State-of-the-Art Reporting of Clinical Trial Results

— Suitability of ICH E3 in a Changing Regulatory Landscape —

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List of Abbreviations

AE	adverse event
CCI	commercially confidential information
CIOMS	Council for International Organizations of Medical Sciences
CORE	Clarity and Openness in Reporting: E3-based
CSR	clinical study reports
CTD	Common Technical Document
CTIS	Clinical Trial Information System
EMA	European Medicines Agency
EMWA	European Medical Writers Association
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GCP	Good Clinical Practice
ICH	International Council on Harmonisation
MAA	marketing authorization application
MAH	marketing authorization holder
PD	pharmacodynamics
PK	pharmacokinetics
PPD	protected personal data
QTL	quality tolerance limits
SAE	serious adverse events
SAP	statistical analysis plan
TMF	trial master file

1 Introduction

The ICH E3 Guideline on the Structure and Content of Clinical Study Reports (CSRs)[1] was released in 1995. It took the expert working group several years and many drafts before Step 4 of the ICH guideline procedure (i.e. endorsement of the final draft by the ICH steering committee) was achieved. And yet, users in the pharmaceutical industry have criticized it from the beginning as being too vague, incomplete, and contradictory. Despite all good intentions to come up with a user-friendly and flexible template, the scope of the guideline expanded during development to cover topics such as trial design, data collection, and statistical analysis. Although the section numbering reflects the guideline structure and not a CSR based on the guideline, both structure and numbering are taken by many users as a carved in stone template[2].

The introduction of the guideline entails a statement to clarify that this is not to be understood as a rigid template and provides the possibility for change of structure and numbering[1]. This statement is vague enough to imply that deviations should be the exception and not the rule. In addition, the interpretation of ICH E3 as rigid template (i.e. a requirement) may have been supported by the ICH M4 guideline for the Common Technical Document (CTD), which refers to the specific structural elements in ICH E3, e.g. section headings[3].

The ICH E3 Q&A document from 2012 made it very clear that the underlying guideline is not a template or a set of rigid requirements that must be followed. Modifications that contribute to a better presentation of trial results are encouraged, including deleting/adding, reordering, or renaming of sections as appropriate[4]. This Q&A document was mainly triggered by subject matter experts from pharmaceutical companies, who expressed their concern about the requirement to be ICH E3 compliant in reporting and yet be able to report results in an appropriate manner.

Over the past 25 years, clinical studies have become far more complex – from substantial changes of clinical trial designs to increased globalization, study complexity, and technical

evolutions. Our approach to clinical research needs continuous modernization to keep pace with the scale and complexity of trials and to ensure appropriate use of technology.

The International Council on Harmonisation (ICH) continuously acts on the evolution of clinical drug development, e.g. by regularly revising the ICH E6 and E8 guidelines which are globally used in clinical research and serve as international ethical and scientific quality standard for the planning and conduct of clinical trials.

In addition to the continuous changes in study design and conduct, the approach to analyzing and reporting of study results has significantly changed over the last two decades. The European Medicines Agency (EMA) and the EU Parliament have undertaken great efforts to further increase the transparency of clinical studies and the public disclosure of clinical trial data to benefit patients and foster scientific discovery.

In April 2014, the Regulation (EU) No 536/2014 on the conduct of clinical trials of medicinal products for human use (EU-CTR)[5] was released and has just become effective in January 2022. In addition to the harmonization of authorization and reporting procedures for (multinational) clinical trials, the EU-CTR includes new requirements like the submission of Lay Language Summaries to complement the existing forms of results disclosure, such as registry postings and scientific publications[5].

In October 2014, the Policy on the Publication of Clinical Data for Medicinal Products for Human Use (hereafter Policy 0070)[6] has significantly changed the way we report clinical trial results. The requirement to proactively publish the CSRs (and some appendices) has triggered the need for text redaction to prevent publishing of material that could potentially allow re-identification of individual participants or that could release commercially confidential information[6].

In November 2019, ICH E9(R1) has provided us with the framework for estimands to improve the planning, design, analysis, and interpretation of clinical trials[7].

The Greek philosopher Heraclitus is quoted as saying “change is the only constant in life”, which can be easily expanded to clinical research — except for some ICH efficacy guidelines such as ICH E3. Not surprisingly, the ICH E3 users across the industry have come up with best practices to continuously evolve the way of CSR writing. This knowledge has been shared in books, publications, conferences, or workshops. In 2016, the Budapest Working Group released the Clarity and Openness in Reporting: E3-based (CORE) Reference user manual for creation of CSRs in the era of clinical trials transparency[8]. In 2018, TransCelerate Biopharma Inc. added a CSR template to its Clinical Template Suite that offers a ready-to-use and state-of-the-art structure for the CSR body with limited guidance text[9].

2 Objectives

This thesis aims to analyze the usability of ICH E3 (and the supplementary ICH E3 Q&A document) as a template and/or guidance for state-of-the-art reporting of clinical trial results in the current regulatory environment. A systematic evaluation of the applicable EU legislation for interventional clinical trials serves as basis of this thesis.

The following major regulatory changes have a significant impact on the content of a CSR and the way of writing: the ICH guidelines E6, E8 and E9, the EU-CTR, and the EMA Policy 0070. In addition, there are best practices that shape results reporting.

This thesis will analyze the gaps in ICH E3 compared to the current regulatory framework and industry standards, lay out the implications, and provide recommendations on how to best report results in a state-of the-art CSR.

A particular focus is laid on the potential need for a dedicated CSR template supplementing the ICH E3 guideline. The CORE Reference document and the TransCelerate CSR template will be analyzed for usability.

3 Methods

The analysis is focused on interventional clinical trials (Phase 1 to 4) within the EU. To identify potential gaps and ambiguities of ICH E3 in the current regulatory landscape, the guidelines and tools below have been analyzed towards their impact on reporting of clinical trial results. The terms 'study' and 'trial' have been used interchangeably.

3.1 ICH E3 and ICH E3 2012 Q&A

The ICH E3 Guideline on the Structure and Content of CSRs was finalized by ICH under Step 4 in November 1995[1]. Despite the significant changes in the conduct of clinical studies and technical evolutions, the ICH E3 guideline has remained static ever since. The only addition to the original text was released in July 2012 as supplementary ICH E3 Questions and Answers document to clarify key issues (ICH E3 Q&A)[4]. The EMA CPMP approved the original ICH E3 in December 1995, with an effective date in July 1996. EMA announced the adoption of the ICH E3 Q&A with immediate effect[10,11]. The section structure of ICH E3 is provided in Appendix 1.

3.2 Other ICH Efficacy Guidelines

The ICH E6 Good Clinical Practice (GCP) Guideline is globally used in clinical research and serves as international ethical and scientific quality standard for clinical trials. The first version of this guideline was finalized in 1996. The need to provide a formal report describing the conduct and findings of a clinical trial was stated in Section 5.2.2 of the guideline. To keep abreast with the advancements in the clinical trial landscape, a substantial amendment was released in November 2016. ICH E6(R2) is an integrated addendum to ICH E6(R1); only insertions were made to keep the original structure intact[12]. EMA announced the adoption of ICH E6(R2) on 15 December 2016 with an effective date of 14 June 2017[13].

Since the development of ICH E6(R2), clinical trials have continued to evolve with new designs and technological innovations. In January 2017, ICH released their two-step GCP Renovation Plan for the modernization of ICH E8 and the subsequent renovation of ICH E6.

ICH E6(R3) will be an overarching principles document supplemented by two Annexes. Annex 1 will address interventional trials and Annex 2 will address nontraditional interventional clinical trials[14]. The core document and Annex 1 will replace the current ICH E6(R2)[15]. A draft of ICH E6(R3) was released for review in April 2021; an updated concept paper for Annex 2 is anticipated in 2022.

The ICH E8 guideline on General Considerations for Clinical Studies was first released in 1997. By the announcement of the planned modernization, ICH had acknowledged that the document was not only outdated but could actually impede the required flexibility for effective and ethical modern clinical trials. The long-awaited revision ICH E8(R1) became effective in October 2021. It provides new internationally accepted quality principles for the design and conduct of clinical studies of drug and biological products[16]. EMA adopted the guideline on 14 October 2021, and it became effective on 14 April 2022 [17].

The ICH E9 guideline on statistical principles for clinical trials was first released in 1998 to define the principles of statistical methods in clinical trials for marketing authorization applications (MAAs)[18]. The ICH E9(R1) addendum on estimands and sensitivity analysis in clinical trials was released in November 2019, after release of a concept paper in 2014 [7]. EMA adopted the guideline on 30 January 2020, and it became effective on 30 July 2020 [19].

3.3 Results Disclosure and EMA Policy 0070

Since 2014, clinical trial summary results are posted in the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database (also known as the EU Clinical Trials Register at www.clinicaltrialsregister.eu)[20]. The EU Clinical Trials Register displays registration details for 42.771 clinical trials (status 02 October 2022) with a EudraCT protocol, i.e. interventional clinical trials conducted in the EU or trials associated with the EU Paediatric Investigation Plan[20].

For all interventional clinical trials in adults completed on or after 21 July 2014 under the Clinical Trials Directive 2001/20/EC[21], the results should be posted in the EudraCT database ≤ 12 months after the end of the trial (≤ 6 months for pediatric trials; §4.3 Commission

Guideline 2012/302 03/EC)[22]. The content of the results-related information is set out in the Commission Guidelines 2012/302 03/EC and 2009/C28/01 [22, 23].

The disclosure rules based on the Clinical Trials Directive 2001/20/EC could have been considered as 'soft legislation' and there has been room for interpretation between an obligation to post results or a mere recommendation. Due to the lack of awareness and of legal enforcement, the compliance rate for results posting on EudraCT was only 68.2% (status April 2019)[24]. Therefore, EMA and the Heads of Medicines Agencies reminded all stakeholders in June 2019 to submit their results-related information for public disclosure as per Commission Guideline 2012/302 03/EC and to emphasize that this requirement will be enforced under the EU-CTR[24].

In 2014, EMA released the Policy on the Publication of Summary Results of Clinical Trials with Medicinal Products for Human Use, which is known as Policy 0070 (last revision 2019)[6]. It requires the publication of clinical trial data submitted to EMA in the context of MAAs for human medicines under the centralized procedure[6]. Data publication under Policy 0070 happens via the EMA clinical data website[25] and includes CSRs (ICH E3 Section 1 to 15, 16.1.1, 16.1.2, and 16.1.9) and other CTD modules (e.g. Module 2.5 Clinical Overview or Module 2.7 Clinical Summaries)[6]. Policy 0070 Phase 1 (publication of clinical reports; not individual participant data) is effective since 01 January 2015, i.e. the publication of CSRs (anonymized and/or redacted) is theoretically required for approved medicinal products[26]. However, on 05 December 2018, EMA suspended its activities on publication of clinical data for centrally authorized medicines as a result of the implementation of the third phase of EMA's business continuity plan and the relocation to Amsterdam[26]. As of September 2022, the publication activities remain suspended due to ongoing business continuity linked to the COVID-19 pandemic and only clinical data for COVID-19 medicines are published as an exceptional transparency measure[26]. The EMA clinical data website[25] reflects the published non-COVID-19 medicines with CHMP opinions between January 2015 and December 2016.

Of note, neither the trial results summaries of any clinical trials on EudraCT nor the disclosure of redacted CSRs for approved medicinal products equals the full raw data disclosure[6].

Disclosure requirements under Policy 0070 are summarized in Appendix 2. The EU Clinical Trials Register is currently still being used to store information on clinical trials performed in the EU. Trials are marked as "Trial now transitioned" if the legal framework was changed towards the EU-CTR; in such cases, trials can be further followed in the Clinical Trial Information System (CTIS)[20].

3.4 EU Clinical Trials Regulation 536/2014

On 31 January 2022, the new EU Clinical Trials Regulation 536/2014 (EU-CTR) has come into effect and is replacing the EU Clinical Trial Directive 2001/20/EC[5,21]. As a regulation, the EU-CTR is binding on all EU member states in its entirety. It was designed to simplify and harmonize clinical trials in the EU, aims to increase transparency and to restore the Europe's clinical research competitiveness[5]. The Directive will be replaced gradually in a 3-year transition period; from 31 January 2025 onwards, all clinical trials must be regulated under the EU-CTR.

The implementation is under the responsibility of the EMA. EMA also manages CTIS, which contains the central EU portal and the database for clinical trials under the EU-CTR[27]. Disclosure requirements under EU-CTR are summarized in Appendix 2.

