, and viral diseases.

Mutual Recognition Procedure

The MRP is a MAA route that leads to a MA based on a mutually recognized product. This procedure is followed if the drug in question is already authorized on a national basis in at least one EU MS. The MA can then be expanded and applied to another MS or to several MS. The MS with the existing MA is then the RMS and the other MS are CMS. The CMS can then mutually recognize the MA already existing for the RMS. If a MRP is applied several times, including after a DCP, to include further MS that were not involved in the original MRP, it is called a repeat use procedure.

1.6 Accelerating Clinical Trials in the EU: Publication of 2022-2026 Workplan

To ensure a smooth transition and acceleration of clinical trials in the EU (ACT EU), a four-year workplan covering the period 2022 to 2026 has been established, jointly led by the European Commission, the Heads of Medicines Agencies (HMA) and the EMA. The program is structured in the form of a matrix, with specific areas coordinated by individual parties with corresponding positions within the network. The workplan highlights the main objectives, namely innovation in clinical trials, increased collaboration between stakeholders and competent bodies, and improved methodologies.(30)

ACT EU was introduced in January 2022, together with the new Clinical Trials Regulation (CTR), which came into force at the same time. The main objectives of ACT EU are to change the way clinical trials are designed, initiated, and conducted. By changing the way clinical trials are conducted, the governing bodies aim to put clinical research in the EU at the center and create a hub for the development of safe and highly effective medicines. These goals will ultimately lead to better scientific research and, as a result, a better European healthcare system and better treatment for patients and the public.

The multi-annual workplan is based on the three main pillars of the CTR and aims to support its objectives in terms of protection of study participants, reliability of data and transparency. The ACT EU is not only based on the CTR but has also been prepared on the basis of two other important documents: Strategy of the Network of European Medicines Agencies until 2025 and the European Commission's Pharmaceutical Strategy for Europe.(18,31)

The background for this study was the observation that Europe theoretically has great potential for a strong research sector and resources to conduct clinical trials. 40% of clinical trials are mainly sponsored by academia, which results in clinical trials being relatively uniform and limited to one country. The remaining 60% of clinical trials are sponsored by the pharmaceutical sector. Although both sponsors are different in many ways, both need support and incentives to continue their research and contribute to the economic development of Europe.(32)

The COVID 19 pandemic made it very clear that there is a lack of impact in Europe, considering that the data show that clinical trials are predominantly registered and requested for single members and single states. Although the lack of impact and multistate trials cannot be attributed to a specific cause, it is a combination of factors that make it more difficult to conduct clinical trials in the EU. Initiatives have already been taken to reduce these factors, for example in the form of the CTR and with the ACT EU.

1.7 Objectives of the ACT EU

The workplan has been established six objectives and ten priority actions for 2022-2023. One of the goals is to optimize the EU environment to support and promote clinical research and education. However, patient protection, data reliability and increased transparency remain top priorities. To ensure that the goals of optimizing the EU environment for clinical trials are achieved, four initiatives have been proposed: (A) Strengthening leadership and coordination in the authorization and conduct of clinical trials. (B) Involving ethics committees in the life cycle of clinical trials and medicines to reduce ethical oversight. (C)

Focus on conducting and approving clinical trials in multiple states with a broad geographic capacity and (D) simplifying processes and reducing administrative burden. (32)

ACT EU states also intend to support clinical trials conducted for an unmet medical need in the form of orphan drugs or drugs for rare diseases. They are also focusing on vaccines and therapeutic treatments for world crises by increasing support for these clinical trials and their donors. Another initiative to ensure increase in the above-mentioned therapeutic areas is to enable stakeholders to be patient-centered and develop therapeutic treatments for all patients around the world.

To further support innovation in clinical trials, ACT EU plans to promote highly qualified and expertly coordinated scientific advice. These experts will assist with regulatory approval, MA, and the entire clinical trial life cycle. Furthermore, to secure that the next generation of qualified experts is also available, one of the goals is to promote education, research, and science in the field of drug discovery and development and to inform collaborations, training and initiatives. Finally, the last objective focuses on unification, with an emphasis on calling on MS to remain united as the EU and to have a clear vision on the international stage.

1.8 Priority Actions of the ACT EU

To ensure that these objectives are translated into action and that the ACT EU goals are achieved, the following ten priority actions have been identified for the time period of 2022 to 2023.(32)

Mapping and Governance

The European regulatory organization is complicated and has many working groups with specific focuses. However, the individual responsibilities are sometimes not clearly defined and can therefore lead to confusion and complications. The plan to overcome this problem is to create an overview of the existing initiatives and develop a strategy to streamline strategies and projects and align expert groups. The plan is divided into two phases, with coordination in phase one focusing on the main governance bodies: the Clinical Trial Coordination and Advisory Group (CTAG), the Clinical Trial Coordination Group (CTCG), the Clinical Trial Commission Expert Group (CTEG) and the Good Clinical Practice Inspectors Working Group (GCP IWG). In step two, the other network groups are assessed within the framework of a regulatory network responsibility assignment (RACI) matrix.

Successful Clinical Trials Regulation Implementation

Another priority action focuses on the successful implementation of the new CTR and its objectives. To sufficiently support this project, initiatives have been launched in the form of monthly reports tracking key performance indicators (KPI) metrics on clinical trial activities in Europe. In a following chapter 3.6 Key Performance Indicators January 2023 these reports are further discussed. Regular surveys of sponsors have also been conducted to identify issues and strategies to address them. Another focus of this priority action is to increase academia involvement by encouraging larger, multinational clinical trials sponsored by universities and supporting universities in general.

Multistakeholder Platform

Part of the ACT EU is the creation of a new platform specifically for multi-stakeholders, which include patients and a stakeholder analysis. It is an opportunity to start discussion and have better communication between the individual parties involved in clinical trials.

Good Clinical Practice Modernization

A renewal of the International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use guideline on good clinical practices (GCP) is going to be implemented. The main aim is to enable the modernization of good clinical practices and to focus on adapting the GCP on the diversity of clinical trial types as well as data resources. A smooth transition and implementation are of upmost importance.

Clinical Trials Data Analytics

Over the past years a wealth of data has been collected and the goal is to evaluate that data from clinical trials sponsored by academic, non-profit, European, and international initiatives. The conclusions drawn from this data will hopefully help to identify trends and help supporting evidence-based decision making. Another objective is to increase public access to the gathered data through a dashboard.

Targeted Communication Campaign

Today, there are many different ways of communication and information technology to reach people. The goal is to strive for individual communication channels to personalize information as much as possible. To achieve the best way of sharing information and to reach stakeholders in the best possible way. Therefore, the priority action aims to establish a targeted communication group to connect all stakeholders and actors.

Scientific Advice

At the moment, scientific advice on clinical trials is given by different stakeholders throughout the EU. To further unify processes the main aim is to link experts for advice on clinical trials and their design and methodology.

Methodologies

The way and means of clinical trials are carried out or set up is also changing over time. There are more complex and innovative methodologies available nowadays. To help share best practices the goals is to publish a guidance document to support key methodologies in certain clinical trials, e.g., complex trials.

Clinical Trial Safety

Priority action 9 focuses on developing a safety monitoring for clinical trials and link to the EU4Health Joint Act. Supporting the integration of this safety monitoring into the existing pre-marketing and post-marketing surveillance framework.

