

Regulatory Public Disclosure

SECTION EDITORS



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Getting to grips with the EU CTR and CTIS

Editorial

A great deal has happened in the world of regulatory public disclosure in Europe in 2022 with the EU Clinical Trials Regulation (CTR) 536/2014 coming into force at the end of January 2022. We collectively attempt to assimilate knowledge and experience of protocols prepared for and conducted under the Regulation as a first learning step, and to appreciate the nuances of how trials registered under the CTR will be entered and displayed in the Clinical Trials Information System (CTIS).

There are multiple CTR impacts on the

documents traditionally written by medical writers, many of which will be subject to public disclosure. Although impacts are incorporated into publicly available resources such as the TransCelerate Common Protocol Template (<https://www.transceleratebiopharmainc.com/assets/clinical-content-reuse-solutions/>) which can be used to author protocols, and CORE Reference (www.core-reference.org) which can be used to inform clinical study report (CSR) authoring, a number of important EU CTR-related considerations are worthy of further exploration here:

1 Before obtaining informed consent, potential trial participants should receive information in a prior interview in language they can understand. Additional documentation about the prior interview will be required. Adequate time for participants to consider their decision is needed and separation between this interview and the actual consent interview is required. This poses a number of legitimate questions. Would MWs be involved in preparation of such prior interview document templates? Where and how should timing of the prior interview and the consent interview be captured? The interval between interviews may need to account for different types of trial design, some of which can be highly complex, and difficult to understand. Would some participants require more time than others? There are no straightforward answers, and many will be study-specific, but this should raise awareness of the need to consider developing processes to support this requirement.

2 The protocol authorised under the CTR must define the purposes and conditions for which the data of the participants will be processed. The participants should be properly

informed on the processing of their personal data in the Informed Consent Form (ICF).

3 A serious breach of the protocol or the CTR is a breach likely to affect to a significant degree the safety and rights of participants, or the reliability and robustness of the data generated in the clinical trial. Serious breach reporting in CTIS is to be no later than 7 days from becoming aware of the breach. The process for serious breach reporting should be described in the protocol and any actual serious breaches will need to be reported in the CSR. Considering that systematic serious breaches affecting the data may be discovered after the operational conduct of the study has concluded, the serious breach process development or review should involve input from team members outside of clinical operations, and should include functions as broad as programming, biostatistics, and medical writing. It is also worth noting that if a systematic serious breach occurs in a multi-regional clinical trial outside of the EU, if there was potential for that breach to also occur in the EU, then this must also be reported in CTIS within the 7-day timeframe. All this is relevant for clinical trial reporting, and would appear in publicly disclosed documents.

Chair: Sam Hamilton
Committee members: Margaret Bray, Vivien Fagan, Zuo Yen Lee, Alison McIntosh
Advisor: Art Gertel
Supporting member: Raquel Billores (MD-SIG)

THE CORE REFERENCE PROJECT

The Clarity and Openness in Reporting: E3-based (CORE) Reference Project aims to provide continuous professional development for the regulatory medical writing community through open-access resources and intelligence dissemination on clinical study reporting and public disclosure of clinical-regulatory documents.

contact@core-reference.org

4 A summary of study results needs to be submitted in CTIS within a year from the end of the trial (and within 6 months for paediatric trials), and this should include a summary understandable to lay persons. Content for the summary report is in Annex IV and for the lay summary in Annex V of the CTR. If it is not going to be possible to submit a



Some members of the CORE reference Project Committee at the EMWA Berlin Conference in May 2022. Left to right: Art Gertel, Sam Hamilton, Alison McIntosh, and Margaret Bray.

summary of results in the given timeframe, it should be submitted as soon as possible thereafter. In such cases, the protocol must specify when the results are going to be submitted, together with a justification for the delay.

In short, it is wise to recognise that implications for the protocol and the clinical trial application in CTIS may have downstream granular impact on the ICF and/or the CSR, and may require some head-scratching in terms of process development and template considerations because the medical writing-owned document outputs are complex, interrelated, and should be considered a continuum.