Irrespective of the outcome of the trial, the Technical Results Summaries (as per EU-CTR Annex IV) and the Lay Language Summary (as per EU-CTR Annex IV) shall be submitted to the CTIS portal within 12 months after completion of the trial (EU-CTR reason 37)[5]. In addition, in case of granted marketing authorization, a redacted CSR is to be submitted to the EU database within 30 days upon approval, completion of procedure, or withdrawal by the applicant. Sharing of raw data will remain a voluntary action by the sponsor (EU-CTR, Article 37, Number 4)[5]. The requirement for expedited results disclosure in pediatric trials, i.e. within 6 months of the end of the trial, remains in force as per Paediatric Regulation (EC) No 1901/2006 [28]. In contrast to Policy 0070, the EU-CTR has immediately and automatically become domestic law in the EU member states as per Article 288 of the Treaty on the Functioning of the European Union. The EU-CTR explicitly requires that all member states adopt penalties for infringement of the regulation, in particular for noncompliance with the

public disclosure of information on CTIS (Article 94 EU-CTR)[5], i.e. sponsors failing to share their trial results would be violating national law.

For category 1 trials (e.g. Phase 1 trials such as first in human, PK/PD, bioequivalence/bioavailability, biosimilarity) deferral rules apply for the publication of data (Technical Summary and Lay Language Summary) up to 30 months after completion of the trial[29,30].

3.5 The CORE Reference

The CORE Reference (Clarity and Openness in Reporting E3-based) is a resource for guidance on CSR writing[8] which was released in 2016. It was produced by the 'EMWA Budapest Working Group' as a response to regulatory changes for public disclosure of clinical trial data and can provide direction and interpretation of the ICH E3 guideline. The European Medical Writers Association (EMWA) assembled a group of experts in May 2014 at the annual spring conference in Budapest. This Budapest Working Group consisted of regulatory medical writing and statistical professionals, who developed the CORE Reference over 2 years. They incorporated stakeholder expertise from global industry associations, regulatory agencies (including EMA and FDA), patient advocacies, academia, and principal investigator representatives[8,31]. The CORE Reference is neither a complete rewrite of the guideline nor a ready-to-use template, but a content suggestion that incorporates ICH E3 and ICH E3 2012 Q&A, provides clarifications on the interpretation of ICH E3, and encourages informed choices during CSR authoring. Although it closely resembles the original ICH E3 sectional structure, the CORE Reference provides greater granularity and some restructuring for E3 Sections 8 to 13. The structure is outlined in Appendix 1. A mapping tool is available comparing the CORE Reference to the original ICH E3 section structure[32].

The CORE Reference provides content suggestions for a "*primary use CSR*" (EMA term scientific review version, i.e. full CSR text and all appendices) and flags text parts that could potentially impact the creation of a "*secondary use CSR*" (EMA term redacted clinical report, i.e. CSR for disclosure with redacted text and selected appendices)[32]. It provides intelligent anonymization

approaches to reduce the redaction efforts. The authoring team has already included hints to the ICH E6(R2) and ICH E9 guidelines in their guidance text.

The CORE Reference is not routinely updated, nor does it implement user feedback on an ongoing basis. However, users are encouraged to share feedback and a core team is surveilling the regulatory and public disclosure landscapes for 'periodic' updates[32]. In 2019, the Budapest Working Group critically reviewed the newly released TransCelerate CSR template and simultaneously released their first update, Version 2 of the CORE Reference Terminology Table[33].

3.6 TransCelerate CSR Template

TransCelerate BioPharma Inc. is a nonprofit organization fostering collaboration across the biopharmaceutical industry, to design solutions for efficient and high-quality delivery of new medicines. The Clinical Content & Reuse Initiative strives to enhance clinical trial processes by increasing content reuse across clinical documents[9].

A dedicated workstream of regulatory medical writing professionals from the sponsor companies has developed the Clinical Template Suite to facilitate the writing of clinical trial protocols, statistical analysis plans (SAPs), and CSRs. This includes Microsoft Word based and technology-enabled templates. This thesis has exclusively worked with the basic MS Word edition of the CSR template. The CSR template was first released in November 2018. The template has since been annually updated to reflect changes in the regulatory landscape, feedback from users and TransCelerate member companies and to ensure alignment with the Clinical Template Suite[9]. If not otherwise specified, the Version 4 (released in 2021)[34] was used, which is the most current version at the time of this thesis.

The TransCelerate CSR template provides a common and streamlined CSR structure, which is compliant with the ICH E3 required content, enables public disclosure, and seamlessly integrates the TransCelerate protocol and SAP templates[9]. The TransCelerate CSR template contains only the CSR body and leaves appendices and statistical outputs to the company

standards[34]. It is complemented by a mapping to ICH E3 and the CORE Reference as well as a cumulative summary of changes and comparison versions[9].

Another driver for this template was the concept of lean medical writing, which for example uses crossreferencing rather than encyclopedic style repetitions. For example, the description of the trial and trial plan is fairly limited, and the details are covered in the clinical study protocol and its amendments. The CSR should focus on 'what actually happened' and not provide a reiteration of the protocol. This strategic decision was made based on the fact that a CSR is not stand-alone in the context of regulatory authority review because agency reviewers will always have access to the protocol, its amendments, and the SAP. Appendix 1 summarizes the structural differences of the CORE Reference tools and the TransCelerate CSR template compared to ICH E3.

The TransCelerate CSR template is issued without warranty of any kind. TransCelerate does not take any responsibility for loss of any kind, e.g. loss of revenue. The user bears the sole and complete responsibility for compliance with all applicable laws and regulations[9].

4 Findings

4.1 Inherent Issues with the ICH E3 Structure

When applying ICH E3 to a modern clinical trial design and an CSR in PDF format, users face some inherent structural issues, ranging from redundancies to unclarities about results reporting. Both the CORE Reference and the TransCelerate CSR template provide interpretations and solutions to overcome these inherent issues. In general, the CORE Reference provides recommendations for streamlined content while staying close to the classic ICH E3 structure. The TransCelerate CSR template applied a more pragmatic approach by providing a CSR structure that fulfills ICH E3 content requirements but is detached from the classic sectional numbering.

4.1.1 Redundancy Between Sections

Just by skimming through the ICH E3 headings (Appendix 1), the inherent redundancy between some section becomes obvious. Two examples are outlined below.

Treatment under Study

The treatment under study is described in E3 Sections 9.1 and 9.4.1; the rationale for dose selection is described in E3 Section 9.4.2 and 9.4.4 [1]. These are already four sections touching different aspects of the treatment under study, which leads to a scattered display of information or at best in one detailed description and three cross-references.

- The **CORE Reference** acknowledges that the E3 Sections 9.4.4 and 9.4.5 often have extensive overlap if completed as per ICH E3. It proposes to consolidate the content under a single section, e.g. Section 9.4.4. Selection of Dose(s) and Timing of Dose for Each Subject.
- The **TransCelerate CSR template** takes a different approach to the descriptions of treatment under study, by combing the information in a single section within a summary table including all details as requested by ICH E3 (template Section 3.4.1). The summary table can be derived from the TransCelerate protocol template, reused in the CSR, and adapted as needed, e.g. by adding actual batch numbers.

Method of Assigning Participants to Treatment Groups

The method of assigning participants to treatment groups is described in E3 Section 9.4.3 [1]. This section focuses solely on the methodology of assigning participants (e.g. randomization), while the details on blinding are only provided later in Section 9.4.6.

- The **CORE Reference** resolves this redundancy by merging the E3 Sections 9.4.3 and 9.4.6 under an appropriately named Section 9.4.3.
- The **TransCelerate CSR template** follows the same principle and merges the two topics in a single section (template Section 3.4.2). A slight difference in the sections heading was made.

4.1.2 Objectives, Variables, Measurements, and Endpoints

ICH E3 mandates that trial objectives and endpoints should be described in Section 8, ideally divided into Subsections 8.1 and 8.2 to describe objectives and endpoints separately. The variables for data collection and analysis are to be described in E3 Section 9.5 [1]; therefore, at least a cross-reference to the endpoints in Section 8.2 is required to establish the relationship between variables and endpoints. Applying this structure literally makes it very difficult for the reader to link objectives to endpoints and endpoints to variables. If the protocol and the SAP were not exceptionally well-written, the resulting CSR may even have objectives that are not tied to endpoints or endpoints that don't relate back to a specific trial objective.

The requirement for results positing has made this issue more prominent and users have started to optimize their CSR templates. Recently, this question has become more complex with the rollout of the estimands concept[7] (see Section 4.4).

- The **CORE Reference** has amended the E3 Section 8 heading to reflect both, trial objectives and endpoints, but still presents them in separate back-to-back subsections. Hence, it can still remain a challenge to match objectives with endpoints and to ensure that there are no loose ends. The description of variables is provided later in Section 9.5.1. The tool suggests a detailed substructure to ensure all measurements and parameters are adequately summarized. This approach may provide more clarity than the original ICH E3 instructional text, but it certainly does not reduce complexity or intra- and inter-document redundancy. Estimands are only marginally mentioned throughout the document without specific instructions.
- The **TransCelerate CSR template** relies on the Common Protocol Template, which defines a clear relationship between trial objectives and endpoints in a single table. This table can be reused as overview section (as in template Section 2) and in the CSR synopsis. It summarizes the most important information for interpreting the trial results and refers to the SAP for further details on statistical methods. Version 4 of the template provides solutions for implementing the concepts of estimands, either in a full tabular view or a combination of an overview table and free text. The overview table is very useful for the subsequent

structuring of the results sections because it almost delivers a blueprint. In addition, the tabular view facilitates results reporting in complex trial designs with multiple readouts. The sponsor can clearly identify which endpoints are presented in the underlying report or which endpoints will be reported later (e.g. later data cutoff or additional results becoming available at a later timepoint). For endpoints that have already been reported in a previous CSR (e.g. in case of interim analyses), version and report date can be given, which provides utmost transparency and traceability of results reporting.

4.1.3 Statistical Methods

According to E3 Section 9.7.1, a description of the planned analyses as per protocol is required[1]. This is in the best case an invitation to a copy and paste exercise, including a change of tense. In the worst case, the protocol text is not only summarized, but paraphrased to reflect several amendments or iron out ambiguities in the protocol text. Both scenarios require careful review and quality control to mitigate the risk of inconsistencies between both documents. In addition, ICH E3 fails to mention the final SAP which provides further details or even changes to the protocol that do not require a protocol amendment. If the CSR tries to reflect these SAP nuances as well, the risk of errors increases because of the fine line between summarizing statistical details and omitting essential methodological details.

- The **CORE Reference** tries to address the need for clarity on the planned analysis from the protocol, protocol amendments, and methods that changed prior to unblinding without requiring an amendment. In addition, it suggests using subheadings to separate methodologies according to the endpoint (see Appendix 1, CORE Reference Section 9.7.1.1 to 9.7.1.7). These are structural aids to ensure that the CSR provides a fully-fledged description of methods from different sources in an organized manner. However, this approach does not mitigate the risk of inconsistencies and ambiguities.
- The **TransCelerate CSR template** follows a different approach for the description of statistical methods. The template suggests crossreferencing to the final SAP and the protocol (including its amendments) and only provides a high-level description (if any) in the CSR. This approach is much more straight forward than retrospectively summarizing the

applied methods with the risk of ambiguity and inconsistency between documents, but it also directs the regulatory reviewer to at least two additional documents. However, this approach is the smartest way for any trial without protocol amendments or only nonsubstantial amendments. In case of major or substantial amendments, the template suggests adding at least a high-level description of the changes in statistical methods.

4.1.3.1 Changes in the Conduct of the Trial or Planned Analyses

ICH E3 Section 9.8. combines two different aspects: changes in the trial conduct and changes in planned analyses[1]. Although changes in the conduct often impact the planned statistical analysis, there is always the SAP as a source of truth, with method descriptions tied to special conditions. Especially in complex trial designs, the SAP could already include variations of analyses, e.g. for additional cohorts or extension cohorts while the underlying protocol would first need to be amended before the new cohort can be recruited.

- The **CORE Reference** keeps the E3 Section 9.8 but proposes to split the section in at least three subsections ordered chronologically: Section 9.8.1. Changes in the Conduct of the Study, Section 9.8.2. Changes in the Planned Analyses, Section 9.8.3. Changes Following Study Unblinding and Post hoc Analyses. Using the subsection helps untying the knot especially for any changes after database lock.
- The **TransCelerate CSR template** clearly distinguishes between operational and methodological changes. It summarizes the statistical methods changes in two different sections based on their timing, which clearly helps identifying post hoc analyses: Section 3.7.2 Changes in Planned Analyses Prior to Unblinding or Database Lock and Section 3.7.3 Changes Following Study Unblinding/Database Lock and Post hoc Analyses. While Section 3.7.2 would make use of crossreferencing to the SAP (and its amendments, if any) and protocol amendments, Sections 3.7.3 would be one of the few data-independent CSR sections in this template that would require a more elaborate description. In addition, Section 3.1.2 summarizes all other operational changes in trial conduct, either by crossreferencing to the respective protocol amendment or by a brief summary. This

structural change is logical as not all changes in planned analyses result from trial conduct changes and vice versa.