Training Curriculum

To further support the European scientific sector the ACT EU plans to promote academic training on drug development and discovery and regulatory sciences in the form of a curriculum for universities and subject matter experts.

The EU ACT should be implemented through a targeted and coordinated approach using existing frameworks and systems. In addition, externally created initiatives, networks and mechanisms should be used. To have more streamlined communication and seamless efforts core secretariat should be established, composed of the European Commission, NCA and the EMA, with the EMA taking the lead. And, as mentioned above, consistent, and continuous monitoring and reporting on priorities and targets.

1.9 Clinical Trials Coordination Group

In October 2004, the HMA established the CTCG following the implementation of the Clinical Trials Directive (CTD) 2001/20/EC earlier that year. Its main objective was to promote a common approach to regulatory requirements specific to clinical trials. The CTCG consisted of members who were professionals from EU or EEA medicines agencies and were instrumental in preparing the publication and implementing the CTR (EU) No. 536/2014. They have assisted MS with the upcoming amendments and contributed to the development of the CTIS.(33)

The CTCG is a group mandated by the HMA to deal with the regulatory aspects of clinical trials with the aim of increasing the attractiveness of conducting clinical trials in the EU. The objectives of the new regulation, namely harmonization, patient protection and increased safety reporting, are in line with the approach and objectives of the CTCG. They want to drive harmonization of all aspects of clinical trials and increase the number of clinical trials and approvals.

They want to focus on a strong clinical research environment that not only allows patients to access new treatments, but also creates jobs, as this is an industry that is vital to the economy. They also want to build a state-of-the-art scientific and technological network that will, in turn, promote and advance clinical research, which can create opportunities for clinical trials.

Their mandate is to support the full and seamless implementation of the CTR and the CTCG would like to focus on the well-established cooperation between the NCA of the different MS. They also want to use this cooperation to advance the harmonization of national decisions on clinical trials. Such networks are intended to promote general communication in order to identify urgent regulatory problems and their causes and to find a solution together. For ethical issues, the CTCG also turns to the European Commission's CTEG and CTAG for additional expertise.(33)

As part of the new workplan, the CTCG also aims to consult and engage with other groups relevant to the specific issues within the European Medicines Regulatory Network (EMRN). The overall aim is to use these links and the different expertise of each group to address crisis situations, particularly in the area of public health and critical trials. The main objective of all these different groups is for experts to work together and be at the forefront of crisis situations to respond quickly and accurately and apply problem-solving methods. Joint training and assessments are a top priority to realize their goals.

2 Methods

The methodology for this master thesis was mainly based on literature research using specific keywords. In addition to the literary part of the work, in which the background of clinical trials, EU, CTD and CTR was established an expert interview was conducted in the empirical part of the work.

For the literature research, websites and publishers' sites were searched for articles, blogs, and documents about clinical trials. Depending on the results of the keyword search, the suggested articles and publications were evaluated for credibility. The criteria used were the number of citations, the source of the publications, and the year of publication to ensure relevance. A large proportion of the results were taken directly from the websites of the authorities: European Union and European Medicines Agency. Some general search engines were also used: google scholar and google. As the new regulation has only recently entered into force (January 2022), not many articles were found, and most publications were blogs and editorials.

The keywords used for the literature search were (independently and in combination with each other): clinical trials, Clinical Trials Regulation, clinical trial guidelines, transition period, Clinical Trials Regulation (EU) No. 536/2014, Clinical Trials Directive 2001/20/EC, CTR, CTD, Regulation vs. Directive, main features, aim, objectives, amendments, 2001, 2004, 2022, January 2022, European Union, EMA, EU committees, clinical trial KPIs, CTCG, ACT EU, workplan 2022-2026; The CTD and CTR were carefully studied, analyzed and compared to each other, focusing specifically on the differences between the two legislations.

The empirical part of the work was carried out based on an expert interview. The basic principles were already presented in the literature research and then confirmed or refuted based on the expert interview. The answers were thus summarized, the results could be recorded, and final findings could be drawn from them.

The selection of the interview partner was crucial for the quality of the information and the significance of the research results. The interviewee was contacted in person and asked for an interview. The interview partner was personally known to the interview leader and the interviewee was briefly informed about the topic of the questions and the duration of the interview before the interview began. The interviewee verbally agreed to the recording of the interview and the purpose of the interview, the master’s thesis, before the questions were

asked. The interview took place in person. The interview was recorded on a telephone and then transcribed.

The interview was a semi-structured interview. An interview guideline was developed, and the interview was based on it. All questions were open questions and prepared by the interviewer. The questionnaire consisted of an introduction, two introductory questions, five key questions and four additional questions. The introduction served to establish the expert status of the interview partner and to establish the connection between the research topics and the role of the respective expert. The introductory questions served to better understand how often the expert deals with the topics related to the master's thesis and research questions, and to better understand what the persons´ activities are. The key questions dealt specifically with the research questions. There were main questions and follow-up questions that emerged only through the conversation.

3 Results

The legal regulation of clinical trials in the EU were not clearly regulated for a long time which led to delays and increased complications throughout the entire process. Therefore, several measurements were launched to harmonize regulations and authorizations concerning clinical trials in the EU. The first attempt was the introduction of the CTD 2001/20/EC in 2001 (34).

3.1 Clinical Trials Directive 2001/20/EC

The CTD 2001/20/EC was the essential document of legislation governing clinical trials in the EU established by the European Parliament and the Council of the European Union. It was adopted on April 4th 2001 and three years later implemented in national regulation on May 1st 2004.(35) In the EU there are different types of legislations e.g.: a regulation is a binding act and has to be implemented within the entire EU. A directive on the other hand is a specific goal that must be reached and achieved by the EU. Because a directive is not binding on its own, every single EU country has to implement it into their national law. Due to the nature of the legislation type, it has to be introduced into the national law in order to be fully legally applicable.(36)

The CTD provided guidance and rules for sponsors, investigators, national authorities, and many others to follow when submitting and conducting a clinical trial. The official title is: “Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the MS relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.”(34)

Before the CTD was implemented, each MS had different protocols, requirements, and processes for clinical trials. The document comprises the life cycle of a clinical trials from application to the final submission of reports. The directive was introduced to simplify this process and harmonize between MS. It was the first practical attempt to harmonize, regulate and simplify the administrative rules for clinical trials across the EU. Nevertheless, the CTD was based on already existing documents and guidelines such as the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects 1964, ICH-GCP guidelines drafted in 1990 by the European Commission.(37,38)

3.2 Problems and Criticism

After its implementation it was observed that the number of clinical trials conducted in the EU decreased. Annually the EMA authorizes approximately 4000 clinical studies conducted in the

EU. However according to the European Commission, from 2007 to 2011, the number of MAs for clinical trials in the EU has decreased by 25%, while prices and waiting times have significantly increased.(39,40)

This significantly severe decline in clinical trials in Europe was a major disadvantage for the EU in terms of remaining competitive and relevant compared to other countries and regions. The reason for the generally reduced number of clinical trials in EU cannot be pinpointed to one specific cause, as it is a multifactorial problem. However, the decline in clinical trial approvals can be attributed to one main reason: the general difficulty in applying for a clinical trial in the EU, due to increased bureaucracy and procedures that make the application difficult and time-consuming, facilitated by the CTD.(40)

This decreasing activity in the field of clinical trials, encouraged the EU Parliament and the Council for Clinical Trials on Medicinal Products for Human Use to implement the new CTR (EU) No.536/2014.(41) This regulation will eventually repeal the CTD after a predefined transition period.