In highlighting these points, I'd also like to point you to the lovely green banner showcasing the value of **The CORE Reference Project**. Not only is CORE Reference the 'go to' resource for authoring CTR-compliant CSRs because the resource is globally applicable, but the

ongoing continual professional development aspect ensures that anything impacting CSRs and public disclosure of CSRs that you need to know, for both ICH and regional jurisdictions, is brought to you in "real time" Choose whether to receive alerts direct to your inbox (sign up at: <https://www.core-reference.org/subscribe>), or to periodically check the News Summary page of the website (<https://www.core-reference.org/news-summaries/>) where the information is archived monthly. After 6 years since the launch of CORE Reference, I am delighted to have assistance from a small but perfectly-formed committee (see banner for details). Together, we will readily maintain the due diligence needed to keep the information that you have come to expect flowing. A selection of the most relevant information in the world of Regulatory Public Disclosure (RPD) since the start of 2022 is below. Enjoy!

Kind regards
Sam

EMA News

CTR 536/2014 and CTIS

The EU Clinical Trial Regulation 536/2014 (<https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN>) is in force, together with the platform that gives a single-entry point for clinical trials conducted under the Regulation – the EU Clinical Trials Information System (CTIS) – which is now live. If you missed the January 31, 2022 launch, check out the press briefing at <https://www.ema.europa.eu/en/events/joint-press-briefing-clinical-trial-regulation-enters-application-eu>. In the early days of CTIS this page provides updates and links to useful reference materials and is updated regularly as CTIS develops:

<https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system/development-clinical-trials-information-system>. The "CTIS Newsflash" articles appear regularly and can all be accessed at the end of the page. The learning curve is bound to be steep in these early days so the January 2022 minutes from a DIA MW Community meeting that include responses from EMA to questions submitted by this group on CTR/CTIS, are useful and can be viewed here: <https://www.core-reference.org/news-summaries/january-2022/>. The CTIS training Programme Guide is an excellent resource, regularly updated: https://www.ema.europa.eu/en/documents/other/guide-ctis-training-material-catalogue_en.pdf

Note that Module 13 in the Guide is "Clinical Study Reports submission". It is also helpful to have the Draft "Guidance document on how to approach the protection of personal data and commercially confidential information in documents uploaded and published in the Clinical Trial Information System (CTIS)" which is open for consultation until Sept 2022. In short, processes and best practice under Policy 0070 are echoed for CTIS: <https://www.ema.europa.eu/en/documents/other/draft-guidance-document>

[how-approach-protection-personal-data-commercially-confidential-information_en.pdf](#)

For those of us supporting investigator-led trials, EMA's support initiatives to help universities and hospitals to navigate CTIS should be passed onto our academic colleagues: <https://www.transparimed.org/single-post/ctis-training-support>

On March 31, 2022, the first Clinical Trial Authorisation (CTA) was issued through CTIS (https://euclinicaltrials.eu/view-clinical-trial?p_p_id=emactview_WAR_emactpublicportlet&p_p_lifecycle=0&p_p_state=normal&p_p_mode=view&p_p_col_id=column-1&p_p_col_count=1&_emactview_WAR_emactpublicportlet_number=2022-500137-89-00&_emactview_WAR_emactpublicportlet_facesViewIdRender=%2FWEB-INF%2Fviews%2Fview%2Ftabs%2Fsummary.xhtml). This trial was originally registered under the Directive and in EudraCT, but has been moved under the CTR and into CTIS.

As medical writers take on the challenge of writing "Plain Language Summaries (PLS)" (also known as "lay summaries") mandated by EU CTR 536/201, we will need to assimilate process and procedural knowledge, and to this end a survey has been devised to help better understand trends in PLS, which can be taken here: <https://www.surveymonkey.com/r/PLS-Survey-DIA>. The eventual aim when the survey results are published is to aid with benchmarking your process against your peers.