4.1.3.2 Statistical/Analytical Issues

ICH E3 bears another structural difficulty by mixing methods and results sections. The E3 Section 11.4.2 on statistical/analytical issues is part of the results section (starting from E3 Section 10)[1]. However, methods for investigating specific statistical issues are better described in the methods part in Section 9.7.1 to have a complete distinction between methodologies and results.

- The **CORE Reference** suggests this separation by changing the section name to Section 11.2 Results of Statistical Issues Encountered During the Analysis. This is one of the few places where the tool suggests renaming a section title for clarity, but it does not diverge far enough from ICH E3 to allow for a clear separation between results and methods. In reality, this section is often not used as intended and is either not populated or misused as some kind of results summary mixed with a discussion.
- The **TransCelerate CSR template** assumes that any statistical issues that arose during the analysis (i.e. after database lock) would result in post hoc analyses, which would be presented per affected endpoint and clearly labeled as such. As such, Section 3.7.3 Changes Following Study Unblinding/Database Lock and Post hoc Analyses would entail the methods description, while the Section 5.x would only display the results of the new analysis. If no specific analyses were to be described, the template offers Section 5.10 for interpretation on the validity or limitations of trial results at the very end of the results part.

4.1.4 Description of the Study Population

4.1.4.1 Disposition of Patients

ICH E3 provides the pure numerical description of the study population in Section 10 [1]. However, beyond the disposition, there are more data collected during the conduct of the trial that put results of efficacy and safety analyses into perspective. The ICH E3 Section 11 presents

efficacy results and starts with subsections on the analyzed data sets, demographic and other baseline characteristics, measurements of treatment compliance, and extent of exposure[1]. However, these subsections apply to the entire trial, including the safety results and are therefore misplaced in E3 Section 11 or 12.

- The **CORE Reference** suggests that subheadings such as listed above, that apply to both efficacy and safety, should be handled in Section 10 to provide the full picture of the study populations. A clear distinction is made between treatment discontinuation and study discontinuation, which is lacking in ICH E3. It is also encouraged to display the disposition of the participants in a flow chart, as in the example flowchart in ICH E3 Q &A.
- The **TransCelerate CSR template** uses the same approach for the structure of the section, with minor differences in the heading levels. For the graphical display of the participant disposition, a flowchart is also recommended.

4.1.4.2 Protocol Violations

Despite all efforts in the design and conduct of clinical trials in accordance with ICH GCP, which outlines the safeguards for the rights, safety, and wellbeing of participants, protocol deviations do occur. Obviously, they differ in their impact, which needs to be carefully assessed.

ICH E3 Section 10.2 requests accounting of important protocol deviations and Annex IVa of ICH E3 recommends providing the number of participants withdrawn from the study due to "*protocol violations*." It states that "*all important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment should be described*"[1]. The CSR body should summarize the information and Appendix 16.2.2 should entail the detailed listings.

Unfortunately, neither the term protocol violation nor important protocol deviation are defined in ICH E3 or any other ICH guideline. This was only clarified in the ICH E3 Q&A with formal definitions (including important protocol deviations).

1. *"A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol."* [4]
2. "*Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or wellbeing.*"[4]

To facilitate the use of terminology and to avoid further confusion, the ICH E3 Q&A suggested replacing "*the phrase protocol violation in Annex IVa with protocol deviation*"[4]. ICH E3 lists examples of important protocol deviations that should be described in Section 10.2 and included in the listing in Appendix 16.2.2 [1]; however, this constitutes the minimal requirement and should be adapted as applicable.

- The **CORE Reference** more or less reflects the ICH E3 text and refers to an example of such a listing in its Annex III (corresponds to ICH E3 Annex VI). This could be interpreted in a way that important protocol deviations are only to be reported when resulting in exclusion from the efficacy analysis. However, this is only a subset of the protocol deviations, as clarified in the ICH E3 Q&A, and would undermine the reporting of protocol deviations. With ICH E6(R2), the focus has shifted towards quality-by-design and risk management. Hence, it is important to assess GCP compliance overall and to acknowledge that a CSR should also accurately report the trial conduct, including any deviations to ethics, study intervention, reliability of the procedures at the site, or safety issues (including third party vendor oversight).
- The **TransCelerate CSR template** text reflects the broader scope outlined in ICH E3 Q&A and specifically points to serious GCP violations and/or site closures. It suggests adding more details of GCP noncompliance issues to the appendices and creates a link to deviations from Quality Tolerance Limits (QTL). Overall, the instructional text of this template ensures a more wholistic description of various types of deviations in the scope of ICH E6(R2/R3). Hamilton et al. commented that such GCP violations, audit findings etc. should be described in additional subsections[33].

4.1.5 Structure and Content of the Efficacy Results Section

4.1.5.1 Display of Efficacy Results

ICH E3 lacks guidance on the structural organization of the results sections, especially Section 11. Structuring by trial objectives does usually not add much granularity, while structuring by endpoint is often used as a reasonable starting point. In addition, the SAP and the statistical outputs provide another structural element. It seems to be self-evident that the primary endpoint dictates the pivotal trial results, and it is absolutely plausible to align the order of results presentations with the testing hierarchy. It is also logical to proceed with secondary endpoints; however, there are usually several of these and there are many approaches to the presentation, e.g. following the order as laid out in the protocol or SAP, or present only secondary endpoints with meaningful results in the CSR body. Thereafter, the same question applies to further or exploratory endpoints.

However, the situation becomes rather complex, if the primary endpoint of the trial is a safety endpoint or a pharmacokinetics (PK) or pharmacodynamics (PD) endpoint. One can argue that the instructional text in ICH E3 provides enough flexibility and that e.g. PK warrants a separate section, and it may even take the lead if PK is the primary endpoint. But does this mean that PK is the first section in the efficacy section or even a stand-alone PK section on the same level as efficacy and safety? And if the hierarchy of endpoints is the driver, does this mean the safety section leads if safety is the primary endpoint?

- The **CORE Reference** tool follows the ICH E3 structure and presents efficacy results in Section 11 and safety results in Section 12. As per ICH E3 Q&A Point 1, the PK results would still be placed in a subsection of efficacy[4]; however, this placement is only a suggestion that can be adapted. If efficacy is the primary endpoint, results would be reported in Section 11.1. A clarification is added that allows changing the title of Section 11 in case PK is the primary endpoint. In general, the tool suggests structuring according to the endpoint hierarchy, from primary to other efficacy endpoints. It states that post hoc analyses could be presented separately if not integrated in previous sections. Otherwise, the tool sticks to

the ICH E3 structure on statistical issues encountered during the analysis including all stipulated subsections as options.

- The **TransCelerate CSR template** has solved part of the problem by bringing the efficacy, safety, and PK section to the same hierarchical level from Section 5.1 to Section 5.3. Further subheadings may be inserted as applicable for the relevant topics. If estimands were designed in the trial, the instructions suggest describing the applicable analyses for each estimand (e.g. primary analysis, sensitivity analyses, and [optional] supplementary analyses). An alternative approach by endpoint is also visualized.

  The overall instructional text of the template Version 4 provides even more flexibility than the CORE Reference. For the results section (Section 5), Level 2 and lower headings are suggested and can be deleted/added/modified as needed to accommodate trial design. In Version 1 (released 2018), the instructions allowed Level 2 and lower headings to be deleted/modifies/added, but rearranging was not allowed. The order of subsections in Section 5 was in line with the Common Protocol Template and the tech-enabled template. This rigidness was criticized by the Hamilton et al.[33] as well as users. There may still be reasons for the rigid approach, e.g. a tech-enabled templates or component authoring systems, but the current template is now very easily customizable to a given trial design if desired by the sponsor.

4.1.5.2 Handling Pharmacokinetics, Pharmacodynamics, or Immunogenicity

ICH E3 handles PK or PD measurements in the efficacy section. Also, other aspects like biomarkers or immunogenicity measurements, which are heavily used in modern clinical trial designs, are handled in the efficacy section. In addition, PK data should be correlated with adverse events or laboratory changes as indicated in ICH E3 Section 12.1 (Extent of Exposure)[1].

- The **CORE Reference** provides clarity on where to report PK, PD, or biomarker (if not a primary endpoint) by adding a subsection in Section 11.3. Unfortunately, state-of-the-art topics like immunogenicity are not yet mentioned, which opens room for debate about the

best location in the CSR (as it can be a safety and/or efficacy related topic) and presents the regulatory reviewer with a variety of CSR structures. Maintaining efficacy and safety on a Level 1 heading certainly reflects their importance, but also brings some rigidness to the structure if neither is the primary endpoint.

- The **TransCelerate CSR template** leverages the flexibility provided in ICH E3 and presents PK/PD/immunogenicity etc. in separate sections on the same level as efficacy and safety.

  The more rigid structure of template Version 1 would have placed PK/PD after the safety section, irrespective of the endpoint hierarchy. Hamilton et al. have criticized this inflexibility and recommend positioning PK/PD before safety, as in the CORE Reference[33]. Otherwise, the results of the primary PK endpoint in a clinical pharmacology study would be hidden after safety. This justification would only apply if the regulatory reviewers would read a CSR like a book instead of navigating via bookmarks. Nevertheless, this suggestion was considered and implemented even more rigorously in following updates. In the current template Version 4, a Phase 1 clinical pharmacology study with PK as primary endpoint could start the results presentation with the primary PK endpoint, followed by safety, and have further exploratory efficacy results presented last.

  The criticism of wasting Level 1 headings by listing all topics as subsection of Section 5 is still valid; however, the newly implemented flexibility in Level 2 headings has the advantages of a one-fits-all template with full flexibility for different types of trials.

4.1.6 Display of Safety Results

ICH E3 Section 12 is designed to present safety data in three levels: the extent of exposure, the common adverse events (AEs), and serious adverse events (SAEs) and other significant AEs[1].

As indicated in Section 4.1.4.1, the exposure section should rather be moved to the description of the trial population in Section 10 because the exposure informs not only the safety profile but also the efficacy of a treatment under investigation.

Both, the **CORE Reference** and the **TransCelerate CSR template** suggest this structural change and it is one of the most widely applied deviation from ICH E3.

The description of common AEs starts with a brief summary in text form followed by more detailed tabulations[1]. The way ICH E3 is written invites users to repeat the table content in text, which adds to the overall redundancy of the safety section. The summary section is followed by an in-depth analysis of common AEs by body system, severity, and causality, as well as combinations thereof[1]. The tabulation part is followed by an analysis of common AEs, in which a subgroup analysis, e.g. by demographic factors or baseline features, is recommended. The common AE description ends with a subsection of line listings, which in the best case is an exhaustive collection of cross-references to E3 Section 16.2 [1]. In summary, this common AE section can become hard to digest, and becomes noninformative, when followed strictly.

The next level of the safety sections focuses on a subset of AEs, namely deaths, other SAEs, and other significant AEs[1]. This structure invites redundancy in data presentation because all these events have already been presented in the common AE sections, ignoring the seriousness criteria. In addition, sponsors have to be very clear about presenting death as a stand-alone category of SAEs (versus SAEs excluding deaths) or deaths in addition to the full display of SAEs. There is no consensus across the industry, which makes it difficult to compare CSRs form different sponsors.

Individual participant narratives are required per ICH E3 and should either be placed in Section 14.3.3 or the CSR body[1]. In reality, this requirement has often led to some duplication of information, i.e. a mini-narrative with a brief description of baseline characteristics, AE, outcome, and causality has been included in the CSR body, with a cross-reference to the full narrative. However, there are two different sources for narratives: 1) the Suspect Adverse Reaction Reports for regulatory reporting or Council for International Organizations of Medical Sciences (CIOMS) forms derived from the pharmacovigilance database or 2) the augmented well-written narratives derived from the clinical database reconciled against the pharmacovigilance database. CIOMS forms are event-based, hard to read and often include a

string of updates for upcoming new information. The augmented narratives are participant-based, well-written, and present only the final outcome. Some more guidance would be required for better harmonization across the industry because these narratives are a high risk for identifying a participant and are included in a section that is subject to disclosure after extensive redaction (see Section 4.2.2).

- The **CORE Reference** keeps the AE description close to the ICH E3 structure. It provides a huge amount of guidance on the level of detail required in the CSR body and the end-of-text tables (e.g. event count, verbatim terms) and is a valuable source for any novice to CSRs. It also explicitly states that in-text summary tables should not be repeated by describing the content in detail in text. The authors have used the flexibility provided by ICH E3 Q&A and adapted section titles or clarified the level of detail in the CSR body vs. end-of-text tables vs. listings. For example, the ICH E3 Section 12.2.2 Display of Adverse Events and Section 12.2.3 Analysis of Adverse Events have been removed because it was not clear what to include in the CSR without being repetitive to an unjustifiable extent.

