Regulatory Public Disclosure

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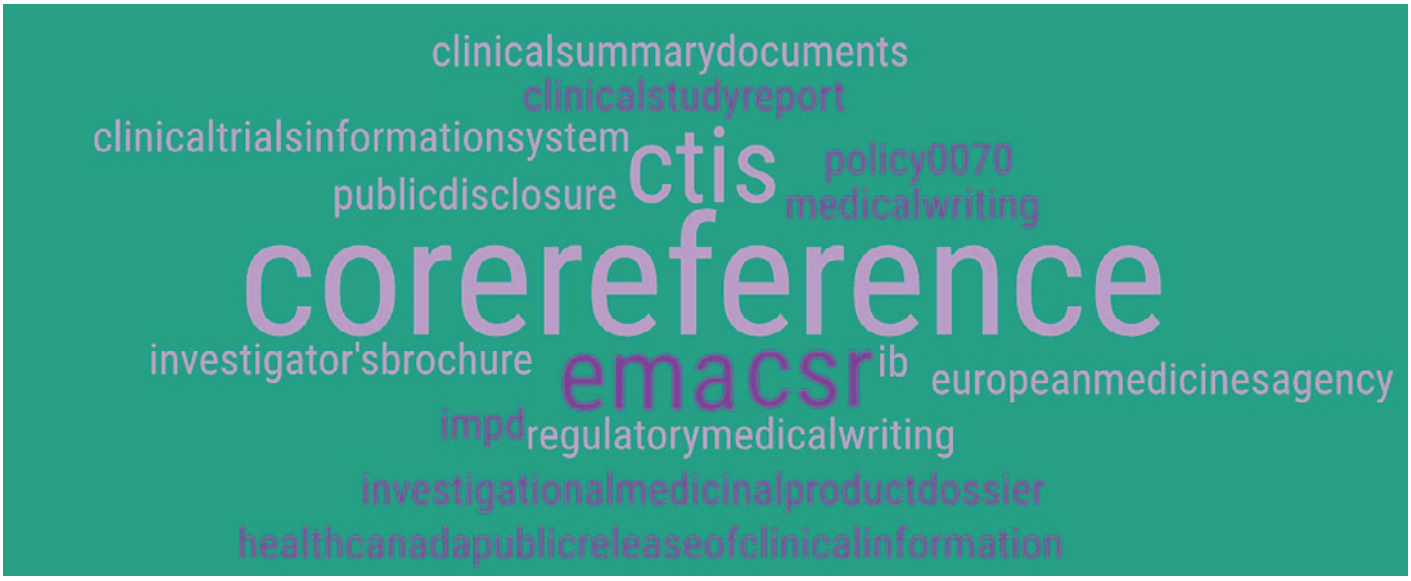

Editorial

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EU Clinical Trials Regulation and Clinical Trials Information System

It is now 14 months since the EU Clinical Trials Regulation (CTR) 536/2014 came into force at the end of January 2022. As of January 31, 2023, all sponsors of clinical trials became obliged to use the Clinical Trials Information System (CTIS) and follow the same process to apply for clinical trial authorisation in the EU/EEA. For individual companies, changes to and enhancements of processes have been necessary at the application stage of the clinical trial to support the use of the CTIS platform. Not all of the publicly disclosed documents fall under the ownership of medical writers now that this has broadened to include for example, the Investigator's Brochure and Investigational Medicinal Product Dossier (IMPD), and Risk Management Plan (RMP). This rather depends on individual company processes and document ownership responsibilities. However, the techniques that the regulatory medical writing function has employed for the past 6 years or so in creating proactively authored documents fit for public disclosure with minimal need for redaction, are proving invaluable. We have the opportunity to educate cross-functionally to ensure that Commercially Confidential Information (CCI) is excluded from documents that are going to find their way into the public domain – because most often CCI redactions are not permitted. Keep the mantra "if in doubt, leave it out" in mind at all times! Come and learn more about the impact of CTIS on medical writing at the Expert Seminar Series Session 3 on May 12, 2023 (morning) at the upcoming EMWA Conference in Prague. (The conference takes place May 9–13).