DARWIN EU

In February 2022, EMA established the Coordination Centre for the Data Analysis and Real World Interrogation Network (DARWIN EU®): <https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu>. On February 24, a webinar was held to introduce the initiative and highlight opportunities for collaboration, and can be viewed here: https://www.ema.europa.eu/en/documents/presentation/presentation-darwin-eu-multi-stakeholder-information-webinar_en.pdf

EMA are publishing a quarterly progress update on the work of the HMA-EMA Big Data Steering Group titled "Big Data Highlights". An article in the first issue titled "Regulatory capability to analyse data: pilot on raw data use" is of particular relevance: <https://www.ema.europa.eu/en/documents/newsletter/big-data->

[highlights-issue-1_en.pdf](#)

"EMA, in partnership with the Advisory Group on Raw Data comprising representatives of the Big Data Steering Group, NCAs, EMA committees, and working parties and patients' representatives, is preparing a pilot to clarify the benefits and practicalities of access to individual (raw) patient data from clinical trials in the assessment of medicines. The pilot, which is expected to start in the second quarter of 2022, will analyse raw data from selected marketing authorisation applications to support the CHMP assessment. The results of the pilot, expected in 2023, will help the EU medicines regulatory network to make an informed decision on the place of raw data in regulatory decision-making".

UK MHRA

In January 2022, the MHRA set out the UK legislative proposals for clinical trials; the consultation period closed on March 14, 2022. Some proposed changes to definitions that include replacing the term "subject" with "participant", updating the definitions of "clinical study" and "clinical trial" and adding "low intervention clinical trial", per the EU CTR are of interest. The term "substantial amendment", however, will be retained in contrast to the new EU CTR change of the term to "substantial modification". The full proposals can be viewed here: <https://www.gov.uk/government/consultations/consultation-on-proposals-for-legislative-changes-for-clinical-trials/proposals-for-legislative-changes-for-clinical-trials>.

As MHRA gets into its stride as a medicines regulator, we see the drive towards clinical trial transparency and patient centricity, akin to other jurisdictions including the EU, through policy development and initiatives. These guiding principles hold true for the UK as we see with the multi-agency "MakeItPublic" initiative <https://www.hra.nhs.uk/planning-and-improving-research/best-practice/public-involvement/putting-people-first-embedding-public-involvement-health-and-social-care-research/> explained by the Head of Policy and Engagement at the National Health Service (NHS) here: <https://www.hra.nhs.uk/about-us/news-updates/making-transparency-happen-blog-dr-naho-yamazaki-head-policy-and-engage-ment/> and an initiative to boost clinical trial reporting that is working well already: <https://www.transparimed.org/single-post/mhra-hra-isrctn>. The MHRA GCP Inspectorate Blog (sign up for direct alerts to your

inbox here: <https://mhrainspectorate.blog.gov.uk/subscribe/>) helps Sponsors understand what the Regulator has been finding and expects during its inspections. So overall, the UK vision appears clear and so far, the policies and initiatives seem to be supporting that vision.

FDA Guidance and News

FDA has produced guidances in 2022 that continue to speak to improved real-world applicability for trial results: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/digital-health-technologies-remote-data-acquisition-clinical-investigations?utm_medium=email&utm_source=govdelivery and improved patient centricity in drug development: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-methods-identify-what-important-patients?utm_medium=email&utm_source=govdelivery

The collection and analysis of population pharmacokinetics (PK) data is included in early phase clinical trials and is used to guide drug development and inform recommendations on therapeutic individualisation. The new final guidance on this topic was released in February 2022: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/population-pharmacokinetics?utm_medium=email&utm_source=govdelivery.

Draft FDA Guidance titled: "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials" is open for comment. Per the Introduction: "Adequate representation of these populations in clinical trials and studies supporting regulatory submissions helps ensure that the data generated in the development program reflect the racial and ethnic diversity of the population expected to use the medical product if approved..." Read the guidance in full at: <https://www.fda.gov/media/157635/download>.

These and other guidances can be viewed at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/>.

NIH's Final Policy, effective January 2025, will mandate data management planning and public sharing of clinical trial data for NIH funded studies: <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-013.html#:~:text=October%202022%202020-,January%202025%2C%202023,-Related%20Announcements>.

