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An ESMO-EORTC position paper on the EU Clinical Trials Regulation and EMA's Transparency Policy: Making European research more competitive again

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Abstract

Background

The Clinical Trials Regulation (CTR) (EU No 536/2014) repealing the EU Clinical Trials Directive (2001/20/EC) is expected to be implemented in all EU countries in 2016.

The European Medicines Agency (EMA) policy on publication of clinical data for medicinal products for human use "Policy 0070" became operative as of 1 January 2015.

Content

The CTR represents an opportunity to overcome an era when European clinical oncologic research has become less competitive due to bureaucratic restraints. The main achievements are:

- A single EU clinical trials portal created by EMA where all communications between stakeholders take place, especially between EU Member States and sponsors
- A new category of "low-intervention clinical trials" with simplified risk-proportional monitoring
- A commitment by the EU and EMA to data transparency because data in the clinical trials portal will be publicly available
- Increased access to data through EMA Policy 0070 which protects patient confidentiality and provides easier data access by researchers/trialists to perform analyses independent of the sponsor; once a drug has entered the EMA approval process outside of the CTR frame it will generally not be protected any longer as commercially confidential information and this should become valid likewise for the preponderant situation where EMA is executing CTR
- "One-time consent" from patients for use of their data and tissue beyond the clinical trial

Conclusions

The success of the CTR depends on the national players because many important aspects still require national implementation. Stakeholders, including academic trialists, will need to learn how to use the new EU portal system. ESMO and EORTC will support trialists by providing them with information about the CTR and by educating their members on how to use the new EU portal. The one-time consent provision, a key feature of the CTR, should be paralleled in the new EU General Data Protection Regulation.

Key Words:

Clinical Trials Regulation (CTR), European Medicines Agency (EMA), central EU portal, low-intervention clinical trial, data transparency, one-time consent

Key Message (396 characters)

The Clinical Trials Regulation (CTR) intends to make clinical research in Europe more competitive. Among the most important features are the creation of a central portal by the EMA, the introduction of “low-intervention clinical trials”, EMA’s dedication to transparency, and the “one-time consent” for use of patient data and tissue. In a joint effort, ESMO and EORTC will provide information on the CTR to support harmonised national implementation across Europe.

Introduction

The European Society for Medical Oncology (ESMO) and the European Organization for Research and Treatment of Cancer (EORTC) welcome the adoption of the Clinical Trials Regulation (CTR) by the European Union (EU) as a clear signal that the EU supports research while fully respecting patients' rights and safeguards. The CTR is a step in the right direction to correct years of serious challenges faced by researchers when performing clinical trials. However, there are still many unresolved issues that may yet take research efforts down the wrong path. In this editorial, the pros and cons of several major features of the Regulation are analysed from the standpoint of academia and are outlined in a systematic way, thereby recognising the achievements of the CTR, highlighting ongoing or newly created challenges, and offering proposals for solutions.

Background

The European CTR [1] was adopted by the Council of the EU and the European Parliament and published in the official journal of the EU on 27th of May 2014. It is currently in the early stages of implementation and is likely to become applicable in 2016. It repeals Directive 2001/20/EC, which resulted in loss of competitiveness for European trialists and a reduction in trials of up to 25 per cent since 2007 [2] [3] due to, among other reasons, an excess of bureaucratic requirements which were especially challenging for non-commercial cancer clinical trials.

Achievements – Challenges – Solutions

Single registration portal

Achievement: The CTR harmonises the rules for setting up and conducting clinical trials. It offers the use of a single, free-of-charge online portal, administered by the European Medicines Agency (EMA), as an exclusive platform for stakeholder interaction in the clinical trial process, mainly for submission and maintenance of clinical trial applications and authorisations within the EU.

Challenges: The CTR will not take effect until the portal is fully operational, i.e. not before June 2016. We envisage three essential challenges. First, the portal must be as user-friendly as possible and take into account different types of users. Second, the portal should facilitate the work of investigators running academic trials who rarely have robust administrative support yet will now be encouraged to submit all information simultaneously. Information submitted should be kept to the strict minimum, otherwise it will delay submission even longer than current practice because

initiating sites need time to collect all documents especially for international trials. Third, the assessment process requires a strict workflow procedure and tight timelines, and should support stakeholders with appropriate automatic reminders and deadline warning programmed into the system.