3.3 Transition Period

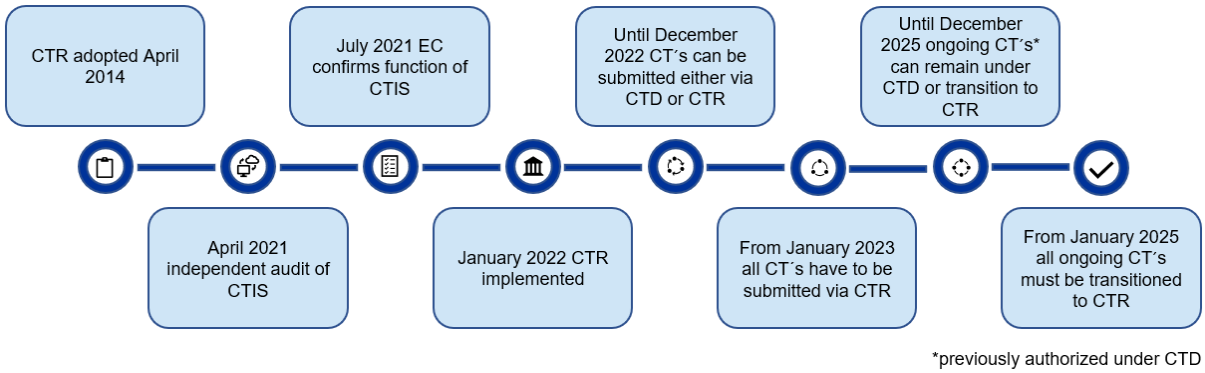

Figure 3 Transition Period Timelines

Describes the proposed timeline for the transition between the CTD and the CTR. It begins with a schematic overview of when the CTR was adopted and then follows with information about the Clinical Trials Information System and its development. The CTR was then implemented in January 2022 and from that point onwards four important milestones were marked.

Source 3 Author´s Chart

In January 2022, the CTR was officially implemented, and a three-year transition period began from that date. The purpose of this transition period is to ensure a smooth transition for sponsors, agencies and everyone affected by the regulatory changes. Since the transition from the old directive to the new regulation has major differences and introduces several new

procedures and systems, it was necessary to allow sufficient time for acclimation to the new regulation.(42)

The above depicted time diagram, Figure 4, shows the timing of the transition period of the new CTR. The CTR was adopted in April 2014 and due to the fact that the majority of changes from the CTR are based on new centralized technical systems, it was crucial to wait with the implementation of the CTR until all necessary and important systems were correctly developed and ready for the end user. In April 2021 the Clinical Trials Information System (CTIS), which is the main system, was independently evaluated in order to ensure proper function. Based on this evaluation, the EMA announced that the system, and therefore the regulation, will enter into force on January 31st, 2023. For further approval, ethics committees (EC) reviewed and confirmed that the CTIS functions in July 2022. In January 2022, the CTR was implemented as announced and the CTIS became operational.

Under the three-year transition plan, sponsors will be able to choose in the first year under which legislation they want to submit a clinical trial application (CTA): either under the CTD and the EudraCT database, or under the new CTR and the corresponding CTIS. As shown in Figure 4, this dual approval period will last until January 2023. After that date, in the second and third years of the transition period, it will be explicitly stated that all new authorization applications must be submitted using the new regulation and CTIS.

Until January 2025 ongoing clinical trials, which have been already authorized via the old CTD and EudraCT database can either remain under the old CTD or already transition to the CTR. After January 2025 all CTAs, ongoing and new, are required to be transitioned and governed by the new CTR.(42)

3.4 Clinical Trials Regulation (EU) No 536/2014

The CTR was adopted in 2014 with the aim of increasing the attractiveness and competitiveness of clinical trials in Europe, thereby creating a more favorable environment with fewer bureaucratic hurdles for entry into clinical trials, from application to reporting up to the completion of the clinical trial. Unlike the CTD adopted in 2001, this legislation has the legal form of a regulation, which is in itself a binding legal act and must be followed and fully applied by the entire EU. This is of importance, as it will ensure that the CTA process as well as the conduction of a clinical trials are identical throughout the EU and are based on the same rules.(43)

In January 2022 the CTR was implemented and has three main objectives: Harmonize procedures such as simplify clinical trials applications especially for multistate clinical trials by providing a single-entry point for submission. Increase patient protection in regards of their safety, rights, dignity and well-being of subjects by simplified safety reporting and ensure the reliability and robustness of all data obtained. Finally, increase transparency through public disclosure of information while ensuring patient data safety.

Since many of the criticisms of the old CTD indicated that there were still too many different procedures in the EU, leading to more bureaucracy and delays, it was necessary to address these issues in the new regulation and focus on greater harmonization within the EU. Another goal of the CTR was to increase confidence in clinical trials and their results. Therefore, ensuring greater transparency at all steps was an important concern, including data protection and the confidentiality of sensitive data and information. Finally, safety reporting should also be facilitated through faster and more reliable communication between sponsors and MS involved in clinical trials.

Clinical Trials Directive		Clinical Trials Regulation
Out of scope: non -interventional trials; definitions for clinical trials, non-interventional trial, sponsor etc.	Scope & Definitions	Entire new class of studies; additional definitions e.g.: low-intervention trials, AMP
European Union Drug Regulating Authorities; Clinical Trials Database (EudraCT)	Centralized Electronic Database	EU portal and database : Clinical Trials Information System (CTIS); EudraVigilance system
SUSAR and DSUR: submitted separately to all CA and ECs; serious breaches: not reported	Safety Reporting	SUSAR and DSUR: EudraVigilance; serious breaches: report within 7 days through CTIS
Application: part 1 collective evaluation; part 2 individual evaluation on national level; NCA and EC approval	Application & Authorization	Single decision from NCA and EC; RMS: responsible for part 1; single entry point for application: CTIS
Only required at the product approval stage	Transparency	Throughout the development process; CT with decision; exception: sensitive patient data
CTA cannot lapse; some timelines not clearly defined e.g.: archiving of the master file	Timelines & Data	Sponsors have 12 days to respond to CTA and queries; master file kept for 25 years CTA can lapse: no recruits after 2 years
Loosely defined criteria and guidelines for informed consent, specific groups and individuals	Patient Protection	Stricter rules: informed consent and participants; coordination and advisory committees and union controls
Lack of guidance for GMP and manufacturing standards	GMP, Manufacturing & Import	More defined regulations; additional certificate if drug does not have MA and is not manufactured in the EU

Table 1 Key Differences between the Clinical Trials Directive and Clinical Trials Regulation

This table summarizes the main differences between the CTD and the CTR. They are divided into eight categories: Scope and Definitions, Centralized Electronic Databases, Safety Reporting, Application and Authorization, Transparency, Deadlines and Data, Patient Protection, GMP, Manufacturing and Importation. The CTD processes relevant to each category are listed on the left-hand side and the corresponding CTR processes on the right-hand side. More detailed information about each category is listed in the chapters below.