COVID-19

The COVID-19 pandemic presented multiple challenges, not least to global regulators as all stakeholders learned together. Some of these challenges are well summarised in a 3-part blog in which MHRA inspectors share their experiences dealing with clinical trials during the pandemic, looking at the initial response: <https://mhrainspectorate.blog.gov.uk/2022/02/08/regulators-experience-of-clinical-trials-during-the-covid-19-pandemic-part-1-our-initial-response/>; what has been learned: <https://mhrainspectorate.blog.gov.uk/2022/02/14/regulators-experience-of-clinical-trials-during-the-covid-19-pandemic-part-2-what-we-have-learned/>; and exploring the challenges ahead for clinical trials: <https://mhrainspectorate.blog.gov.uk/2022/02/18/regulators-experience-of-clinical-trials-during-the-covid-19-pandemic-part-3-looking-forward/>

A JAMA survey conducted in July 2021 and published in February 2022 (<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2789176>) shows that a representative cohort of US adults overwhelmingly support greater transparency at the FDA. It is suggested that the results may reflect the public's improved understanding of the drug development process in the context of the COVID-19 health emergency. A *Lancet Infectious Diseases* article titled "COVID-19 kick-starts a new era for clinical trials and pandemic preparedness in Europe", shows European regulators calling for "structures and partnerships to enable clinical research and identify regulatory hurdles among the challenges for clinical trials": [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(22\)00061-5/fulltext?dgcid=raven_jbs_etoc_email](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00061-5/fulltext?dgcid=raven_jbs_etoc_email)[https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(22\)00061-5/fulltext?dgcid=raven_jbs_etoc_email](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00061-5/fulltext?dgcid=raven_jbs_etoc_email). The determination to learn from the pandemic and to adapt regulatory pathways and frameworks is clear. On March 30, 2022, EMA showed they

mean exactly that by making this statement "Sponsors can adjust the way they run clinical trials that have been affected by the war in Ukraine using the experience gained during the COVID-19 pandemic. They can also apply the approaches and flexibilities agreed in the context of the pandemic." Read more here: <https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials-human-medicines>

FDA Guidance "Emergency Use Authorization for Vaccines to Prevent COVID-19" was updated on March 31, 2022, superseding the May 21 Guidance: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19?utm_medium=email&utm_source=govdelivery.

Transparency and Disclosure Resources

As we move to improve transparency in scientific research generally, and more specifically in clinical trials, several initiatives have taken shape in 2022. The CHEERS (Consolidated Health Economic Evaluation Reporting Standards) team have updated and published reporting guidance for health economic evaluations simultaneously in 16 journals including in the September 2021 issue of *Medical Writing* Sept 2021, and on the updated CHEERS 2022 checklist (March 2022): <https://pubmed.ncbi.nlm.nih.gov/35007499/>

The UK is proposing a global effort to strengthen clinical trial transparency. The UK's draft resolution requests that WHO develop a global action plan for implementing the suggested principles at the 76th World Health Assembly in 2023. This is one to keep an eye on.

An article in *The Journal of Law, Medicine & Ethics* titled "Transparency of Regulatory Data across the European Medicines Agency, Health Canada, and US Food and Drug Administration"

provides a snapshot of current clinical trial information sharing by regulators - for a broader audience than just clinical trials professionals. It is actually a really good introduction to the topic for newer members of the medical writing community too: <https://www.cambridge.org/core/journals/journal-of-law-medicine-and-ethics/article/transparency-of-regulatory-data-across-the-european-medicines-agency-health-canada-and-us-food-and-drug-administration/FFD09EC615E261AEFE3E8AE88A268CBA>.

Patient Centricity

This 2021 CISCRP study highlights clinical trial participant's insights and perceptions: <https://www.openpharma.blog/blog/disclosure/perceptions-and-insights-on-clinical-trial-participation-results-from-the-2021-ciscrp-study/>. We see that the pandemic has improved perceptions around research and improved trust and understanding. Regulators are taking patient **centricity increasingly** seriously and ICH leaders intend to bring patient perspectives into guidelines development: <https://pink.pharmaintelligence.informa.com/PS145721/ICH-Leadership-Aims-To-Bring-Patient-Perspectives-Into-Global-Guideline-Development-Process>.

That's all for this issue. Happy reading.

*With thanks to Margaret Bray
for editorial support.*

RPD Special Interest Group (RPD SIG) News

EMWA's Regulatory Public Disclosure (RPD) Special Interest Group (SIG) "Meet and Share" (held on January 27, 2022) recording and PDF are published on the RPD

SIG page of the EMWA website (<https://www.emwa.org/sigs/regulatory-public-disclosure-sig/>). We are greatly saddened by the loss of our colleague Amanda Hunn, who so generously

shared her experience and knowledge on Plain Language Summaries. The video is shared to honour Amanda's memory and with the kind permission of her family.