CORE Reference Project Team Compare TransCelerate CPT (v009) and Draft ICH M11 Step 2 Templates: A Comparison of Level 2 Headings

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To date, no internationally adopted harmonised standard has been established for the format and content of the clinical protocol to support consistency across sponsors and for the electronic exchange of protocol information. On 26 October 2022, ICH released a Step 2 draft guideline (M11) and harmonised template together with template specifications for public consultation. The scope of ICH M11 is to establish common instructions for protocol content and information. 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 public consultation period is due to end 26 February 2023.

ICH states that the draft M11 template has:

- Synopsis, Schema, Schedule of Activities near the front.
- Use of Main Body/Appendix framework, in which trial-specific information is in the Main Body, while reference details and more general (non-trial specific) information is in the Appendix.
- Unnecessary repetition eliminated wherever possible.

The TransCelerate Common Protocol Template (CPT) core structure has been aligned with the US National Institutes of Health and Food and Drug Administration Clinical Trials Protocol Template since 2017 and is widely adopted with updates to the template released as necessary. The CPT Level 1 and 2 headings are always included in the document and if not relevant for a clinical trial 'Not Applicable' is to be inserted, thus maintaining the numbering of sections. The most current version is 'Clinical Template Suite (CTS) Release Addendum'. This is a track changes CPT (v009) with limited updates on the previous version. The Addendum explains that the next round of templates will be released after Q2 of 2023 in

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order to allow alignment with ICH M11 and EU Patient Centric Clinical Trial Platforms (EU-PEARL).

The **CORE Reference Project Team** has conducted an initial comparison of Level 1 and Level 2 headings in the TransCelerate CPT Addendum (v009; file dated 12 October 2022) versus the Draft ICH M11 template. This comparison shows minimal differences between the two templates in the structure of the main body sections. Of note, some specific information presented under a Level 3 heading in the TransCelerate template is presented under a Level 2 heading in Draft ICH M11 template (e.g., Pregnancy). In addition, differences exist in the presentation of data from Section 10 onwards.

Although there is little difference in the Level 2 headings for protocol information required to be presented in the two templates, it should be noted that there is the potential for further changes depending on feedback garnered from stakeholders during the public consultation period (up to 26 February 2023).

CORE Reference Project Team

TransCelerate CPT (v009, file dated 12 October 2022) Versus Draft ICH M11 Template: 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

Level 1 Heading (per Draft ICH M11)	TransCelerate (2022 Addendum release) Level 2 Heading	Draft ICH M11 Level 2 Heading	Brief Comment
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
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

Level 1 Heading (per Draft ICH M11)	TransCelerate (2022 Addendum release) Level 2 Heading	Draft ICH M11 Level 2 Heading	Brief Comment
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 Utilization 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
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

Level 1 Heading (per Draft ICH M11)	TransCelerate (2022 Addendum release) Level 2 Heading	Draft ICH M11 Level 2 Heading	Brief Comment
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

Supporting Information (accessed 12 December 2022):

ICH Harmonisation Activities Public Consultation M11 EWG: https://www.ich.org/page/public-consultations [then open the 'M11 EWG' drop-down menu for all relevant documents]
ICH M11 Step 2 draft guidelines: Clinical Electronic Structured Harmonised Protocol (CESHARP) M11 template download:
https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m11-template-step-2b_en.pdf
TransCelerate (2022 Addendum release) download:
https://www.transceleratebiopharmainc.com/wp-content/uploads/2022/10/CTS-ITK_2022-CTS-BWE-Track-Changes-Templates.zip