CESHARP – the (draft) ICH standard and template for protocols

Another major milestone was reached in September 2022 when ICH released a Step 2 draft guideline outlining a harmonised template for clinical trial protocols to support consistency among sponsors. The ICH M11 Clinical Electronic Structured Harmonised Protocol (CESHARP) draft guideline (https://database.ich.org/sites/default/files/ICH_M11_draft_Guideline_Step2_2022_0904.pdf), plus template (https://database.ich.org/sites/default/files/ICH_M11_Template_Step2_2022_0904. pdf) and template technical specifications (https://database.ich.org/sites/default/files/ICH_M11_TechnicalSpecification_Step2_2022_1014.pdf), were released for public consultation on October 21, 2022. The scope of ICH M11 is to establish common instructions for placement of content and information on technical attributes. According to ICH, "The guideline aims to have clinical trial protocol templates that are complete, free from ambiguity, well organised, and aligned with quality by design principles as set forth in other ICH guidelines." The template has a core set of information for clinical trials including fonts that should be used in the protocols, numbering for tables and figures, as well as acceptable abbreviations. The consultation period ended in February 2023, so watch out for the next release of this draft guideline and template, which should reflect end-user perspectives. In a related move, TransCelerate Biopharma released their "Clinical Template Suite (CTS) Release Addendum" in November 2022. This is a "track changes" clinical protocol template (CPT v009) with only limited updates. The addendum clarifies that the next round of TransCelerate templates will be released in the second half of 2023, to allow alignment with ICH M11 and EU PEARL – the EU patient-centric clinical trial platform

Table 1. TransCelerate CPT (v009, file dated October 12, 2022) versus Draft (Step 2) ICH M11 Template: A Comparison of Level 2 headings Published open access by the CORE Reference Project Team on December 13, 2022
https://www.core-reference.org/news-summaries/core-reference-project-team-compare-transcelerate-cpt-v009-and-draft-ich-m11-step-2-templates-a-comparison-of-level-2-headings

Level 1 heading (per Draft ICH M11)	TransCelerate (2022 Addendum release) Level 2 heading	Draft ICH M11 Level 2 heading	Brief comment
1 Protocol Summary	1.1 Synopsis 1.2 Schema 1.3 SoA	1.1 Protocol Synopsis 1.2 Trial Schema 1.3 SoA	Similar overall structure
2 Introduction	2.1 Study Rationale 2.2 Background 2.3 Benefit/Risk Assessment	2.1 Purpose of Trial 2.2 Summary of Benefits and Risk	Similar level of detail required
3 Trial Objectives, Endpoints and Estimands	Primary estimand/ coprimary estimands/ multiple primary estimands (non-numbered Level 2 heading) Secondary estimands (non-numbered Level 2 heading)	3.1 {Primary/Secondary/Exploratory} Objective + Associated Endpoint {and Estimand}	Although no definitive Level 2 headings are provided, more comprehensive guidance regarding how endpoints and objectives should be presented is proposed in the TransCelerate template than is provided in the M11 template
4 Trial Design	4.1 Overall Design 4.2 Scientific Rationale for Study Design 4.3 Justification for Dose 4.4 End of Study Definition	4.1 Description of Trial Design 4.2 Rationale for Trial Design 4.3 Access to Trial Intervention After End of Trial 4.4 Start of Trial and End of Trial	Draft ICH M11 requires description of any possibilities for access to trial intervention, beyond completion of the trial (Found in Section 6.7 in TransCelerate CPT)
5 Trial Population	5.1 Inclusion Criteria 5.2 Exclusion Criteria 5.3 Lifestyle Considerations 5.4 Screen Failures 5.5 Criteria for Temporary Delaying Enrollment/ Randomisation/ Administration of Study Intervention	5.1 Selection of Trial Population 5.2 Rationale for Trial Population 5.3 Inclusion Criteria 5.4 Exclusion Criteria 5.5 Lifestyle Considerations 5.6 Screen failures	Draft ICH M11 specifically addresses the selection and rationale for the study population TransCelerate template includes Section 5.5 which is not indicated in Draft ICH M11
6 Trial Intervention and Concomitant Therapy	6.1 Study Intervention Administered 6.2 Preparation, Handling, Storage and Accountability 6.3 Assignment to Study Intervention 6.4 Blinding/masking 6.5 Study Intervention Compliance 6.6 Dose Modification 6.7 Continued Access to Study Intervention after End of the Study 6.8 Treatment of Overdose 6.9 Prior and Concomitant Therapy	6.1 Description of Trial Intervention 6.2 Rationale for Trial Intervention 6.3 Dosing and Administration 6.4 Treatment of Overdose 6.5 Preparation, Handling, Storage and Accountability 6.6 Participant Assignment, Randomisation and Blinding 6.7 Trial Intervention Compliance 6.8 Concomitant Therapy	Overall organisation of information differs slightly between the 2 templates