Source 4 Author´s Chart

Scope and Definitions

In the CTR a number of new definitions have been added, including a definition for low-intervention studies. The definition describes low-intervention studies as a study that poses minimal additional risk to patients compared to current clinical practice and the investigational product either already has a MA or a scientific publication that supports the safety of the investigational product in one of the affected MS. Placebo medicinal products are excluded from this category and therefore cannot be classified as low-interventional studies.

Even though the addition of new definitions might seem minor, the introduction of low-intervention studies allows an entire new class of studies to be conducted under the CTR. This change does not technically change the scope but has a wider reach. Another important new definition introduced by the CTR are Auxiliary Medicinal Products (AMP). AMPs are those products that are used in the clinical trials and described in the protocol but are not the primary investigational medicinal product. As the name already suggests it aids the main investigational product.

Centralized Electronic Databases

In the following chapter the electronic databases and systems important for the CTR will be explained in more detail. It focuses on the two system comprising the CTIS, which are the EU portal and database (EUPD) and the EudraVigilance (EV).In January 2022 a new centralized electronic database known as CTIS has been introduced, which will mainly simplify and streamline information upload and communication between stakeholders. The CTIS is composed of two modules, the clinical trial module, and the safety module.

EU Portal and Database

The clinical trials module consists of the EUPD, which is managed by the EMA in cooperation with the EU MS and the European Commission. The EU portal is a single-entry point for the submission of clinical trial data and documents concerning EU MS and EEA countries. The database itself contains all the documents and information submitted via the EU portal and therefore all information submitted using the portal will be stored by the database.

The EUPD has functions for workflows, collaboration tools and document management. Three different workspaces, depending on the user will provide specific functions. Sponsors have a sponsor workspace, which is secure and will support the sponsors in preparing and gathering data to submit to the database. Clinical trials authorities will in turn have an authority workspace, which is as well secure and can assist with the overseeing of clinical trials for all MS and the European Commission. Finally, there is a public website for people to access information on clinical trials based in the EU in all their official languages.

The EUPD allows the preparation of a single dossier and the submission of a single trial application in all MS where the trial is carried out, which aims to reduce the bureaucratic burden. One of its goals is to provide a centralized platform for efficient communication between the MS during every step of the clinical trials. The portal should especially be used for the CTA and subsequent authorization and evaluation process.

It provides the ability to store non-essential clinical trial information and make it public and available to the public. The goal is to have system, which are compatible with each other and in turn increase efficiency and decrease technical difficulties. The EUPD, will replace the current database European Union Drug Regulating Authorities Clinical Trials Database (EudraCT).

EudraVigilance

The second module of the CTIS, the safety module consists of the EV, which is a system specifically designed for reporting suspected unexpected serious adverse reactions (SUSAR). EV is not only used for safety reporting, but also for its management and analysis. This system is also managed by the EMA on behalf of the EU regulatory network for synergic use.

The EV can be used for a multitude of procedures including exchange of Individual Case Safety Reports in an electronic form between the EMA, NCAs, MAH and the clinical trials sponsors. Additionally, the system supports early detection and analysis of safety signals, which might occur. Under the new CTR, the reporting using the electronic format is obligatory for sponsors and MAHs.(44)

The system is comprised of a fully automated messaging process which is XML-based and used for safety reporting as well as a pharmacovigilance database. The pharmacovigilance database has query and tracking functions and can therefore be used to have more effective product information for authorized medicines. The EMA and NCAs are responsible for identifying safety signals through regular review and evaluation of EV data.

Safety reporting

A simplification of safety reporting, through the EV was one of the main objectives of the CTR, it was of great importance to streamline this process and ensure that reporting requirements meet the highest standards. Sponsors are responsible for reporting all information concerning safety of clinical trials participants to the EU MS and the EEA throughout the entirety of a clinical trial. The requirements on how those safety reports must be conducted vary depending on the legislation.

Under the CTR, SUSAR reports are submitted separately to all Competent Authorities (CA) and ECs in each of the MS concerned and then assessed individually. The same procedure applies to the Development Safety Update Report (DSUR).

Under the new provisions of the CTR, the procedures for safety reporting have changed as sponsors are required to report SUSARs and DSURs through the EV database. As already mentioned earlier, the database is managed by the EMA, who will also forward the electronically generated reports to all MS concerned. Once the MS have access to the SUSAR and DSUR safety reports the evaluation and assessment process can start. This simplifies the process compared to the CTD, as mentioned above.

In some countries, sponsors are additionally required to report SUSARs to their national EC, which must be clearly stated in the respective national legislation. If SUSAR reports cannot be reported through the EV database due to lack of resources, sponsors are advised to report SUSARs directly to the NCA of the MS in which they occurred. The NCA concerned is in turn responsible for reporting the SUSAR through EV. This procedure must be agreed to in advance by the NCAs.(23)

In addition, under the old CTD, serious breaches of the protocol did not have to be reported. Under the new CTR, serious breaches must be reported within seven days, as must all unexpected events that may affect the risk-benefit balance. In addition, urgent safety measures, i.e., measures taken to protect subjects in a clinical trial due to an unexpected event, must be reported. The unexpected event, urgent safety measures, serious breaches, and annual safety reports must be reported through the CTIS.

Application and Authorization

As the CTR aims to harmonize procedures, the legislation provides for a coordinated assessment between the RMS and the other MS. This provision aims to provide a single joint decision on the approval of clinical trials.

Nevertheless, the evaluation is not fully coherent, as the evaluation of the CTA dossier is divided into two separate sections, referred to as Part I of the dossier and Part II of the CTA Dossier. The assessment is done separately for both parts. Part I described the scientific section of the dossier and includes information about labelling requirements, Investigational Brochure (IB), Investigational Medicinal Product Dossier (IMPD), level of intervention, detailed information about manufacturing and importing of the drug in question and the risk-benefit-ratio for subjects.

Part II of the CTA dossier constitutes for the ethical section, which covers the national concerns of each MS involved. It includes subject recruitment, damage compensation agreements, informed consent regulations, data protection and aptness of sponsors as well as the trials

site. As mentioned above, the evaluation of the MA is performed separately for both parts of the CTA dossier, with the evaluation of Part I being performed collectively by all CMS. Part II of the dossier is evaluated individually by each MS, as it is evaluated at national level.

The evaluation is organized by the RMS identified by a sponsor prior to the evaluation process. The RMS is also approved in advance by all MS concerned. The RMS has a period of six days to inform the sponsors and the other MS concerned that it has assumed the role of RMS. The RMS has a major responsibility as it drives the Part I evaluation and assessment process, but also moderates the discussions and is responsible for preparing the first draft of the final assessment report. In addition, the decision of the RMS has more impact as a negative decision on Part I of the CTA dossier is automatically rejected by all MS.

The CTR also sets clear deadlines and timeframes for each procedure, as well as for the evaluation of CTA. Further extension of these deadlines may be granted if necessary to obtain additional information for an adequate evaluation. The timeframe for the evaluation of Part I and Part II of the CTA dossier is set at 45 days, with a maximum additional period of 31 days known as clock stop. The clock stop is a period during which the assessment of application documents is officially stopped and during which applicants have a certain amount of time to answer the regulators' questions. After the applicants' answers are submitted to the authorities, the clock continues to run.(45)

After completing Part I and Part II of the CTA dossier, MS have 5 days to issue their decision officially. If under any circumstances a MS does not respond within a specific timeframe, a tacit approval can be issued.