  The tool keeps deaths, other SAEs, and other clinically meaningful AEs under a single Level 2 heading. The term 'Other clinically meaningful AEs' can be divided into 'discontinuations due to AEs' and 'other AEs of special interest'. Although the ICH E3 Q&A acknowledge the potential for double counting of deaths in two sections[4], the authors left this area of ambiguity to the sponsor's interpretation. However, they clarify that deaths occurring before study intervention should be mentioned in the CSR.

  Although the general guidance text states that information in the primary use CSR that may require redaction in the secondary use CSR should be minimized, there is still an in-text place for narratives in Section 12.2.2 which invites users to add mini-narratives of the most important events in addition to the full narrative in the appendix. In this case, it is extremely important to protect personal data. The tool recommends placing narratives in the E3 Section 14.3.3 for operational reasons and text flow in the main sections, but also acknowledges the ease of downstream redaction.

- The **TransCelerate CSR template** keeps the high-level summary table and suggests reuse in the CSR synopsis. The text description of the summary table is kept to a high-level key message, following lean writing principles. The template is light on instructions for the section on all AEs and recommends subsections similar to the CORE Reference. This allows a high level of flexibility with regard to the extent of the section (e.g. Phase 1 trial in healthy participants vs. Phase 1 in participants with cancer) and the analysis strategy (e.g. descriptive vs. 3-tier approach, MedDRA System Organ Class, NCI-CTCAE grading). The lack of instructional text can lead to very different approaches but leaves room for the sponsor's needs during implementation.

  Topics such as deaths and SAEs are individual sections and not combined under a common heading. Technically this could lead to double counting; however, many sponsors summarize SAEs including death and present fatal cases in a separate section to emphasize their importance. This topic remains inhomogeneous across the industry and the heading needs to reflect the sponsor's standards. There is no subsection for narratives, as they should be included solely in the appendix and only crossreferenced in the CSR body; mini-narratives are discouraged.

4.1.7 Summary, Discussion and Conclusions

The classic ICH E3 derived CSR template provides conclusions in at least four sections: in Section 11 focused on efficacy and other results, in Section 12 focused on safety, in Section 13 the overall conclusion and the synopsis. The level of details for each of the sections remains unclear; only the suggested page limitation for the synopsis is an indication. In addition, the ICH E3 terminology for Section 11.4.7 Efficacy Conclusion/Section 12.6 Safety Conclusion may contribute to the overlap with the content presented in Section 13 Discussion and Overall Conclusion[1].

- The **CORE Reference** provides results summaries at the end of Section 11 (efficacy) and Section 12 (safety). The heading has been changed to 'summary' to specify the expected content in contrast to the overall conclusion section. These two sections should not contain conclusions or interpretations, but merely summarize the results, e.g. in a bulleted list.

- The **TransCelerate CSR template** also provides summary sections; however, it recommends summary sections for each of the topics addressed in the CSR and at the beginning of each topic section, to fully embrace the deductive writing approach.

ICH E3 Section 13 should also include a discussion and a conclusion as per the section title[1]; however, in reality it is often another summary of trial results with repetition of data. ICH E3 remains unclear if cross-references to other CSR sections are acceptable.

- The **CORE Reference** adds subsections for discussion and conclusions. It states that the discussion should be factual and with no or little hypothesizing and with the aim to place the trial results into the context of currently available treatment options as well as ongoing and future clinical development. If data are referred to, they should be stand-alone without cross-reference to other sections. For the conclusion part, a bulleted list structured by objective is suggested to ensure that all objectives/endpoints are addressed.
- The **TransCelerate CSR template** has removed discussion part completely because in real life it is either misused as another summary or over-engineered like in a journal publication. Also, considering the trial results in isolation does not provide sufficient insights into the benefits and risks of the treatment under development and therefore the critical benefit-risk assessment as well as future development opportunities are better placed in the clinical CTD modules. For the conclusions, a bulleted list similar to the CORE Reference is suggested.

4.1.8 Synopsis

ICH E3 provides an example synopsis that should present the most important results and conclusions together with some key elements of trial design[1]. There is some lack of clarity that the synopsis is a stand-alone document and, therefore, should present what was done in the trial, not what was planned. ICH E3 suggests a page limit[1] but fails to provide guidance on where to reduce information, e.g. that only main criteria for inclusion should be included.

Furthermore, there is currently no requirement to present endpoint results in the synopsis; it only states "*the synopsis should provide efficacy and safety results…*"[1]. The lack of specificity

around the term endpoint can be an issue when the synopsis is used as stand-alone document for results posting. ICH E3 clearly needs guidance on the inclusion of endpoints and results to keep the balance between full transparency and respecting commercially confidential information (CCI) (e.g. inclusion of exploratory endpoints, reporting of all secondary endpoints). Furthermore, the inclusion of the endpoint description would render the section 'Criteria for evaluation' redundant and it could be omitted with loss of information.

- The **CORE Reference** clearly points out the synopsis should be stand-alone, as clarified in the ICH E3 Q&A, and provides all available information within the expected page length (3 pages in ICH E3 vs. up to ten pages in ICH E3 Q&A, and ICH M4)[1,3,4]. It requests the presentation of endpoints (limiting to primary and secondary is suggested) in the synopsis. A new section in the synopsis has been introduced for the description of endpoints. Although a clear linkage to objectives is claimed, the two sections are far apart from each other.

  Estimands are already mentioned in an awareness comment, without further guidance because the release of the tool preceded the finalization of ICH E9(R1)[7]. Only the expectation is raised that estimands should be described in the synopsis in the design section.

- The **TransCelerate CSR template** also points out that the synopsis should be stand-alone for further downstream reuse. The template frequently suggests content reuse from the protocol. Template Version 1 was finalized in parallel to the release of ICH E9(R1) and has considered the estimand concept from the very beginning. Since then, the presentation of objectives/estimands/endpoints and results has changed significantly, based on user feedback and to align with the other components of the Suite of Clinical Templates. However, the main feature has not changed, which is the tabular presentation of objectives closely linked to estimands and/or endpoints, which is a significant improvement compared to ICH E3 or the CORE Reference tools.

The EU-CTR adds further to the need for revision of the ICH E3 synopsis section in case the synopsis is interpreted as subject to Annex IV of the EU-CTR, e.g. background and rationale of the trial (see Section 4.2.1.1).

- Both, the **CORE Reference** and the **TransCelerate CSR template** acknowledge these new requests already despite the lack of clarity on the interpretation of EU-CTR Annex IV.

4.1.9 Appendices

The CSR usually contains numerous appendices and ICH E3 provides a list of recommended appendices in Section 16 of the guidance[1]. Some appendices contain data that are specific requirements of individual regulatory authorities and should be submitted as appropriate.

A first attempt to clarify the need for appendices was taken in 2004, in the Note for Guidance on the Inclusion of Appendices to CSRs in MAAs[35]. It provides the minimum requirement to be submitted with each CSR in the initial MAA dossier. Further clarification was provided 8 years later in the ICH E3 Q&A for some aspects around appendices that are available in the Trial Master File (TMF) [4]. For example:

- the per-participant batch number listing in Appendix 16.1.6 is no longer required as it is part of the TMF[4]. However, it is substituted with a simple list of both drug and placebo batch numbers which are still required (without participant linkage) for inclusion in the CSR text and/or synopsis.
- investigator curricula vitae, ethics committee approvals, or informed consent forms do not need to be submitted because they are included in the TMF[4].

However, availability in the TMF is not the only aspect to be considered because any "*documentation needed to review the CSR*" should be appended to the CSR[4] as the TMF is not submitted with the MAA. Furthermore, it needs constant reminders that the required information must be included in the TMF or clinical supply database at the time of MAA filing.

It remains tricky to find the right balance between appending the required information and overloading the CSR with redundant documents. Certain requirements, for example in

Appendix 16.1. Study Information, need to be fulfilled for the validation of MAAs. These details are not covered in ICH E3, but are detailed in the EMA preauthorization procedural advice for users of the centralized procedure[36] or in Validation issues frequently seen with initial MAAs[37].

- The **CORE Reference** provides guidance on CSR appendices in respect to content and hyperlinking. In general, the tool prefers a comprehensive repetition of appended content in the CSR body to set the results in context and does not support hyperlinking to appendices.

  The impending public disclosure requirements have led to appending details of named individuals formerly included in ICH E3 Section 6. For example, the CSR body should only have names of the Coordinating/Principal Investigator and sponsor signatory; other names, personal phone numbers and email addresses should be moved to the Appendix 16.1.4. The tool provides more detailed information on appendices than ICH E3 and covers already most of the requirements of the above-mentioned EMA documents.

- The **TransCelerate CSR template** is focused on the CSR body and does not provide instructions for statistical outputs, narratives, or appendices. However, the instructional text quite often recommends hyperlinking to the respective appendices for the majority of the data-independent content, e.g. introduction, trial design or in-/exclusion criteria.

4.2 Public Disclosure and Transparency

4.2.1 Requirements under EMA Policy 0070 and EU-CTR

In the EU, posting of clinical trial results has been a requirement since 2014, for all clinical trials in the EudraCT database (see Section 3.3). The submission of a CSR to the authorities per se is a legal requirement and has been laid out in domestic legal frameworks, e.g. in Germany as 'Mitteilungspflicht nach der Durchführung' according to § 13 Abs. 9 GCP-V[38] or § 42b AMG[39].

New aspects for public disclosure are related to the EU-CTR requirements of posting trial-relevant documents in addition to the disclosure of data[5]. With the go live of CTIS, CSRs and other documents will be placed into the public database after they were redacted by the

sponsor. The scope of the EU-CTR processes is consistent with the already available EMA Policy 0070 [6]. See Appendix 2 for an overview on disclosure requirements in the EU-CTR and Policy 0070.

The EU-CTR calls for even greater transparency and leverages the new CTIS portal for the upload of all relevant data. After the transition period in 2025, CTIS will ultimately replace the EudraCT forms (e.g. Annex 1, 2 and 3), and will be used for safety reporting (via EudraVigilance), modifications, notifications, corrective measures, results summaries, and other information. With few exceptions, CTIS will make all data and documents in the database publicly available, and it is crucial for the sponsors to realize this increased public transparency. Until now, the transparency activities could have been shifted to the approval stage[6], but the EU-CTR requires transparency throughout the development process, from protocol to MAA[5]. There will be options for deferring publications or exemptions, e.g. for Protected Personal Data (PPD) or CCI, confidential communication between member states or clinical trial supervision by member states. Study related data such as subject information sheet, protocol, IMPD S&E section, Investigator's Brochure and Responses to Requests for Information may be deferred between 5 years (category 2/Phase 2&3 and category3/Phase4) and 7 years (category 1/Phase 1) after the end of the trial[30].

The Technical Summary and the Lay Language Summary are mandated by the EU-CTR to be submitted by the sponsor after the completion of each trial in the EU[5]. Both summaries can only be deferred for category 1/Phase 1 trials for up to 30 months after the end of the trial[30]. In addition, the CSR itself will be submitted by the marketing authorization holder (MAH) after having received the marketing authorization.

4.2.1.1 Technical Summaries according to EU-CTR

The Technical Summary outlined in EU-CTR Annex IV lists the elements that should be included[5], which overlaps to a large extent with the ICH E3 synopsis and is similar to the previous requirements for result disclosure. However, in some aspect the new requirements go beyond the previous, e.g. by requiring information on global substantial modifications,

interruptions or restarts, and potential concerns in the overall results of the clinical trial[5]. Both, the **CORE Reference** and the **TransCelerate CSR template** offer solutions to bridge the gap between ICH E3 and the EU-CTR (Table 1).

Table 1 Elements of Technical Summaries Reflected in the CSR Synopsis

	ICH E3	CORE Reference	TransCelerate CSR template
CLINICAL TRIAL INFORMATION			
Clinical trial identification (title, study number)	Partially	Yes	Yes
Identifiers (e.g. EU trial number)	No	Yes	Yes
Sponsor details (scientific/public contact)	Partially	Yes	Yes
Pediatric regulatory details	No	Yes	Yes
Result analysis stage (incl. information about intermediate data analysis date, interim or final analysis stage, date of global end of the clinical trial)	Partially	Yes	Yes
General information about the clinical trial: • main objectives of the trial • trial design • scientific background • explanation of rationale for the trial • date of the start of the trial • measures of protection of subjects taken • background therapy • statistical methods used	Partially	Yes	Yes
Population of subjects: • actual number of subjects included in in the Member State concerned, in the Union and in third countries • age group breakdown • gender breakdown	Partially	Yes	Yes
SUBJECT DISPOSITION			
Recruitment, including information on the • number of subjects screened, recruited, and withdrawn • inclusion and exclusion criteria • randomization and blinding details • investigational medicinal products used	Yes	Yes	Yes
Pre-assignment period	No	No	No
Post-assignment period	No	No	No
BASELINE CHARACTERISTICS (age, gender, study specific characteristics)	No	Yes, no details	Yes, with details

	ICH E3	CORE Reference	TransCelerate CSR template
ENDPOINTS (definition, endpoint#, statistical analysis)	Yes, no details	Yes	Yes
ADVERSE EVENTS			
• adverse events information • adverse event reporting group • serious adverse event • nonserious adverse event	Yes, no details	Yes, no details	Yes, with details
ADDITIONAL INFORMATION			
• global substantial modifications • global interruptions and restarts • limitations, addressing sources of potential bias and imprecisions and caveats • a declaration by the submitting party on the accuracy of the submitted information	No	No	No

In the preparation of disclosure documents, the scope of disclosed results with respect to primary, secondary, and exploratory endpoints has long been a topic for discussion. The EU-CTR Annex IV states that "*Information shall be provided for as many end points as defined in the protocol.*"[5] The current interpretation is that the final Technical Summary should include at least results of all primary and secondary endpoints defined in the study protocol and in the SAP, not just main or key endpoints[40]. However, endpoints that are exploratory or post hoc in nature are not expected to be disclosed, but the sponsor can choose to do so.