Level 1 heading (per Draft ICH M11)	TransCelerate (2022 Addendum release) Level 2 heading	Draft ICH M11 Level 2 heading	Brief comment
7 Discontinuation of Trial Intervention and Participant Withdrawal from Trial	7.1 Discontinuation of Study Intervention 7.2 Participant Discontinuation/Withdrawal from the Study 7.3 Lost to Follow up	7.1 Discontinuation of Trial Intervention 7.2 Participant Withdrawal from the Trial 7.3 Lost to Follow-Up 7.4 Trial Stopping Rules	Draft ICH M11 emphasises the need to describe trial-specific stopping rules, e.g., guidance on stopping trial for safety reasons, when a cohort or dose escalation should be terminated, and/or treatment arm terminated Notably, TransCelerate does consider specific participant stopping rules based on different variables, e.g., liver chemistry stopping criteria, QTc stopping criteria in Section 7.1 as Level 3 headings, but there is no guidance on stopping a trial/treatment arm
8 Trial Assessments and Procedures	8.1 Administrative and General/Baseline Procedures 8.2 Efficacy and/or Immunogenicity Assessments 8.3 Safety Assessments 8.4 Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting 8.5 Pharmacokinetics 8.6 Pharmacodynamics 8.7 Genetics 8.8 Biomarkers 8.9 Immunogenicity Assessments 8.10 Health Economics OR Medical Resource Utilisation and Health Economics	8.1 Screening/Baseline Assessments and Procedures 8.2 Efficacy Assessments and Procedures 8.3 Safety Assessments and Procedures 8.4 Adverse Events and Serious Adverse Events 8.5 Pregnancy and Postpartum Information 8.6 Medical Device Product Complaints for Drug/Device Combination Products 8.7 Pharmacokinetics 8.8 Genetics 8.9 Biomarkers 8.10 Immunogenicity Assessments 8.11 Medical Resource Utilisation and Health Economics	Draft ICH M11: Section 8.6 is an additional optional section. Notably, in TransCelerate template Medical Device Deficiencies is a Level 3 heading (Section 8.4.9) and further medical device information is included in Appendix 7 Draft ICH M11: Pharmacodynamics level 2 heading present in TransCelerate template (Section 8.6) is not included Notably, while Draft ICH M11 considers Pregnancy as a separate Level 2 heading (Section 8.5), it is a Level 3 heading (Section 8.4.5) in the TransCelerate template

(Continued on next page)

Table 1 (Continued)

Level 1 heading (per Draft ICH M11)	TransCelerate (2022 Addendum release) Level 2 heading	Draft ICH M11 Level 2 heading	Brief comment
9 Statistical Considerations	9.1 Statistical Hypothesis/Hypotheses 9.2. Analysis Sets 9.3. Statistical Analyses 9.4. Interim Analysis/Analyses 9.5. Sample Size Determination	9.1 Analysis Sets 9.2 Analyses Supporting Primary Objective(s) 9.3 Analysis Supporting Secondary Objective(s) 9.4 Analysis of Exploratory Objective(s) 9.5 Safety Analyses 9.6 Other Analyses 9.7 Interim Analyses 9.8 Sample Size Determination 9.10 Protocol Deviations	Although draft ICH M11 uses detailed level 2 structure for the presentation of statistical analyses and considerations, the information covered in the statistical section is generally similar between the two templates Draft ICH M11 Section 9.10 Protocol Deviations is an additional section compared with the TransCelerate template
10 General Considerations: Regulatory, Ethical, and Trial Oversight	10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 10.2. Appendix 2: Clinical Laboratory Tests 10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 10.4. Appendix 4: Contraceptive and Barrier Guidance 10.5 Appendix 5: Genetics 10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention Restart/Rechallenge Guidelines 10.7. Appendix 7: Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies 10.8. Appendix 8: Country-specific Requirements 10.9 Appendix 9: Protocol Amendment History	10.1 Regulatory and Ethical Considerations 10.2 Committees 10.3 Informed Consent Process 10.4 Data Protection 10.5 Early Site Closure or Trial Termination	Some differences exist in the presentation of data from Section 10 onwards: • TransCelerate places all the information in Section 10 using a series of appendices • Draft ICH M11 presents the information in separate Level 2 headings The overall information presented is generally similar between the two templates
11 General Considerations: Risk Management and Quality Assurance	No Section 11	11.1 Quality Tolerance Limits 11.2 Data Quality Assurance 11.3 Source Data	TransCelerate places this information in Section 10.1 Appendix 1 Regulatory, Ethical, and Study Oversight Considerations (Section 10.1.8 Data Quality Assurance, Section 10.1.9 Source Documents)