If a MS disagrees with the opinion of the other MS, it may issue a rejection, but one of the following cases must apply: the clinical trial in question will provide an inferior treatment to the involved subjects compares to the standard treatment in that MS, infringement of their national law, safety concerns for the subjects, or concerns about the robustness and reliability of the produced data.

The CTA can be declined if the opinion on Part I and or Part II of the CTA Dossier is negative, or if the national EC published a negative opinion for a MS. A CTA can also expire in a MS according to the CTR, if no subject has been recruited for the specific clinical trial within two years of time.

Transparency

Previously, transparency was only required at the product approval stage, with the new regulation, data has to be published and made available for the general public throughout the development process. Making more data public and accessible to the general public are measures to increase public confidence in clinical trials and their results and data. The CTR states that the EU database should generally be accessible to the public, with the exception of some sensitive documents: protection of personal data, protection of confidential commercial information, protection of confidential communications between MS related to the evaluation of dossiers, provision of constructive oversight of clinical trials. These documents were selected to protect personal information about individuals involved in clinical trials in order to protect their right to privacy and medical information.

In addition, the regulation stipulates that only data and documents related to clinical trials for which a decision has been made must be published. Once the decision is made, the information must be published at the first possible opportunity, except for the exceptions already mentioned above. In addition, there are also certain data and/or documents whose publication may be deferred by the sponsor, but which must still be published: The IMPD quality section of the dossier, draft assessment reports, names of experts, personal information on sponsor personnel, personal information on the MAH, financial arrangements between the sponsor and the research institution, SUSARs, and annual safety reports.

Even though the general aim is to overall increase transparency and the public access data, it is important to have a balance between the subjects and patients' privacy and the doctors, publics and general medical fields interest in the clinical trials and it´s progress. As well as the facts that developers, researchers and companies want to protect their investment and work.

Timelines and Data

The CTR brought many new changes, as many new processes and workflows were introduced, and with them more timelines and deadlines. Some of these have already been mentioned in the relevant sections. Others include a new deadline whereby sponsors have 12 calendar days maximum to respond to application requests or queries. By default, if the sponsor does not respond appropriately within 12 days, the CTA lapses.

Under the old legislation, the CTD, a CTA could not lapse. Under the new legislation, the application can actually lapse if no subjects are recruited within the first two years of the positive decision on the CTA. Another new deadline added to the CTR is that sponsors must report serious events within 7 days through the CTIS. Before the 2022 regulation went into

effect, there was no timeframe for how long a clinical trial master file had to be kept. The CTR clearly states that the master file of each clinical trial must be kept for 25 years.

Not only have new deadlines been added, but more data must be submitted as certain documents and reports under the CTR. As mentioned above, under the CTR it was not necessary to report serious breaches, however now serious breaches must be reported within seven days through CTIS. Some additional documents also have to be submitted according to the manufacturing guidelines, depending on the authorization status of the Investigational Medicinal Product.

Patient Protection

Under the new CTR, among other things, the guidelines and criteria for informed consent have been changed. This strengthened regulation of informed consent will subsequently increase patient protection. The CTR established more detailed guidelines for the following groups: comprehensive consent, simplified consent for cluster trials, and emergency consent for clinical trials.

Certain groups of individuals are also better protected as their rights have been more clearly defined. These groups include minors, persons incapable of giving consent, pregnant or breastfeeding women, and vulnerable persons. In addition, a Coordination and Advisory Committee specifically for clinical trials has been established to serve as a forum for the exchange of best practices and knowledge among MS. Union-wide controls have been established in MS and third countries where clinical trials are conducted to ensure that the clinical trial is conducted in accordance with the rules and laws of the CTR and is complied with and enforced accordingly.

GMP, Manufacturing and Import

Good Manufacturing Practice (GMP) regulations are very important for the manufacture and quality of the drug product. The CTD did not define GMP at all and lacked guidance on the subject. The CTR has changed this and introduced a section on GMP, which states that documentation on GMP must follow certain rules. No additional documentation on GMP needs to be submitted if the investigational product has not been modified, regardless of whether the manufacturing of the investigational product takes place in the EU or not.

If the investigational product in question does not have a MA, a MA from a third country (part of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH) and is not manufactured in the EU, additional

documentation is required. The additional documentation must be a certificate stating that the manufacturing process complies with GMP, and standards established in the EU. This certification must be signed off by the qualified person. In certain circumstances, mutual recognition agreements can be made, which is the only permissible scenario in which GMP guidelines do not have to fully comply with GMP requirements.

3.5 Experience Report from Karin Gansch

Karin Gansch has been employed by MSD Austria for more than 20 years and currently works as Senior Clinical Operations Manager as well as country point of contact for the EU CTR. In her daily work she has regular contact with the new CTR and is also responsible for the transition of various studies to the CTR as well as for the submission of new clinical trials under the CTR. Enclosed are the main points discussed with Karin Gansch. The full transcript of the interview can be found within the annex.

Based on Karin Gansch's personal experience, the main goal of the EU CTR was harmonization, but she underlines that in her opinion this has not been achieved, as many countries have their own local guidelines, which contradict the CTR. She even points out that at the time of the interview, Austria had still not published any current guidelines valid for the CTA process under the CTR.

The most important change in the CTR is the introduction that a CTA only requires one submission for the first part of the dossier, which is done centrally. She points out that this change will reduce the workload for Global Clinical Trials Operations (GCTO). Another relief, is that only a second part of the dossier must be submitted instead of separate submissions for NCA and EC. Since the CTA is done centrally via the EU portal, the countries have to follow the Eurasia Group in terms of submission timelines and therefore cannot decide independently when to submit. Therefore, there is no direct contact with the health authorities or EC.

When asked if there are any topics that were not addressed in the new CTR, Karin Gansch replied that there is still a lack of experience to fully answer this question. However, one thing she already misses is the function on CTIS to print out CTA documents instead of the current option of only taking screenshots. In general, Karin Gansch also points out that she cannot yet conclusively judge whether the CTR has improved or simplified procedures, as she still has to get used to the new processes and protocols. However, she says that the first step of the transition timeline was indeed sufficient, as the introduction of the CTR was known years before the actual introduction due to the development of electronic systems. Karin Gansch said she expects many additions to the electronic databases and online tools in the coming years.

Finally, one of her strongest arguments was that she and her team working with the CTR depend on national authorities in EU countries aligning and supporting the CTR, and she currently misses this especially in Austria. Austria still has the same requirements as the CTD, and this means that the whole project, which aimed at harmonization, is being called into question.

3.6 Key Performance Indicators January 2023

Following the fact that the CTR repeals the CTD, the European Commission has been publishing monthly impact reports since May 2022. These reports set out the KPIs for scientific and technological progress in the implementation of the CTR. This initiative is part of the ACT-EU program and one of its priority actions, and is a joint effort between the European Commission, the HMA, the CTCG and the EMA.(46)

The data and statistics presented in this chapter are the January 2023 KPI metrics reports published on March 7th, 2023, on the EMA website and include CTA data on two databases. The databases included in the report are the CTIS, which represents the CTA under the CTR, and the EudraCT, which includes data from the CTA under the old CTD. As the CTR and CTIS were launched on January 31st, 2022, these KPI metrics provide an overview of the past year.