In any case, a CSR template that avoids redundancy and has a clear structure linking objectives to estimand and endpoints is a huge benefit to facilitate the development of the Technical Summary and to ensure consistency between the CSR, the Technical Summary, and the Lay Language Summary.

Currently there is no template available for the format of results that need to be submitted to CTIS. EMA refers to the Annexes IV and V of the EU-CTR for the high-level content of the summaries and expects that results will have a tabular format as provided in EudraCT, at least until structured data will be implemented[40].

4.2.1.2 Lay Language Summaries according to EU-CTR

The overall results of the clinical trial should be summarized in plain language[5], directed specifically towards people with low health literacy. This summary is referred to as Lay Language Summary or Lay Summary in Europe, while other jurisdictions refer to it as Trial Result Summary or Plain Language Summary.

Annex V of the EU-CTR lists 10 elements that must be addressed in a Lay Language Summary[5], most of which can easily be derived from the CSR (Table 2). It is important that only results of a single trial are included, using an unbiased and nonpromotional language and consistent information flow in all required translations. This summary includes the main objectives of the clinical trial and should hence reflect at a minimum the primary endpoints and participant-relevant secondary endpoints[40].

Table 2 Ten Suggested Headings in Lay Language Summaries

1. Clinical trial identification	6. Description of adverse reactions and their frequency
2. Name and contact of sponsor	7. Overall results of the clinical trials
3. General information about the clinical trial	8. Comments on the outcome of the clinical trial
4. Population of subjects	9. Indication if follow up clinical trials are foreseen
5. Investigational medicinal products used	10. Indication where additional information could be found

The recommended guideline for authoring of Lay Language Summaries is 'Summaries of Clinical Trial Results for Laypersons - Recommendations of the expert group on clinical trials on Summaries of Clinical Trial Results for Laypersons'[41]. There is also guidance in the Good Lay Summary Practice[42], which provides direction on the process from planning to translation and distribution as well as involvement of patient representatives. A thoughtful and specific, yet nonpromotional, endpoint description is crucial, and the selection of results is prone to unconscious bias.

The Lay Language Summary should be provided at the same time as the Technical Summary of the trial. Developing a template for Lay Language Summaries is highly recommended to drive

the development of a nonpromotional and unbiased summary. Synergies can be gained when the CSR template of the sponsor is shaped in a way to facilitate the extraction of information such as endpoint definition, standard in-text tables for disposition, or safety aspects.

According to the Good Lay Summary Practice, the lay summary should be written based on the CSR, ideally the final CSR or at least an advanced draft[42]. The final Lay Language Summary needs to be checked against the final approved CSR or the full set of statistical outputs. And in addition, the consistency between Lay Language Summary and Technical Summary needs to be ensured. Considering this complexity and the underlying timelines for results disclosure, it would be a tragic waste of opportunity if these three documents are developed in silos instead of being based on well-designed mutually supportive templates with the potential for automation. ICH E3 is not sufficiently addressing the needs of the EU-CTR.

- The **CORE Reference** and the **TransCelerate CSR template** cover most aspects the new disclosure requirements. Due to the continuous industry feedback, further improvements of the TransCelerate CSR template can be expected to reflect the learnings from the first CTIS submissions.

4.2.1.3 Submission of CSRs to CTIS

As per Article 37(4) of the EU-CTR, the MAH must submit a CSR through the CTIS portal within 30 days after the day of marketing authorization approval (or completion of procedure/withdrawal of application)[5]. As the MAA process is performed outside of CTIS there is no due date attached to this task in the portal and it remains the sole responsibility of the MAH to comply with this EU-CTR requirement.

It is important to keep the logic of the CTIS portal in mind while writing the CSR because it is only possible to upload 1 CSR per clinical trial. If a CSR is updated, a new version of the CSR is created in CTIS[43]. This is an important aspect in studies with a long overall duration and multiple readouts for which usually several interim CSRs will be written. It is helpful for any reader to have a statement in the objectives and endpoints section to identify the scope of the given CSR and a reference to results reported in previous versions.

- Both the **CORE Reference** tool and the **TransCelerate CSR template** refer to previous versions of the CSR and to objectives and endpoints that are not included in the underlying CSR; however, including a statement where this information is found would be beneficial.

An excellent example of transparency and traceability of information across multiple CSR versions can be found in the Interim CSR of BioNTech Study C4591001 (Figure 1).

Figure 1 Example of an Informative Objectives and Endpoints Table

Table 1. Phase 2/3 Objectives, Estimands, and Endpoints

Objectives[a]	Estimands	Endpoints	Reference
Primary Efficacy			
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection	Prespecified complete efficacy data are reported in final analysis interim CSR dated 03 December 2020. Updated efficacy data for participants 12 through 15 years of age only are reported in this CSR.
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT	Interim data are reported in final analysis interim CSR dated 03 December 2020. Updated efficacy data for participants 12 through 15 years of age only are reported in this CSR.
Primary Safety			
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the second dose • SAEs from Dose 1 to 7 days after the second dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs	Interim data are reported in final analysis interim CSR dated 03 December 2020.

Taken from the publicly available CSR of BioNTech Study C4591001 (Report Date 14 April 2021), downloaded from EMA clinical data website[25] on 03 January 2022

4.2.2 Handling CCI and PPD in CSRs

The publication process for CSRs (and other clinical CTD modules) raises awareness for PPD and CCI. Despite the aim for transparency, the protection of personal data is a fundamental right of EU citizens. Therefore, participant data have to be anonymized before disclosure to protect participants from retroactive identification. While it is fairly straight forward what is considered PPD and which parts are out of scope for disclosure, the situation for CCI remains more complex. For example, interactions between the sponsor and regulatory agencies during protocol development, exploratory objectives/endpoints/variables (including biomarkers),

information driving the sample size calculation, and analytical methods of PK/PD determination may be considered CCI in CSRs[6].

The External Guidance on the implementation of Policy 0070 [44] provides information on topics that are not considered to be CCI, e.g. because it is in the public interest (Rejection Code 03). Also, any information available in the public domain is not considered CCI. Examples for potential topics where sponsors include sensitive CCI in CSRs are the following:

- Information about assay specifications or information about innovative bioassays/analytical methods as well as analytical methods of PK/PD determination[44]. It is worthwhile to provide as little information as possible in the CSR body and rather refer to the Appendix 16.1.13 Bioanalytical Reports for the details on bioanalytical results. Validation reports can be made available upon request or be included in the eCTD.
- Objectives that are not supportive of a label claim, including exploratory endpoints and efficacy and safety variables[44]. As the exploratory objectives could be used by a competitor to gain insights into future development plans for the product, it is current practice to list them in the protocol and the CSR body, but not in the synopsis or EudraCT. In addition, the results of exploratory endpoints are usually not included in the CSR synopsis, but only in the CSR body.
- The sample size calculation can be CCI based on the intellectual consideration for the determination. The sample size itself is not CCI and should clearly be stated in the CSR[44]; however, the details of sample size calculation should be limited to the Appendix 16.1.9, with effective hyperlinking from the CSR body to the appendix.

Handling personal data in a CSR can be more difficult. In general, participant-level data are considered PPD and will not be disclosed. This is fairly easy as long as participant-level data remains in the respective listing (ICH E3 Section 16.2). If such data are referenced in the CSR body, this will need to be redacted at every instance. Names of signatories, investigators, sites, or sponsor representatives will be disclosed if included in the CSR body; only contact details and the actual signature would be redacted. There should be a crossfunctional effort during

CSR authoring to describe the trial results without adding details of PPD that do not add scientific usefulness to the interpretation of the results or to the evaluation of trial conduct. However, it can be a fine balance between what is needed for regulatory approval versus the eventual publication risk. CSRs for trials with a high risk of re-identification, i.e. due to a small population or rare indication, highly benefit from a strategy meeting to plan the presentation of participant-level data and strategize the use of summary data as risk mitigation.

The individual participant narratives are a classic example. Although the full narratives should usually reside in ICH E3 Section 14.3, the guideline encourages mini-narratives for cases of death or other SAEs in the CSR body[1]. It is worth knowing that full redaction of narratives in the CSR for public disclosure is not allowed[44] and requests for block redaction are usually not accepted by EMA. If results description on a participant-level cannot be avoided, every effort should be made to generalize the text or at least describe the case in a single location and cross-reference for further use.

- Age, sex, or race should be added only if this information is important for the case description; otherwise, the description could start with 'a participant in Group A reported…' without losing scientific value.
- Use of gender-specific pronouns should be avoided or paraphrased. If they must be used, the black bar for redaction must not reveal by its length which pronoun was used.
- If participant identifiers are used, the part identifying the site may be removed to reduce the risk of re-identification and a consistent formatting is highly recommended.
- Relative days should be used instead of the absolute date, in particular in medical history. Age should be used instead of birth dates.

To prevent the need for redaction, it is highly recommended to avoid using PPD and CCI language in the CSRs as much as possible. If it can't be avoided or paraphrased, PPD and CCI should only be used once per document along with effective hyperlinking.

- The **CORE Reference** tool flags all potential CCI topics as per the External Guidance on Implementation of the Policy[6,44]. In several instances CCI is flagged in the document, e.g. for

individual name(s) and affiliation(s), the medical rationale for the development of the study, and the discussion. PPD is marked throughout the tool and the general strategy is to include potential details in a way that achieves anonymity in the primary use CSR (participant-level data) or to exclude details that would anyway be rejected for redaction.

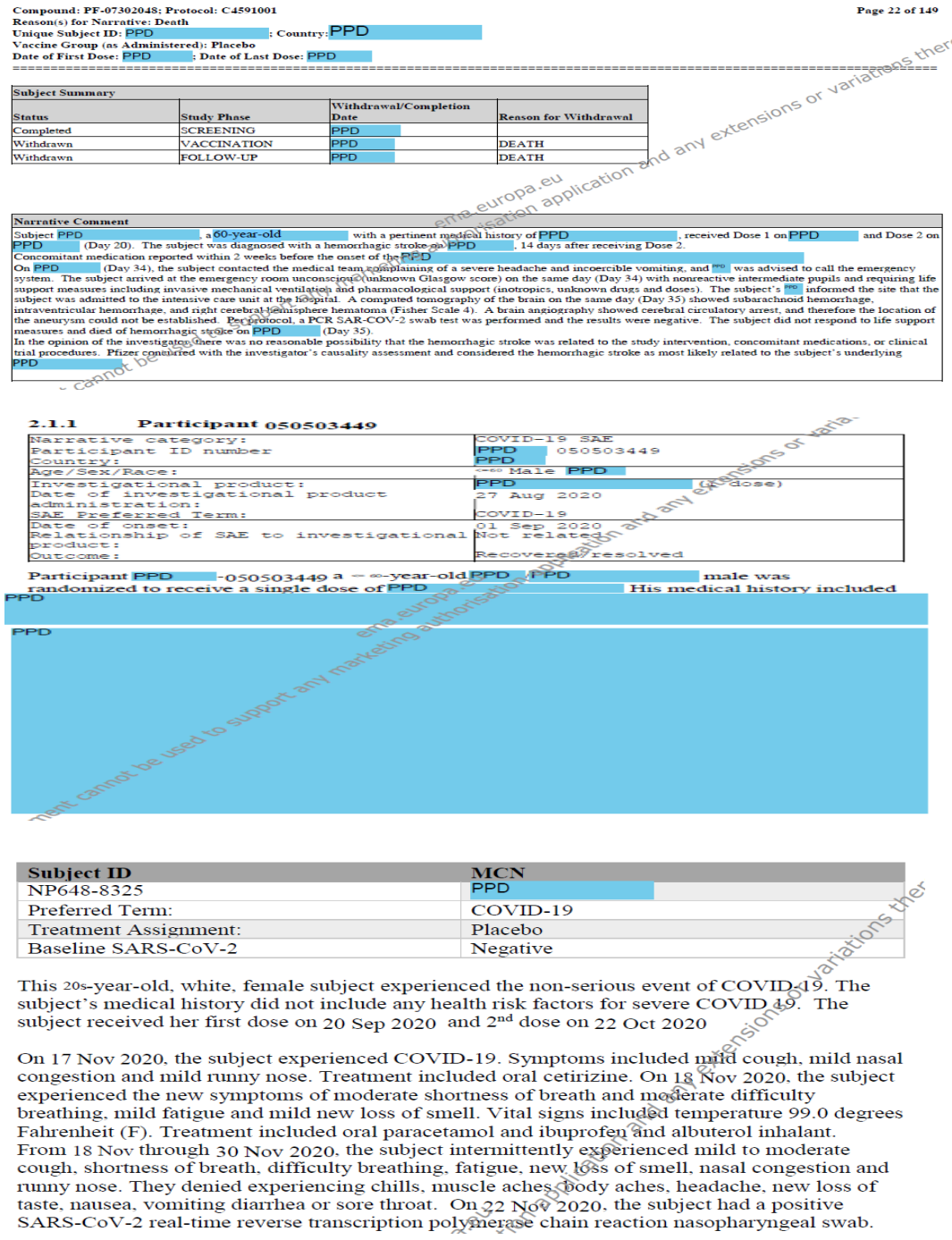
- The **TransCelerate CSR template** is by design less prone to accidentally sharing unnecessary CCI due to the underlying principle of hyperlinking to the protocol or the SAP. Reference to CCI is still made in the introduction. The template generally discourages using names and addresses throughout the CSR, even more strict than the CORE Reference. The template is similarly strict on the inclusion of potential PPD and avoid names and contact details completely in the CSR body; all relevant information is included in the respective appendices. Participant-level description should only be included if necessary while avoiding PPD completely or at least according to current minimum standards for de-identifying data. Referring to the full participant narratives instead of detailed descriptions in the CSR body is encouraged.