Solution: A user-friendly portal that takes into consideration the needs of all possible stakeholders is key, especially for academia. EORTC is one of the academic partners in the EMA Multi-stakeholder Working Group and is dedicated to providing input in order to make the portal as user-friendly as possible.

New category of studies

Achievement: The CTR also introduces a new category of studies: the "**low-intervention clinical trial"** with simplified, risk-proportional monitoring and safety reporting as estimated by the trial sponsor. This should present major savings on costs and a more adequate procedure for many, while also avoiding the often daunting bureaucratic minutiae of prescriptive detail.

Challenge: The concept of a low-intervention clinical trial has been watered down with the removal of simplified assessment procedures.

Solutions: A minimized variant, the central monitoring, i.e. automatic data check using statistical properties of the collected data, that has been shown to be an efficient (superior and cheap) substitute to on-site monitoring, should be considered as alternative. In addition, we invite EU Member States to consider providing at least insurance coverage equal to the coverage for standard treatment as part of the national implementation process.

Data transparency

Achievement: Transparency of clinical trial data is a key issue for regulators and governments, and EMA is confronted therewith while holding two from each other independent positions. Transparency was described by the then EMA's Executive Director, Guido Rasi, as an essential element to "rebuild trust and confidence in the whole system" [4]. In principle, since 2012, EMA has been willing to share full raw data sets, including individual patient data once anonymised. This "Policy 0070" applies to data of clinical trials that are part of the marketing authorisation (MA) applications for medicines that have been or will be authorised by EMA beyond the scope of the CTR, e.g. trials that are conducted outside of the EU, but submitted to EMA for MA in Europe. Whether this will apply also for trials registered via the EU portal based on the CTR may depend on the result of a recent public consultation of the concerned stakeholders by EMA.

Challenge: At first glance, EMA has to be applauded for removing the previous restrictions that allowed post-registration access only to redacted data in a non-downloadable format. EMA's new open Policy 0070 allows the user to download and print clinical study reports (CSRs) that holds true exclusively for EMA's action outside of the CTR frame [5]. But, for the preponderant situation where EMA will execute the CTR, there are challenges to overcome as information can still be categorised as commercially confidential information and the process of accessing individual patient data has not yet been solved. In addition, based on the CTR, only summaries of clinical results data, but not raw data will be made publicly available. EMA's execution of the greatly applauded transparency measures taken so far is critical, because they only apply to non-EU Member States applications which are not subject to the CTR and EU law. EMA's transparency measures should not be undermined by pressure from the pharmaceutical industry, justified on grounds stated as "practising commercially confidential information, in particular through taking into account the status of the marketing authorisation for medicinal product, unless there is an overriding public interest in this closure", when EMA deals within the CTR-based frame applicable to EU Member States [6].

A balanced approach is needed to deal with the juxtaposed topics of transparency of clinical trials and the ongoing discussion on data protection. The EU General Data Protection Regulation (GDPR) should exclusively protect patient confidentiality to the extent this is needed without jeopardising patients' right to transparency of the results of clinical research.

Solutions: We are convinced that researchers know how to responsibly deal with and access raw data for independent re-analysis of clinical trial results. EMA should put in place safeguards to guarantee that the re-analyses of strictly de-identified personal data will be performed exclusively in accordance with the highest scientific ethical standards. This would avoid the criticism that data of clinical trials are presented in a biased manner. Transparency of clinical trial data is of global value. The fact that some pioneer researchers in the pharmaceutical industry have recognised this and are allowing access to de-identified patient data should be a good basis to accept the importance of this concept [7].

We urge the European Parliament, the European Commission and the European Council to make sure that the new EU GDPR does not abolish the progress achieved in the field of transparency.

One-time consent

Achievement: The inclusion of the all-important principle of "one-time consent" in the CTR is a critical milestone in the medical research community because access to patient data and tissue beyond the end and the scope of a trial is essential for successful medical research. The acceptance by a patient that data generated within a specific trial may be used for further investigations outside

that trial – with adequate and monitored protection of privacy and all patient rights – represents a unique and important achievement [8]. This is arguably the greatest sign of respect and self-determination towards patients, many of whom decide to participate in clinical trials for more than personal gain. For them, one-time consent means they can continue to contribute to research by ”donating” their data to research even beyond the scope and the end of a specific trial. This will hasten advances in research because trial databases are a precious source of information, and serve the ultimate goal of providing better treatments without incurring any risk to the patients.