Figure 4 below shows the cumulative number of CTAs submitted through the CTIS since the introduction of the CTR in January 2022. Figure 4 not only shows the number of initial CTAs, but also includes data on CTAs that were resubmitted due to modifications or CTAs where additional MS were added to existing CTAs. A total of 793 CTAs were entered into the CTIS from January 2022 to January 2023. In this one year, 629 CTAs were initial applications, 141 of them were substantial modifications and 23 of the CTAs were due to the subsequent addition of new MS.

Figure 4 clearly shows that the total number of CTAs under the CTR, and therefore also in the CTIS, has increased significantly over the last 12 months. In February 2022, the number of CTAs in the CTIS was nine, and just six months after the launch of the CTIS, in July 2022, the number of CTAs was already 64, an increase of more than seven times. The number of CTA peaks in November 2022 with 99 initial CTAs, 34 substantial modifications and 3 subsequent additions of MS, bringing the total to 136 CTAs. Since then, the number of CTAs has slightly decreased and one year after the introduction of CTIS and CTR, 110 CTAs were submitted using CTIS. This statistical analysis shows the positive progress of the CTR and that the number of CTAs has increased by 120% in the last 12 months.

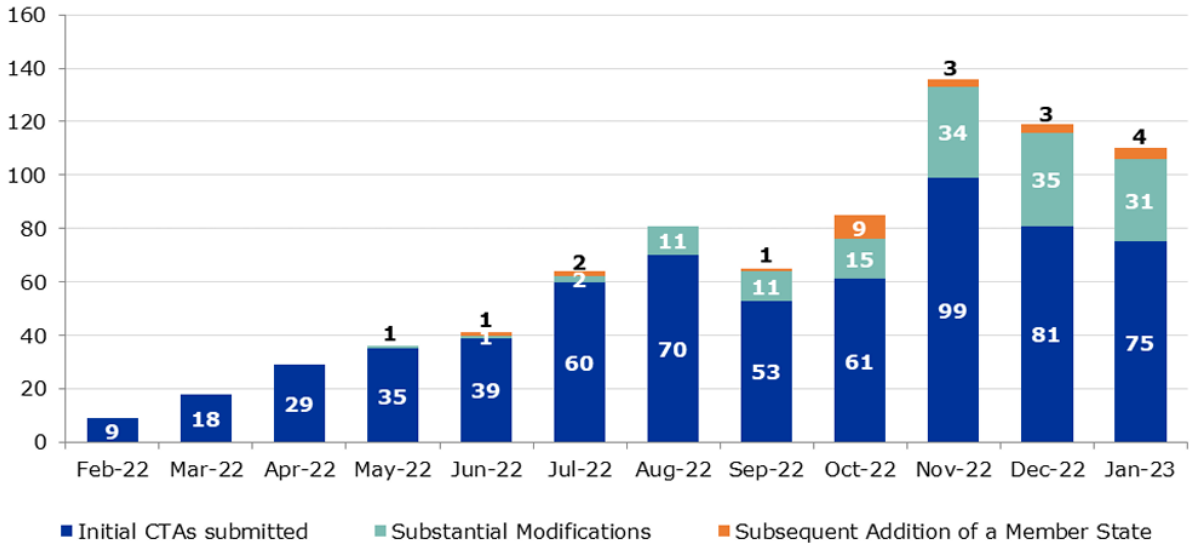

Figure 4 Clinical Trials Application in CTIS per Month

Statistical analysis of the number of CTAs submitted via the CTIS from February 2022 to January 2023. Initial CTAs are shown in blue, substantial modifications in green and additions of MS in orange. The number of CTAs increases gradually over the months until it peaks in November 2022 with 99 initial CTAs, 34 substantial modifications and 3 subsequent additions of MS. The totals then decrease slightly in December 2022 and January 2023.

Source 5 (46)

Figure 5 below shows the number of CTAs submitted via the EudraCT, i.e., under the CTD, from 31 January 2022 to January 2023. The total number of CTAs submitted by MS during this period was 2231 The reason for this low number compared to the following 11 months is that the data is displayed from 31 January and therefore only one day of submissions was included in the statistics.

In the following months from February 2022 to June 2022, the average number of CTAs is 188 until there is a peak of 213 CTAs in July 2022. After that, the following 5 months between August 2022 and December 2022 are constant, with an average of 161 CTAs per month. This is finally followed by another peak in January 2023 with 259 CTAs submitted by MS in EudraCT as the KPI metrics were analyzed.

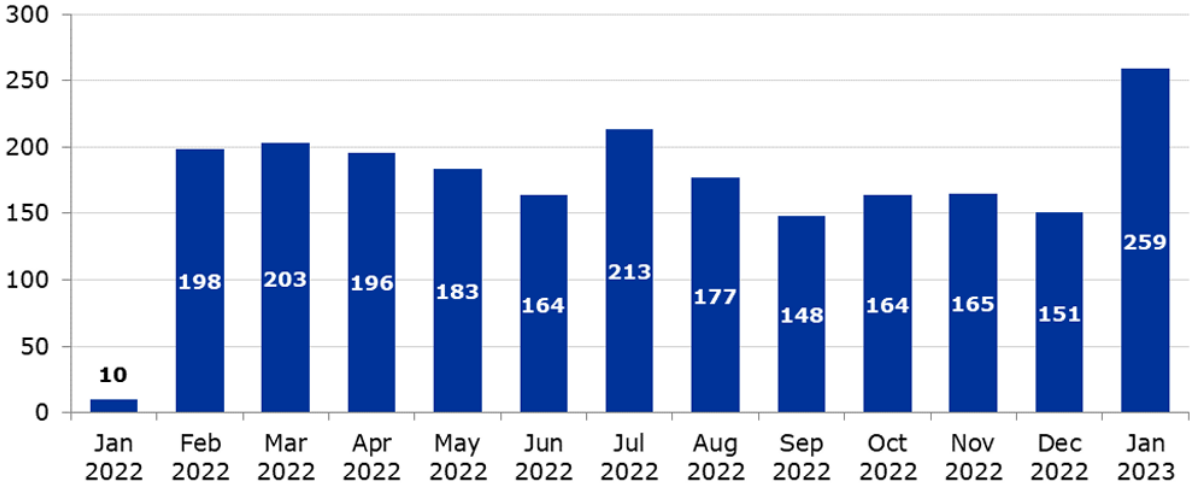

Figure 5 Clinical Trials Applications Uploaded in EudraCT by Member Sates per Month

Statistical analysis of the number of CTAs submitted by MS via EudraCT from January 2022 to January 2023. In January 2022, the number of CTAs submitted was 10. Thereafter, the number of CTAs remains constant over the next five months until there is a peak in July 2022 with 213 CTAs. After that, the number of CTAs remains constant again for five months before reaching another peak in January 2023 with 259 CTAs.