Level 1 heading (per Draft ICH M11)	TransCelerate (2022 Addendum release) Level 2 heading	Draft ICH M11 Level 2 heading	Brief comment
12 Appendix: Adverse Events and Serious Adverse Events – Definitions, Severity, And Causality	No Section 12	12.1 Further Details and Clarifications on the AE Definition 12.2 Further Details and Clarifications on the SAE Definition 12.3 Severity 12.4 Causality	In TransCelerate CPT these sections are addressed in: 10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting
13 Appendix: Definitions and Supporting Operational Details	No Section 13	13.1 Contraception and Pregnancy Testing 13.2 Clinical Laboratory Tests 13.3 Country/Region-Specific Differences 13.4 Prior Protocol Amendments	In TransCelerate CPT these sections are addressed in: 10.2. Appendix 2: Clinical Laboratory Tests 10.4. Appendix 4: Contraceptive and Barrier Guidance 10.8. Appendix 8: Country-specific Requirements 10.9 Appendix 9: Protocol Amendment History
14 Appendix: Glossary of Terms	No Section 14	Define abbreviations and other terms used in the protocol	In TransCelerate CPT this section is presented immediately after the TOC at the front of the document
15 Appendix: References	References are in Section 11	15 Appendix: References	

Abbreviations: CPT= Common Protocol template; SoA= Schedule of Activities

(https://www.imi.europa.eu/projects-results/ project-factsheets/eu-pearl). Knowing that ICH trumps everything, we expect the structure of the clinical trial protocol will be set by the final ICH M11 guidance when it is eventually issued. TransCelerate will wait until ICH M11 is more mature before they comment further. Meanwhile, on December 13, 2022, the **CORE Reference Project Team** published an **open-access** resource titled "**TransCelerate CPT (v009) Versus Draft ICH M11 Template: A Comparison of Level 2 Headings**" to support familiarisation with ICH M11. This resource is available at https://www.core-reference.org/news-summaries/core-reference-project-team-compare-transcelerate-cpt-v009-and-draft-ich-m11-step-2-templates-a-comparison-of-level-2-headings/ and is replicated in Table 1.

It is appropriate in this "Clinical Trials" themed issue of MEW that we hear from Zuo Yen Lee – an experienced medical writer at a global CRO that serves biotechnology companies – about the complexities of oncology design and bias avoidance. Her article, "To bias or not to bias in oncology clinical trials: Perspectives on design, endpoint selection, and reporting", begins on p. 46. As ICH M11 matures, we will undoubtedly see its impact on a range of study designs, including oncology trials.

CORE Reference Project

In November 2022, the CORE Reference Project Team released an animation: https://youtu.be/ANCvoWBULb8 and https://www.core-reference.org. We did this to showcase and promote awareness of this open access resource to those new to our profession. We also have a landing page on the EMWA website (https://www.emwa.org/resources/ core-reference/) that provides the links that underpin the resources. Also in the offing is a planned CORE Reference website overhaul in late 2023/early 2024 that will produce a cleaner, slicker website to improve your visitor experience.

The CORE Reference Team will also be hosting an open introductory and Q&A session on CORE Reference and the CPD resources during the EMWA May 2023 conference in Prague, so do please come and meet us on Friday May 12, 2023, at 17.15-18.15. In June 2023, we plan an online open session on the resources and also featuring T&D in Asia.

Don't forget that you can receive CPD resources direct to your inbox (sign up at: https://www.core-reference.org/subscribe), or you may wish to periodically check the News Summary page of the existing website (https://www.core-reference.org/news-summaries/) where information gathered on matters concerning RPD and clinical study reporting is archived monthly. A selection of the most relevant information in the world of RPD in the last few months is in Table 2. Enjoy!

Table 2. Selected regulatory information shared via CORE Reference (September 2022 – December 2022)