Challenge: According to the CTR, “scientific research making use of the data outside the protocol of the clinical trial shall be conducted in accordance with the applicable law on data protection” [8]. However, the European Parliament’s Resolution Amendment 191 to Article 81 on the EU GDPR insists on specific patient consent for every use of patient data and tissue that would neutralise the concept of a one-time consent, and severely hinder research in Europe [9].

Solutions: We have to make sure that the new EU GDPR may allow the option of the one-time consent also under the perspective of privacy and that the degree to which national countries may derogate is minimized to avoid discrepancies in rules across the EU, with obvious limitations to collaborative research [10].

Procedural Items

National authorities and ethical committees

Achievement: The CTR imposes, though without clearly stipulating it, a coordination process between national authorities and ethical committees (ECs).

Challenge: Currently in most countries, ECs do not - or rarely - communicate with competent national authorities. In some countries, this communication is additionally cumbersome because of the high number of ECs involved in the evaluation of research.

Solutions: National authorities and ECs will require close interaction if unnecessary delay is to be avoided, and the number of ECs will have to be limited to be able to comply with deadlines. It is imperative to assure meaningful communication between all stakeholders if real success is to be achieved and which can only be regulated through the national implementation of the Regulation.

Opt-out option

Achievement: EU Member States have the right to "opt-out" from the clinical trial in case they do not agree on the research proposed. This prevents some Member States from "vetoing" a trial accepted by the others.

Challenge: There is still the possibility of a clinical trial being refused in some European Member States, yet accepted in others. This means that individual countries may decline to participate in a trial even if it has already been accepted by other countries.

Solution: It is hoped that this opt-out option will become less commonly used as European regulations at the national level become more homogenous.

Patient participation

Achievement: The CTR suggests patient involvement in clinical trials.

Challenge: The CTR does not go far enough on patient involvement in clinical trials and only suggests that patients be members of the ECs.

Solutions: Cancer patients clearly have a high degree of interest in participating in the design and decision-making of clinical trials. They should be given the opportunity to become involved with a subject that will frame how research on their disease needs to be conducted, and how the data gained from studying their data and tissue is to be used. While patient involvement can be determined at the national level, a comprehensive definition is required

Next steps for ESMO and EORTC

ESMO will work with EORTC on the issues above, especially through the EORTC-ESMO European Clinical Cancer Research Forum which brings together EU collaborative research groups and which met for the first time in October 2014. One goal of the group will be to provide recommendations to guide Ministries of Health (or Ministries of Justice for issues related to data protection) in implementing the CTR in a harmonised fashion across all Member States on topics such as insurance or ECs. In addition, EORTC will work closely with EU institutions and conduct workshops with focus groups on specific topics and ESMO will gather feedback from its members and national oncology societies to submit it to the EU Clinical Trials Advisory Group that is responsible for answering questions and monitoring implementation of the CTR. Another key task for ESMO will be providing education to ESMO members on how to run clinical trials according to the CTR that is, how to use the new EMA clinical trials portal, paperwork requirements and administrative regulations, a harmonised wording of patient informed consent forms, collaboration with ECs, etc..

Need for European consensus

We hope that our united efforts will result in a consensus for a common position on clinical trials throughout Europe. The CTR represents one of the most important changes in the field of clinical trials in the last decade. Although still very much a work in progress, it is an opportunity to facilitate clinical cancer research in Europe and reduce some of the burdens that have proven so costly in the past. We welcome all readers' thoughts on this topic and are eager to promote debate, especially within national oncology societies. We particularly need that support to assure that this new beginning is not hampered by the new EU GDPR, whose text is currently under revision and absolutely needs to safeguard the future of public health research by allowing a derogation from consent for epidemiological population-based registries, and by including the concept of a broad, but withdrawable one-time consent from patients for use of their data and biobank tissues for future public research as well as in clinical trials. We are concerned whether the specific changes to the Regulation as advocated by the cancer community will prompt the European authorities to adequately address this issue.

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Disclosure

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