4.2.2.1 Examples of Results Disclosure and Applied Redaction

The publicly disclosed CSRs should include the ICH E3 Section 1 to 15, the protocol(s), the sample case report form, and the SAP[6]. The full redaction of narratives is not allowed in the CSR for public disclosure[44], and narratives cannot be removed and should be anonymized to protect PPD. However, EMA has previously accepted full redaction of narratives[45] and up to 50% of narratives had been fully redacted in the past[46]. One such example is given by Pfizer, who had traditionally fully redacted their narratives (e.g. as in CSR for Ibrance/palbociclib)[25].

To date, redaction of narrative details instead of anonymization is still the reality as shown in recently published CSRs on COVID-19 vaccine trials[25]. Figure 2 shows the inconsistent approach to redaction from three clinical COVID-19 trials[25], from which the high need for more guidance in ICH E3 becomes apparent.

Figure 2 Redacted Narratives of Participants in Covid-19 Clinical Trials



Compound: PF-07302048; Protocol: C4591001 Page 22 of 149
Reason(s) for Narrative: Death
Unique Subject ID: PPD ; Country: PPD
Vaccine Group (as Administered): Placebo
Date of First Dose: PPD ; Date of Last Dose: PPD

Subject Summary			
Status	Study Phase	Withdrawal/Completion Date	Reason for Withdrawal
Completed	SCREENING	PPD	
Withdrawn	VACCINATION	PPD	DEATH
Withdrawn	FOLLOW-UP	PPD	DEATH

Narrative Comment

Subject PPD , a 60-year-old with a pertinent medical history of PPD , received Dose 1 on PPD and Dose 2 on PPD (Day 20). The subject was diagnosed with a hemorrhagic stroke on PPD , 14 days after receiving Dose 2.
Concomitant medication reported within 2 weeks before the onset of the PPD
On PPD (Day 34), the subject contacted the medical team complaining of a severe headache and incoercible vomiting, and PPD was advised to call the emergency system. The subject arrived at the emergency room unconscious (unknown Glasgow score) on the same day (Day 34) with nonreactive intermediate pupils and requiring life support measures including invasive mechanical ventilation and pharmacological support (inotropics, unknown drugs and doses). The subject's PPD informed the site that the subject was admitted to the intensive care unit at the hospital. A computed tomography of the brain on the same day (Day 35) showed subarachnoid hemorrhage, intraventricular hemorrhage, and right cerebral hemisphere hematoma (Fisher Scale 4). A brain angiography showed cerebral circulatory arrest, and therefore the location of the aneurysm could not be established. Per protocol, a PCR SAR-COV-2 swab test was performed and the results were negative. The subject did not respond to life support measures and died of hemorrhagic stroke on PPD (Day 35).
In the opinion of the investigator, there was no reasonable possibility that the hemorrhagic stroke was related to the study intervention, concomitant medications, or clinical trial procedures. Pfizer concurred with the investigator's causality assessment and considered the hemorrhagic stroke as most likely related to the subject's underlying PPD

2.1.1 Participant 050503449

Narrative category:	COVID-19 SAE
Participant ID number	PPD 050503449
Country:	PPD
Age/Sex/Race:	<=60 Male PPD
Investigational product:	PPD dose)
Date of investigational product administration:	27 Aug 2020
SAE Preferred Term:	COVID-19
Date of onset:	01 Sep 2020
Relationship of SAE to investigational product:	Not related
Outcome:	Recovered/resolved

Participant PPD -050503449 a <=60-year-old PPD PPD male was randomized to receive a single dose of PPD His medical history included PPD

PPD

Subject ID	MCN
NP648-8325	PPD
Preferred Term:	COVID-19
Treatment Assignment:	Placebo
Baseline SARS-CoV-2	Negative

This 20s-year-old, white, female subject experienced the non-serious event of COVID-19. The subject's medical history did not include any health risk factors for severe COVID-19. The subject received her first dose on 20 Sep 2020 and 2nd dose on 22 Oct 2020

On 17 Nov 2020, the subject experienced COVID-19. Symptoms included mild cough, mild nasal congestion and mild runny nose. Treatment included oral cetirizine. On 18 Nov 2020, the subject experienced the new symptoms of moderate shortness of breath and moderate difficulty breathing, mild fatigue and mild new loss of smell. Vital signs included temperature 99.0 degrees Fahrenheit (F). Treatment included oral paracetamol and ibuprofen and albuterol inhalant. From 18 Nov through 30 Nov 2020, the subject intermittently experienced mild to moderate cough, shortness of breath, difficulty breathing, fatigue, new loss of smell, nasal congestion and runny nose. They denied experiencing chills, muscle aches, body aches, headache, new loss of taste, nausea, vomiting diarrhea or sore throat. On 22 Nov 2020, the subject had a positive SARS-CoV-2 real-time reverse transcription polymerase chain reaction nasopharyngeal swab.

Upper panel: from BioNTech Comirnaty downloaded 11 October 2021. Middle panel: from Astra Zeneca AZD122 (ChAdOx1 nCoV-19) downloaded 11 October 2021. Lower panel: from Moderna TX, Inc. Spikevax downloaded 20 April 2021

All examples were downloaded from EMA clinical data website25 in September 2022. Redacted content appears as a light blue box with a black 'PPD' label.

Under the pandemic, companies like Pfizer have experienced significantly more pressure from regulatory authorities to not redact their narratives of the clinical COVID-19 vaccination trials[45]. The regulators have accepted redaction of demographic data, dates, locations, or participant identifiers, but in many instances refused redaction of medical information. Hence, the narratives may still include medical details that increase the re-identification risk per se in particular in a trial that continuous in blinded manner.

Although disclosure activities have been suspended in 2018, the high need for transparency in the COVID-19 pandemic has led the EMA to their exemption[26]; also because the disclosure requirement now applies universally under the EU-CTR[5]. Hence, we can expect that EMA will not accept the redaction of an entire narrative anymore; exceptions need to be clearly justified in the anonymization report.

- Unfortunately, neither the **CORE Reference** nor the **TransCelerate CSR template** provide enough details towards state-of-the-art participant narratives. Narratives have been mostly out of scope of lean writing initiatives and general disclosure awareness activities. However, this is an area that needs more attention and guidance in future.

In addition to the technical hurdles of redaction, clinical trial participants were actively sharing PPD on newspapers and social media, even including injection dates, AEs, study site, and medical history. The more information trial participants shared on the media, the easier it was to identify them in the redacted CSRs that became publicly available at the same time. Together this has been an unprecedented risk to the integrity of clinical trial data and the protection of participants' rights.

4.2.3 Disclosing Prematurely Discontinued Trials

Clinical trials can be stopped prematurely for various reason. In the best case, the rationale is an outstanding benefit signal, such as in the Jardiance® (empagliflozin) Phase 3 EMPA-KIDNEY trial in participants with chronic kidney disease. The trial was stopped prematurely after the Independent Data Monitoring Committee confirmed clear positive efficacy following a formal interim analysis[47]. These trial results will be subject to an MAA and a full CSR will be written

followed by the standard disclosure activities. In most cases, clinical trials are stopped prematurely due to operational reasons, such as insufficient recruitment rate, strategic reasons or issues in conduct, or based on accumulated trial data such as lack of efficacy or safety findings[48].

EMA Policy 0070 as well as Article 34(7) of the EU-CTR describe the need to report the trial results irrespective of the trial outcome[5,6]. Prematurely terminated trials need to be notified via the End of Trial notification form to the national competent authorities, who are responsible to amend the information on the status of the trial in the EudraCT system. In the CTIS portal, the trial status needs to be displayed as prematurely ended and results need to be posted along with a rationale.

If a trial ended prematurely, the Lay Language Summary and the Technical Summary are still needed in addition to the CSR.

- The CSR is usually a part of the end of trial notification, albeit usually submitted subsequently to the actual notification. The sponsor has to submit the CSR within 12 months after the end of the trial (for pediatric trials 6 months) (refer to e.g. Article 34(7) EU-CTR)[5]. Format, content, and its accessibility for the public is referenced in the Commission Guideline 2009/C28/01 and 2008/C168/02 and their implementing technical guidance documents[23, 49,50]. The CSR can be a full CSR as per ICH E3 or an abbreviated or synoptic CSR, if the regulatory requirements are fulfilled. If an abbreviated format is chosen, safety is fully reported, while efficacy or other endpoints (if analyzed) may be omitted in the CSR body and only referred to in the statistical outputs[51].

  For both abbreviated and synoptic CSRs, it is crucial to display the results in a meaningful way, but with a keen eye on data privacy because of the high risk for re-identification of participants (e.g. due to a small population or rare indication).

  The **CORE Reference** mentions abbreviated CSRs only on the Title Page and the **TransCelerate CSR template** mentions this report type only in the template instructions.

Both documents refrain from providing any further guidance beyond the minimal available regulatory instructions, such as the widely adopted FDA Guidance[51].

- The Technical Summary will be based on the outcome data, as far as available in the CSR. If possible, the primary endpoint (if analyzed) is reported, while safety will always be reported.
- The Lay Language Summary will be based on the primary outcome data, if available in a full CSR or abbreviated CSR. If no data are available or statistical analysis cannot be provided, the Lay Language Summary should still include a statement indicating that sound statistical analysis of the information was not possible due to insufficient data; the primary endpoint data may be excluded[40]. Descriptive safety data would be expected to be reported in a full CSR or abbreviated CSR to the extent possible. Given the potential lack of interpretability of incomplete or premature data, the Lay Language Summary needs to be carefully worded. In addition, the rationale for early closure of the trial needs to be provided, e.g. lack of efficacy, safety events, or poor recruitment.

A special measure of precaution is needed if the trial was prematurely terminated with only a small number of participants. In such cases, summary tables are often skipped, and individual participant listings and descriptions are used, e.g. individual mini-narratives. It needs a skilled coordinator of the crossfunctional authoring to identify and avoid protected information early on (e.g. relative days, age only if meaningful for the event, gender-specific pronouns, participant identifiers or verbatim text).

Caution is also needed beyond the CSR body or the synopsis because it may be very tempting to merge the few pieces into a single published PDF. Additional redaction rework can be avoided by ensuring that all documents are placed in the correct eCTD structure (e.g. report body, signature pages, statistical outputs/listings/narratives). Incorrectly placed documents may be difficult to claim as 'out of scope' for disclosure once they are submitted to the health authorities.

4.3 ICH E8 General Considerations for Clinical Trials and ICH E6 Good Clinical Practice

4.3.1 ICH E6(R2) — Integrated Addendum

ICH E6(R2) included a focus on a proportionate, risk-based approach to the design and conduct of clinical trials[12]. This major addendum acknowledges the diminishing reliance on paper-based data collection and reporting as well as the increase of digital technologies and enhanced risk management processes. The most significant changes were:

- the implementation of a quality assurance and risk assessment process and the specification of monitoring plan components;
- the clarification and expansion of responsibilities for sponsors, e.g. implementing a robust risk-based quality management system, or demonstration of adequate vendor oversight;
- the clarification and expansion of responsibilities for investigators[12].