Source 6 (46)

Figure 6 shows the number of CTs uploaded to CTIS in the last 12 months and for which at least one decision has been made by a MSC in CTIS. At the end of January 2023, there are a total of 251 CTs with a decision in the CTIS in the period from 31 January 2022 to January 2023. They categorized as: authorized, authorized with conditions or not authorized. Six of the previously authorized CTs were reported as closed and thus terminated.

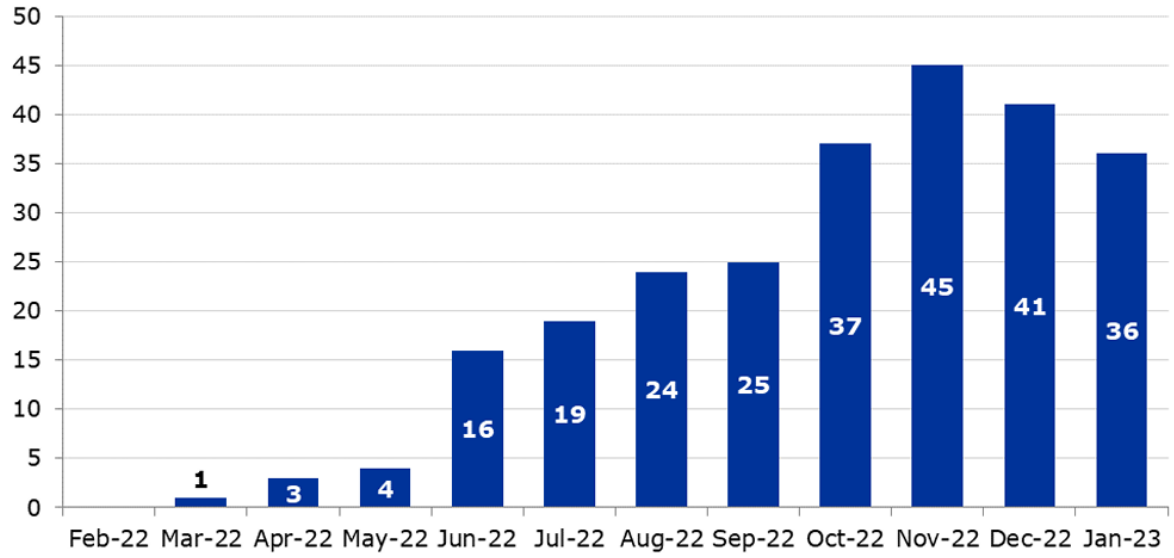

Figure 6 Clinical Trials with a Decision in CTIS per month

Shows the number of clinical trials in the CTIS per month for which at least one decision was made by a MSC. The trend of the graph is a steady increase from March 2022 to November 2022, followed by a decrease in CTs in December and January 2022.

Source 7 (46)

Figure 7 below shows the number of clinical trials uploaded in EudraCT from the first MS that received a decision from its NCA and an opinion from its EC. These CTs are presented as individual clinical trial protocols and are data from 31 January 2022 to January 2023.

Similar to Figure 5, the data for January 2022 only refers to CTs uploaded on 31 January, which explains why the number is 7. In the following months, there is an increase in February and March 2022 with an average of 127 CTs. There is a decrease in April, May, and June 2022 as the average drops to 93 CTs per month.

After peaking in July 2022 at 129 CTs, the number of CTs decreases steadily over the next 5 months until 5 CTs are recorded in EudraCT in January 2023. The cumulative total number of CTs is 930 in January 2023, and this number may increase with additional information uploaded to EudraCT by MS.

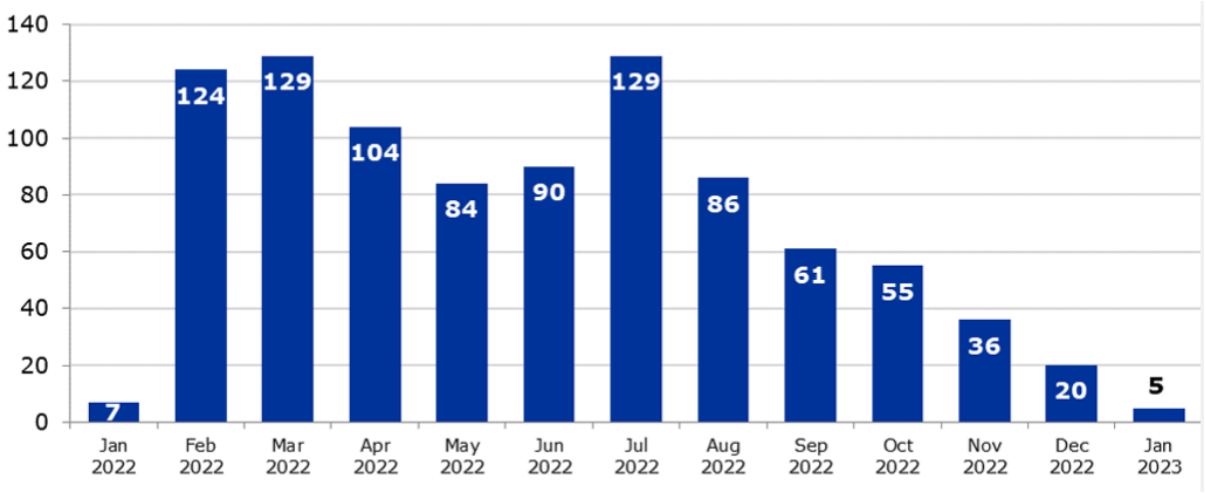

Figure 7 Clinical Trials in EudraCT per month

Shows the number of CTs with an NCA decision as well as an EC opinion in EudraCT. The trend of the graph is that the numbers fluctuate frequently, with two peaks at 129 CTs, followed by a steady decline until January 2023.

Source 8 (46)

4 Discussion and Conclusion

It is evident that the two documents CTD and CTR have some similarities, as the CTR is based on the CTD. Nevertheless, they differ fundamentally in their legislative character, in the length of the document and in the scope of their content. The CTR contains extensive supplements to each chapter and paragraph of the document. As mentioned above, the main differences can be summarized in eight categories: scope and definitions, centralized electronic databases, safety reporting, application and authorization, transparency, timelines and data, patient protection, GMP, manufacturing and import.

In some of these categories, there are only minor additions where the changes are important but do not have a serious impact, nevertheless are essential in order to fulfill the aim of CTR. For example, stricter guidelines and deadlines are introduced to improve patient protection, and certain data must be published and made available to the public to increase transparency. Specific breaches and documents have to be reported in a predefined timeline.

In other categories, such as the centralized electronic databases and the application and authorization process, there is a completely new structure and process that will massively change the way things are done and thus have a significant impact on the clinical trials sector. The introduction and implementation of the CTIS, which is divided into EUPD and EV, is a massive undertaking, as it is a completely new system. The effort that needs to be put in to familiarize oneself with the system and learn all its applications is enormous, and many of the CTR changes are linked in one way or another to the EUPD or the EV and are therefore essential to the whole legislation.

It is also clear from the interview that the latter two categories are at the main topics of the CTR and are essential for its proper implementation. However, as they involve the biggest changes, they are also the ones that are not yet fully integrated and could potentially be a barrier. For a seamless implementation, it is crucial that national authorities as well as national legislation are aligned with the CTR to make full use of it. Otherwise, there will be inconsistent procedures that do not comply with national law and ultimately lead to more confusion and unharmonized procedures.