Disseminated information	Brief description	Link
September 2022 Highlights		
Final FDA guidance: "Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products"	Encourages sponsors to identify in their submission certain uses of RWD/RWE. Also applies to submissions for investigational new drug applications, new drug applications, and biologics license applications that contain RWD/RWE intended to support a regulatory decision regarding product safety and/or effectiveness	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-documents-using-real-world-data-and-real-world-evidence-fda-drug-and-biological-products?utm_medium=email&utm_source=govdelivery
TransCelerate and Association of Clinical Research Organizations Member Companies: Points to consider	Points to consider when developing a CSR which has interruptions due to unforeseen circumstances e.g., war, a pandemic or other public health emergency, or any geospatial disruption.	https://www.transceleratebiopharmainc.com/wp-content/uploads/2022/09/ACRO-TC-CSR-Statement-9.12.22-FINAL-for-posting-1.pdf
NIH Plain Language Checklist for Lay Brief Summaries	Checklist refers to plain language best practices to help investigators write brief summaries of clinical trials that can be easily understood by the general public	https://prsinfo.clinicaltrials.gov/Plain_Language_Checklist_for_Lay_Brief_Summaries.pdf?utm_medium=email&utm_source=govdelivery
Canadian Institute of Health Research Policy Guide	Clinical trials must be registered and results published within the mandated time frame in order to remain eligible for any new funding	https://cihr-irsc.gc.ca/e/52820.html
Good Publication Practice (GPP) Guidelines for Company-Sponsored Biomedical Research: 2022 Update	Update to the GPP guidelines	https://doi.org/10.7326/M22-1460
October 2022 Highlights		
FDA final guidance entitled "Multiple Endpoints in Clinical Trials Guidance for Industry"	Describes various strategies for grouping and ordering endpoints for analysis and applying some well-recognised statistical methods for managing multiplicity within a study in order to control the chance of making erroneous conclusions about a drug's effects. The final guidance also incorporates a reference to the International Council for Harmonization's (ICH) E9(R1) guideline on estimands and how these fit into primary and secondary endpoint families.	https://www.fda.gov/media/162416/download
BMJ open access paper	Describes novel issues specific to the registration and reporting of results for master protocols and proposes an approach to support transparent, complete, and timely reporting to trial registries and results databases such as ClinicalTrials.gov. The process has the potential to be applied broadly to other trial registries and results databases.	https://doi.org/10.1136/bmj-2021-067745
Publication asking: "Is Intention to Treat Still the Gold Standard or Should Health Technology Assessment Agencies Embrace a Broader Estimands Framework?"	Insights and perspectives from the National Institute for Health and Care Excellence and Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E9 (R1) Addendum	https://doi.org/10.1016/j.jval.2022.08.008

Disseminated information	Brief description	Link
ICH released a Step 2 draft guideline (ICH M11) outlining a harmonised template for clinical trial protocols to support consistent reporting among sponsors.	The draft guideline, plus template and template technical specifications, were released for public consultation. The scope of ICH M11 is to establish common instructions for placement of content and information on technical attributes.	Link to draft guideline: https://database.ich.org/sites/default/files/ICH_M11_draft_Guideline_Step2_2022_0904.pdf Link to template https://database.ich.org/sites/default/files/ICH_M11_Template_Step2_2022_0904.pdf
November 2022 Highlights		
EMA – guidance to companies on the retention/removal of Protected Personal Data and identification of Commercially Confidential Information during the preparation of Risk Management Plans (RMPs).	Contains changes of editorial nature that should be implemented in the RMP during the scientific review process prior to the opinion and adoption of the final RMP version.	https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-anonymisation-protected-personal-data-assessment-commercially-confidential-information_en.pdf
TransCelerate released Clinical Template Suite (CTS) Release Addendum	This is a track changes clinical protocol template (CPT v009) with limited updates. The addendum also explains that the next round of templates will be released after June 2023, in order to allow alignment with ICH M11 and EU Patient Centric Clinical Trial Platforms	https://www.transceleratebiopharmainc.com/assets/clinical-content-reuse-solutions/
EMA released the updated (Rev. 14) "Guidance for Applicants seeking scientific advice and protocol assistance".	Update clarifies the scope and nature of scientific advice and protocol assistance, such as requests for paediatric development, structure/content of the briefing package, and the procedure for fee determination and payment. The major changes to the document are for clarity and conciseness	https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-guidance-applicants-seeking-scientific-advice-protocol-assistance_en.pdf
CTIS online training modules updates	• CTIS Evaluation Timelines – overview of timelines and deadlines for tasks and actions across the Clinical Trial Application process. • Management of Roles and Permissions – step by step guide on how to request the high-level administrator role for CTIS. • FAQs - Management of Roles and Permissions – answers to questions regarding basic principles to access CTIS for the first time, roles and permissions, CTIS user management approaches, user profile management and the main user groups.	• https://www.ema.europa.eu/en/documents/other/clinical-trial-information-system-ctis-evaluation-timelines_en.pdf • https://www.ema.europa.eu/en/documents/other/step-step-guide-high-level-ctis-administrator-management-roles-permissions-ctis-training-programme_en.pdf • https://www.ema.europa.eu/en/documents/other/faqs-management-roles-permissions-ctis-training-programme-module-07_en.pdf

Abbreviations - CTIS: Clinical Trials Information System; GPP: Good Publication Practice; RMP: Risk Management Plan(s); RWD: Real-World Data; RWE: Real-World Evidence

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