One topic that was newly introduced to the industry in Sections 5.0.4 and 5.0.7 are QTLs. These QTLs are measures of the modern quality management system and are important indicators of the status of data reliability and participant safety and wellbeing[12]. Unfortunately, ICH E6(R2) only paved the way for QTLs and introduced an obligation to report important QTL deviations and associated remedial actions in the CSR, without further specifying the requirements.

Clearly, QTLs are another gap to be filled in a potential ICH E3 update. ICH E3 Section 9.6 requires that it should be stated if no quality assurance and quality control systems were used[1]. However, the risk-based quality management system is now mandatory for all trials (as part of the EU-CTR[5]) and the non-adherence to this protocol requirement, such as important QTL deviations, needs to be reported in the CSR.

- The **CORE Reference** tool suggests including the description of the quality management approach and a summary of the important deviations from predefined QTLs in the ICH E3

Section 9.6, as suggested in ICH E6(R2); however, no guidance is included on the content or format.

- The **TransCelerate CSR template** has a detailed quality assurance section with suggested standard text. The guidance is more comprehensive than ICH E3 or the CORE Reference, especially with regards to the description of QTL deviations. Consistently with the lean writing approach, the detailed description of QTL deviations is suggested to be included in a new appendix. Inclusion in the CSR body could lead to a significant increase in the size of the data-independent section and derail the focus from the primary objective of the CSR, i.e. results reporting. Although, the template provides guidance on when, what, and where to summarize important QTL deviations in the CSR, this guidance has no official character and therefore regulatory authorities will see a variety of approaches across the industry, i.e. either as a summary within the body of the CSR, as an appendix of the CSR, or as a combination of both.

4.3.2 ICH E8(R1) — General Considerations for Clinical Studies

ICH E8(R1) provides us with fundamental design elements for clinical studies[16] that should be carefully considered before entering the conduct phase of under ICH E6 applicability. It acknowledges the increasing complexity of trial designs and the wider range of source data, brings the patient-centric drug development to its focus, and introduces the new quality-by-design approaches. New terminology has been introduced and older existing principles have been reinforced[16]. ICH E8(R1) can also be regarded as first step towards the renovation of GCP.

This guideline lays out general principles for the conduct on clinical trials from design to reporting. While it is stressed at several instances that the "*foundation of a successful study is both scientifically sound and operationally feasible protocol*"[16], we can expect downstream effects on the SAP and the CSR. Ultimately, ICH E8(R1) demands that the ICH Efficacy guidelines should be considered in a holistic and integrated way[16]. To achieve this goal the ICH Efficacy guidelines should be mutually supportive and not contradictive (worst case), which clearly highlights the overdue revision of ICH E3.

4.3.3 ICH E6(R3) — the Renovation of GCP

In January 2017, ICH released their GCP Renovation Plan[14] and today ICH E6(R3) is close to being released and will mark a change in how clinical trials will be planned, conducted, and reported. Having two revisions of a major guideline within only five years reflects the rapid changes in clinical development, e.g. the increase of remote and decentralized trials, use of new technologies, or new designs such as platform trials. Therefore, ICH E6(R3) aims to provide a framework for as many scenarios as possible while providing enough flexibility for future advancements in technology[14].

Despite ICH E6(R3) being a major revision, most principles have not changed, except for editorial alignments; however, the renovation introduces four new principles to ICH E6. See Appendix 3 for a comparison of ICH E6(R2) and ICH E6(R3)[12,14].

ICH E6(R3) Principle #7 states "*Quality should be built into the scientific and operational design and conduct of clinical trials*" [14].

The quality concept has already been touched on in ICH E6(R2), with the requirement to have systems in place to ensure the quality[12]. With ICH E6(R3), we will be progressing from creating systems to track trial quality and being reactive to events towards proactively building quality into the design of clinical trials. The subprinciples elaborate on the amount and quality of data generated and how this should support faster decision making[14]. The analysis and reporting are not specifically mentioned in this principle, but without scientifically sound analysis and structured reporting, even good quality data are not enough to achieve the overarching goal.

Subprinciple 7.4 requires the implementation of strategies "*to avoid, detect and address serious noncompliances with GCP*" [14]. This goes hand in hand with the Guideline for the notification of serious breaches of the EU-CTR or the clinical trial protocol[52]. This guideline is already effective since 31 January 2022 and provides a non-exhaustive list of serious breaches and reinforces the sponsor's reporting responsibility[5]. Important deviations from the protocol, GCP or regional legislation have been subject to reporting in CSR as per ICH E3 [1]. However, the

definition of a serious breach and an important protocol deviation are not equivalent, and it is clearly stated that all serious breaches should be included in the CSR[1,5,52].

- The **CORE Reference** has no specific instruction on the topic beyond ICH E3 Section 9.6.
- The **TransCelerate CSR template** has this topic covered on a high level in Section 3.6 (E3 Section 9.6). Per instructions, any misconduct or serious noncompliance is to be documented and a cross-reference should be made to the protocol deviations (if applicable) to reflect the potential overlap between the concepts.

In addition, the eCTD Module 1 requires a short discussion of the GCP compliance status for pivotal studies, including a listing of any GCP noncompliances or breaches of GCP[37]. This information needs to be derived from the CSR or at least be consistent with the CSR. However, ICH E3 requests only a *statement indicating whether the "study was performed in compliance with GCP"* [1], which could be as simple as a yes/no tick box.

ICH E6(R3) Principle #11 states "*Roles, tasks and responsibilities in clinical trials should be clear and documented appropriately*" [14]

ICH E6(R2) and ICH E6(R3) require fully qualified study personnel to perform the assigned tasks[12,14]. However, ICH E6(R3) calls out more functions by name ("*physicians, scientists, ethicists, technology experts, and statisticians*")[14], which makes the definition of roles and responsibilities more important than ever.

ICH E6(R3) requires documentation of the qualification and tasks[14]. While the full-fledged documentation is surely within the TMF, the CSR according to ICH E3 also requires reporting the list of investigators and important study personnel[1]. Owing to the disclosure requirements the **CORE Reference** and the **TransCelerate CSR template** discourage displaying this information in the CSR body; however, with ICH E6(R3) on the horizon, some more emphasis should be given to ICH E3 Appendix 16.1.4 to ensure that it goes beyond the list of investigators.

4.4 ICH E9(R1) — the Estimands Concept

The estimands concept was introduced to clinical trials with the ICH E9(R1) guideline[7] and is a new paradigm in clinical research. Estimands are a systematic description of the treatment effect that needs to be quantified to answer the research objective of the clinical trial. The estimand consists of the five attributes: treatment, population, variable, population-level summary, and handling of intercurrent events. Estimands are defined for primary and secondary objectives in the clinical trial protocol[7].

The estimand concept should help defining the explicit scenarios that the collected trial data could address. It changes the focus of intercurrent events from a disturbance towards additional and important information on efficacy or safety of the trial medication. By defining upfront the most meaningful questions in the clinical context, with the most relevance for the patient, ultimately allows writing of a higher quality CSR than compared to the previous endpoint definitions in clinical study protocols. The results section of a CSR needs to be organized around the estimand, not only the endpoints, e.g. by also describing the occurrence and timing of intercurrent events[7].

- The **CORE Reference** was developed while ICH E9(R1) was still a concept paper. Hence, only awareness comments were included to indicate how the estimands guidance may impact the authoring of CSRs.
- The **TransCelerate CSR template** Version 1 was released shortly after ICH E9(R1) was available and has therefore included guidance on estimands from its very beginning. Since then, plenty of industry feedback has been implemented to present estimands in a statistically meaningful way that still allows efficient disclosure of endpoint definition and statistical outcomes. Two examples are provided to structure the efficacy section around estimands and the different types of statistical analyses.

5 Discussion

Every seasoned regulatory medical writer, who has written dozens of CSRs, and every experienced regulatory operations manager, who has published even more CSRs, know ICH E3 with eyes closed. But ICH E3 was written back when CSR submissions were done as huge binders of paper documents and so it is not surprising that the ICH E3 structure is designed accordingly. To be more illustrative, ICH E3 was released shortly after Microsoft launched Windows 95 and 2 years before Google went online.

ICH E3 has taken many drafts and years of development and leaves the impression that the scope has been shifted during development. The root cause for such carefully worded guidelines and compromises is often the argument around minor scientific issues[2]. One can only imagine the magnitude of complexity and politics around this guideline.

This thesis has analyzed many of the intrinsic challenges and pitfalls of ICH E3 and it has become clear that a CSR that is compliant with ICH E3 but ignorant of the surrounding new regulatory developments would fall behind on the expectations of regulatory reviewers. Although ICH E3 was never meant to be considered in isolation, the volume of additional sources needed to develop a state-of-the-art CSR has grown to an extent that is barely feasible to handle.

Unfortunately, ICH has declared their "*wish to remain insular in developing guidance and have stated in a letter to Sam Hamilton (Chair CORE Reference project) received August 2015, that they do not plan to update ICH E3*"[53]. However, the overarching guideline ICH E8(R1) clearly states in Section 6.3 that the format used for reporting of clinical study results should be adequately chosen[16]. This statement substantiates the fact that ICH E3 is not meant to be a CSR template, and should it is be used as such.

The question remains if a CSR template would ultimately be the solution. Clearly, there is a need from users in the industry, which has led to the unfortunate interpretation of ICH E3 and has sparked the industry-led development of tools, such as the CORE Reference and the TransCelerate CSR template.

The CORE Reference has already identified some flaws in the inherent ICH E3 structure and proposes an improved structure. In addition, the tool provides clearer guidance on the required content. Although the tool goes a bit beyond the ICH E3 Q&A, it still stays relatively close to the original structure. The rationale is that the tool is first and foremost a supportive guidance document and not a pure template and it was a clear decision to stick as closely to ICH E3 as reasonably justified because of the wide use of its terminology across other guidance documents[8].

Standardizing CSRs according to the CORE Reference would ultimately lead to CSRs with a logical presentation sequence, including all the guideline-required content, while being as disclosure-ready as possible. However, the CORE Reference is a very static document that represents the writing standard of 2016 and the guideline content from the mid-1990s. The resulting CSR would indeed be stand-alone and summarizes protocol and SAP throughout the data-independent sections, which corresponds to the original intent of ICH E3 from the era of paper-based submissions.

TransCelerate provides a true template that provides a document structure and formatting setting. It presents information consistently, allows room for customization to specific therapeutic area requirements , facilitates assimilation and assessment of the information by its ultimate user, and includes format and model content to enable downstream automation. The Suite of Templates aims to simplify the regulatory review task and improve transparency, while making it immediately apparent if information is missing or incomplete[9]. In addition, standardization will ultimately save time in developing documents as clinical development teams can stop discussing standard elements and focus on the critical content. There is no intent of it serving as guidance and therefore it refers to ICH E3 itself, the CORE Reference, and other sources for further information[9].

The structure of the TransCelerate CSR has been developed using a greenfield approach and reflects the experience of many users, the recommendations from the CORE Reference and all the little ICH E3 deviations that have successfully been used in real life CSRs, such as a different numbering of sections. As the CSR template belongs to the Clinical Template Suite, the sections

headings have been aligned with the protocol and SAP template[9]. The extensive use of cross-references to the protocol and the SAP may lead to the impression that the resulting CSR deviates from the ICH E3 requirement for an integrated report. However, regulatory reviewers will always have parallel access to the protocol and SAP and going back to the original resources for review is in any case the more robust approach to document review rather than relying on paraphrased text in the CSR. With the disclosure requirements on CTIS, the protocol and SAP will also be publicly accessible in a redacted manner.

6 Conclusion and Outlook

This thesis aimed to analyze the usability of ICH E3 as a template and/or guidance for state-of-the-art CSRs in an evolving regulatory landscape. It points out that ICH E3 was never meant to serve as a template and even ICH E3 Q&A has failed to clear up the misunderstanding that led to its use as an authorative template.

Many inherent structural issues have been analyzed and clearly demonstrate that a CSR template strictly following the unintentionally implied ICH E3 format would ultimately lead to a CSR that is not fit for purpose in a modern clinical development setting. On the flipside, a completely customized CSR template may still be perceived as deviation from the guideline - internally, by CROs, investigators, or even global agency reviewers.

Beyond the already existing inherent structural flaws, clinical development has changed drastically since 1995, with for example new technical advancements, digitalization, electronic submissions, databases. Along with these changes came a completely different approach to risk management and the urgency for public results disclosure.

ICH E3 clearly should be rewritten in a way that makes it crystal clear that the document is a recommendation for content. Similar to the renovation of GCP, the guidance text needs to be become leaner in some parts by removing repetition and inconsistencies. The new language in ICH E6, E8, and E9 needs to be included or crossreferenced to ensure state-of-the-art CSR writing. In the future, CSRs should be written within the spirit of ICH E3 while meeting the needs of electronic submissions and allowing for further technical advancements.