In summary, it is difficult to outline all the changes introduced by the new regulation as they are very extensive and diverse. Therefore, the impact of this legislation will need to be monitored very closely after the end of the transition period to ensure that the number of clinical trials in the EU increases and that the objectives of the CTR are achieved.

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6 Annex

6.1 Interview Questionnaire

1. Can you please introduce yourself and tell us what your role is at MSD?
2. What are your points of contact with the CTR in your daily work?
    - What was your experience working with it?
3. In your opinion what is the main aim of the new CTR?
4. Can you briefly summarize the main changes that you think will result from the CTR compared to the CTD?
    - What aspect of clinical trials will be impacted the most because of CTR?
    - Are there any topics/points that were not addressed at all or not enough in your opinion?
5. Do you think the overall procedures of Clinical trials have been improved or simplified because of the new CTR?
6. What is your opinion about the transition timeline?
    - Was it enough time for you to adjust to the new regulation?
7. What is the future of CT legislations in your opinion?

6.2 Transcribed Interview with Karin Gansch dated February 2nd 2023

I: Hello thank you for taking the time to do an interview with me for my master thesis on the clinical trial regulations. Can you please introduce yourself and tell us your role at MSD?

B: Yeah, my name is Karin Gansch. I am at MSD since ’99 and my current role is senior com.

I: Thank you, so what are your points of contact with the clinical trials regulation in your daily work?

B: Uhh… at the moment I am also the CPOC for EU CTR and also the change managements I’m responsible for this part. Uhh we are doing different studies in transition phase at GCTO and also have already submitted two initial EU CTR submissions.

I: Okay, thank you. So in your opinion, what is the main aim of the new clinical trial regulation?

B: The main aim … it should be harmonization. (**I:** laughs) But to be honest, this is not true, because a lot of countries have their own local guidelines implemented (**I:** Hmm) and for Austria its not yet official, but we have seen a draft what should be implemented. But its not posted yet…

I: …its not posted yet. So you think harmonization was the main aim, but the goal has not been achieved with the regulation?

B: Correct.

I: Okay, thank you. So, then can you shortly summarize, for you, what the most important changes were resulting from the regulation? Compared to the old directive?

B: The main, important thing for us would be that only for one submission is required for part one. (**I:** Hmm) It would the same like for health authority. This also would reduce the work in the local GCTO. And for part two documents, like similar for ethics committee, ah, this is really, ah, for us a new strategy. Ah because we cannot decide independently at which date we would submit. So we always have to look what the Eurasia group – this is the main contact for us for the submission. They are coordinating the submission timelines. And this is a point what we cannot influence and this is also a little bit stressful for our COM, CRAs and for the sites. And there is no direct contact with the health authority and ethics committee. And also in Austria we do not know who is the current EC portal contact for each submission. But in case we would need the contact or to know which EC is responsible for transition or initial submission, ah, we can contact the health authority. Their contact person is Stefan Strasser. And he can provide us a name of the ethics committee. We already used these contacts.

I: Okay. But there is no person to contact for the, for the portal itself?

B: No. Because the EC portal is not yet working.

I: Aha. Okay, that is …

B: … the link is not yet working and this was announced. It can be found on health authority, on the BASG page in intranet. They announced. They posted it on thirtyfirst of January. Ah. Important links and guidance. This is also posted and also with the EC portal when approximately it will be working.

I: Okay, so the, that the application, that there's only one – was heißt nochmal Einreichung? … (**B:** …submission) one submission for part one is in your opinion the post important change that happened?

B: Yes because. This would reduce in future our work. But for EC part we will see how it will work.

I: Okay, thank you. So, yeah. Are there, in your opinion, any topics or points that were not addressed at all, or not enough, in the CTR?

B: Hmm… yehh…. We do not have enough experience, to be honest. But maybe what we can see on the CTIS portal are you cannot really print like a submission documents directly from CTIS. There are only screenshots. So its not so easy for filing at the sites the kind of cover letter with the overview with all the documents. What we can see at the moment on the CTIS portal.

I: Okay, something for the future to improve. Okay, so, just a general question: do you think the overall procedure of clinical trials, like the submission and application, has improved or simplified because of the new clinical trial regulation?

B: To be honest I don't know because of course its not routine yet. But in Austria we ah just tried to prepare a kind of templates what we have to submit now to the portal with the new documents and to simplify the process. But at the moment, so, we just started last year. (**I:**

Yeah, that's true). And the documents always also changing for us. The guidelines. (**I:** Yeah, it's a million documents). Weekly or monthly at least we have new updates.

I: Okay, hard to keep up, I can imagine.

B: Correct.

I: Okay, uhm, so what is then your opinion on the transition timeline they proposed for transitioning from the guideline, ah, from the directive to the regulation?

B: Ah, you mean from submission to the approval? (**I:** No.) For the country or ….?

I: No, I mean the transition timeline they had from implementing the regulation?

B: Ahh, it was quite a long time period. (**I:** Yeah?) Because it was not working. The portal at the beginning.

I: So, what do you think they could have done better?

B: Because the first announcement was, I think, in 2017. That it will be implemented an d then it took until 2022. That is quite a long time. I don't know, its, ahm, a think, the problem was also a technical issue. And they are still having a lot of technical issues with the system. The down times are not working. So the technical issues are the main problem for the tool. For all stakeholders.

I: And from the implementation timeline it was, the implementation was forced into, it was implemented in January 2022. And I think from January 2023 you now have to use the CTR. Do you think this one year was enough time? Or… ?

B: Yes, yes I think. Because if you prolong it always, then it will never be implemented. (**I:** Yeah.) I think it was enough time.

I: What is then, in your opinion the future of the clinical trial regulation? Will there be another revision? You already mentioned that there might be something in the works?

B: I know that they will always implement some technical tools to improve it. And also requests from, ah, for example for academic studies. They already have implemented tools, that a sponsor, for example, the marketing authorization holder for products can also submit information in case academic studies are using it. The product. And they are not allowed to have all the information. So both parties can submit. So, they always updating the system.

I: Okay, so a lot of technical (**B:** Yes.) additions to the system. Additions. And from the legislation part? Do you think there is going to be a new one? Or is this going to be … (**B:** This I don't know). You don't know.

B: I have no insight.

I: Okay.

B: I have no insight.

I: Okay, so just as the final question: your overall opinion. About everything. About the process, the implementation, how it is working now, what you're working with daily. Are you happy with he new regulation? Or …?

B: I try to be neutral. (**I:** Okay). Because its new, everybody is excited and busy, yeah. I try not to see the negative aspects. Because as already discussed, for part one, this is not longer our responsibility. This will be done centralized. And in country we are only responsible for party two. And, ah, for us its really important that all the national requirements, wishes, however they call it, that they are posted. And they are valid for all stakeholders. But what I can see, it looks like that in Austria, they still wants to see the same requirements as for the directive. And this is not really good I would say.

I: That was not the initial goal.

B: Correct. There is no harmonization. If all countries have their own guidance or wishes.

I: It should be worked on that, to actually harmonize the, the procedure. Well, yeah, thank you for taking your time and answering my questions. Thank you.