ICH E3 will not be able to reflect the different approaches to clinical result posting and transparency and this is not the objective of this ICH guideline. EMA and Health Canada are frontrunners in this field, but it is a global concept and there will always be different regional requirements and technical approaches to results disclosure. Nevertheless, some common themes around PPD and to what extent it is included in the CSR could still be established by ICH E3.

ICH E3 itself should not be a template and this needs to be a stronger message in a potential revision. A codified template is too rigid for results reporting in a continuously changing landscape. The ICH M11 working group has just circled back on the template concept and will ultimately only provide a high-level structure. The right balance between standards and flexibility needs to be achieved and official guidelines, like those from ICH, are too slow paced to keep up with the advancements. ICH has recognized this fact as clearly shown in the GCP renovation.

Yet the need for guidance with a faster turnaround time will persist and may even grow with the increasing need for transparency. Making clinical data publicly available is in the interest of public health in terms of transparent regulatory decision making and better-informed use of medicines. The primary objective of the regulatory activities has been met as demonstrated for the COVID-19 medicines throughout the pandemic.

Since the EU-CTR came into force in January 2022, results disclosure is legally binding and EU member states will need to start imposing sanctions for noncompliance. According to the lasted figures in the EU trial tracker[54], set up by researchers form the Bennett Institute for Applied Data Science at the University of Oxford in 2018, sponsors have reported 83.6% of their due trials. This increase in compliance as compared to in April 2019 (68.2% compliance)[24] shows that at least large pharmaceutical companies with their compliance departments have taken the EU-CTR effective date and the reminders from EMA seriously and prepared for the legal requirement of results posting.

Two industry derived tools have been analyzed in this thesis for their suitability to make up for the gaps in ICH E3.

The CORE Reference document represents a sound proposal for an industry wide applicable CSR that is ICH E3 compliant and yet less rigid and redundant than the original structure. The CORE Reference document also includes many aspects of results disclosure. The tool helps evolving CSRs to meet the modern needs; however, closely following the tool will still lead to complex and large CSRs with a high level of redundancy, limitations in results presentation, use of new technical developments and best practices such as lean and deductive writing.

The TransCelerate CSR template is a ready-to-use template that can be further customized to the sponsors preferences and processes as well as to the individual study needs. It fulfills the current ICH and EU requirements and leverages all the benefits of lean and deductive writing. Beyond all other available CSR writing guidances, the TransCelerate CSR template is part of an overall document approach and positions itself right in the center between protocol development and public results disclosure. The possibility for the industry to provide feedback and suggest improvements to the template, or simply challenge certain decisions, is a unique feature of this Suite of Templates and will persist being the state-of-the-art source for sponsor customized templates.

Using the most current version of the TransCelerate CSR template and the CORE Reference as manual for specific and detailed questions is a scientifically and regulatory sound approach for the development of a customized and state-of-the-art CSR template.

The posting of clinical trial details on social media that happened in real time to the official results posting has brought the topic of PPD to another level. Authorities and industries will need to work more closely together to arrive at more robust and reliable rules for CSR writing. Organizations like TransCelerate and its Suite of Templates offer a very valuable source for any interventional clinical trial and the annual review of the toolbox ensures a state-of-the-art CSR. The only disadvantage compared to the CORE Reference is the lack of official feedback from regulatory authorities.

7 Summary

Writing of CSRs is based on a more than 25-year-old guidance document that can be considered as one of the few pillars in a clinical development landscape. This landscape has been subject to substantial changes in trial design, globalization, digitalization, and transparency. This thesis analyzed if the ICH E3 guideline is still usable for state-of-the-art reporting of clinical trial results or if the evolution of the scientific and regulatory landscape has rendered the guidance revision overdue. The analysis focused on applicable EU legislations, such as the EU Clinical Trial Regulation 536/2014, and the recently revised ICH guidelines E6, E8 and E9. In addition, the two industry derived tools, the CORE Reference and the TransCelerate CSR template, were analyzed for their feasibility to bridge the identified gaps.

By laying out the structural flaws and inconsistencies of ICH E3 it becomes obvious that the guidance was never meant to be used as authorative template although its unintentionally implied format has been the basis for many sponsor templates. More than 15 years after its release, a hesitant revision was launched in form of a Q&A document, which has failed to clear up the misunderstanding that led to the use of ICH E3 as an authorative template. Both the CORE Reference and the TransCelerate CSR template were analyzed for their approaches to the identified inherent structural flaws of ICH E3 and both tools provide valuable solutions.

In addition to the evolution of clinical development and the renovation of GCP, the new EU-CTR will have a huge impact on results reporting and results posting. ICH E3 is no longer sufficient to deliver a CSR that is technically state-of-the-art and fit for purpose between the poles of maximum transparency and protection of PPD and CCI. Global requirements for disclosure are still too diverse to be reflected in a potential revision of ICH E3 on a broader scope; however, basic concepts of PPD and CCI could be implemented with rather simple changes to the guidance text.

A revision of ICH E3 is overdue and would be one of the logical next steps in a holistic renovation of ICH Efficacy guidelines. However, the analysis also shows that an authorative

template, that would potentially be codified by authorities, is not a recommended solution. But the CORE Reference and TransCelerate CSR template are valuable tools to develop a sponsor customized CSR template for which TransCelerate already delivers the basic MS Word backbone. In addition, the annual updates ensure a top quality CSR template that reflects industry wide best practices.

8 Literature

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9 Appendix

Appendix 1 Comparison of Section Numbers and Titles of ICH E3, CORE Reference, and the TransCelerate CSR Template

ICH E3	CORE Reference	TransCelerate CSR template
1 Title Page	1 Title Page	Title Page
2 Synopsis	2 Synopsis	Synopsis
3 Table of Contents for the Individual Clinical Study Report	3 Table of Contents	Table of Contents
4 List of Abbreviations and Definition of Terms	4 List of Abbreviations and Definition of Terms	List of Abbreviations [and Definition of Terms]
5 Ethics	5 Ethics	Ethics
5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)	5.1 Independent Ethics Committee and/or Institutional Review Board	Independent Ethics Committee and/or Institutional Review Board
5.2 Ethical Conduct of the Study	5.2 Ethical Conduct of the Study	Ethical Conduct of the Study
5.3 Patient Information and Consent	5.3 Subject Information and Consent	Participant Information and Consent
6 Investigators and Study Administrative Structure	6 Investigators and Study Administrative Structure	Moved to Section 3.2
7 Introduction	7 Introduction	1 Introduction
8 Study Objectives	8 Study Objectives and Endpoints 8.1 Objectives 8.2 Endpoints	2 Study Objectives, Endpoints and Estimands Objectives and Endpoints [Primary Estimand / Coprimary Estimands / Multiple Estimands] Secondary Estimand(s)
9 Investigational Plan	9 Investigational Plan	3 Investigational Plan
9.1 Overall Study Design and Plan - Description	9.1 Overall Study Design and Plan	3.1 Overview of Study Design
9.2 Discussion of Study Design, Including the Choice of Control Groups	9.2 Discussion of Study Design, Including the Choice of Control Groups	3.1.1 Discussion of Study Design
9.3 Selection of Study Population	9.3 Selection of Study Population	3.3 Selection of Study Population

ICH E3	CORE Reference	TransCelerate CSR template
9.3.1 Inclusion Criteria	9.3.1 Inclusion Criteria	3.3.1 Inclusion/Exclusion Criteria
9.3.2 Exclusion Criteria	9.3.2 Exclusion Criteria	
9.3.3 Removal of Patients from Therapy or Assessment	9.3.3 Removal of Subjects from Therapy or Assessment	3.3.2 Removal of Participants from Intervention or Study
9.4 Treatments	9.4 Treatment	3.4 Study Intervention
9.4.1 Treatments Administered	9.4.1 Treatments Administered 9.4.1.1 Investigational Product(s) 9.4.2.2 Non-investigational Product(s)	3.4.1 Study Intervention(s) Administered
9.4.2 Identity of Investigational Product(s)	9.4.2 Identity of Investigational Product(s)	Section name NOT INCLUDED; provided in Section 3.4.1
9.4.3 Method of Assigning Patients to Treatment Groups	9.4.3.1 Methods of Assigning of Subjects to Treatment Groups	3.4.2 Measures to minimize Bias Methods of Assigning Participants to Study Intervention Blinding
9.4.4 Selection of Doses in the Study	9.4.4 Selection of Dose(s) and Timing of Dose for Each Subject	Section name NOT INCLUDED; provided in Section 3.4.1
9.4.5 Selection and Timing of Dose for each Patient	9.4.4 Selection of Dose(s) and Timing of Dose for Each Subject	Section name NOT INCLUDED; provided in Section 3.4.1
9.4.6 Blinding	9.4.3.2 Blinding and Unblinding	Unnumbered subheading under Section 3.4.2. Measures to minimize Bias
9.4.7 Prior and Concomitant Therapy	9.4.6 Prior and Concomitant Therapy	3.4.4 Prior, Concomitant, [and/or] Post-intervention Therapy
9.4.8 Treatment Compliance	9.4.5 Treatment Compliance	3.4.3 Study Intervention Compliance
9.5 Efficacy and Safety Variables	9.5 Efficacy and Safety Variables	3.5 Study Assessments and Procedures
9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart	9.5.1 Efficacy and Safety Measurements Assessments 9.5.1.4 Safety – Adverse Events 9.5.1.5 Safety – Clinical Laboratory Evaluation	3.5.1 Planned Measurements and Timing of Assessments

ICH E3	CORE Reference	TransCelerate CSR template
	9.5.1.6 Safety – Vital Sign Measurements 9.5.1.7 Safety – Physical Examination 9.5.3 Pharmacokinetic and Pharmacodynamic Measurements 9.5.3.2 Pharmacokinetic Parameters 9.5.3.3 Pharmacodynamic Measurements 9.5.3.4 Pharmacodynamic Parameters 9.5.4 Other Measurements	
9.5.2 Appropriateness of Measurements	9.5.2 Appropriateness of Measurements	3.5.2 Appropriateness of Measures
9.5.3 Primary Efficacy Variable(s)	9.5.1.1 Primary Efficacy Measurement	3.5.1 Planned Measurements and Timing of Assessments
9.5.4 Drug Concentration Measurements	9.5.3.1 Pharmacokinetic Measurements	3.5.1 Planned Measurements and Timing of Assessments
9.6 Data quality assurance	9.6 Data Quality Assurance	3.6 Data Quality Assurance 3.6.1 Study monitoring 3.6.2 Investigator Training 3.6.3 Laboratory procedures 3.6.4 Investigator Responsibilities 3.6.5 Clinical Data Management 3.6.6 Clinical Quality Assurance Audits 3.6.7 Quality Tolerance Limits
9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size	9.7 Statistical Analysis Methods Planned in the Protocol and Determination of Sample Size	3.7 Statistical Analysis
9.7.1 Statistical and Analytical Plans	9.7.1 Statistical Plans 9.7.1.1 General Approaches 9.7.1.2 Primary Efficacy Endpoint Methodology	3.7.1 Statistical Analysis Plan

ICH E3	CORE Reference	TransCelerate CSR template
	9.7.1.3 Secondary Efficacy Endpoint Methodology 9.7.1.4 Other Efficacy Endpoint Methodology 9.7.1.5 Safety Endpoint Methodology 9.7.1.6 Pharmacokinetic and Pharmacodynamic Endpoints Methodology 9.7.1.7 Other Endpoint Methodology	
9.7.2 Determination of Sample Size	9.7.2 Determination of Sample Size	Section name NOT INCLUDED
9.8 Changes in the Conduct of the Study or Planned Analyses	9.8 Changes in the Conduct of the Study or Planned Analyses 9.8.1 Changes in the Conduct of the Study 9.8.2 Changes in the Planned Analyses 9.8.3 Changes Following Study Unblinding and Post-hoc Analyses	3.1.2 Changes in Study Conduct 3.7.2 Changes in Planned Analyses Prior to Unblinding or Database Lock 3.7.3 Changes Following Study Unblinding/Database Lock and Post-hoc Analyses
10 Patients	10 Study Subjects	4 Study Participants
10.1 Disposition of Patients	10.1 Disposition of Subjects	4.1 Disposition of Participants
10.2 Protocol Deviations	10.2 Protocol Deviations	4.2 Protocol Deviations
11 Efficacy Evaluation	11 Efficacy and Other Evaluations	5 Evaluation of Response to Study Intervention 5.1 Efficacy
11.1 Data Sets Analysed	10.3 Data Sets Analysed	4.3 Analysis Sets
11.2 Demographic and Other Baseline Characteristics	10.4 Demographic and Other Baseline Characteristics 10.4.1 Demography 10.4.2 Baseline Disease Characteristics 10.4.3 Medical History and Concurrent Illnesses 10.4.4 Prior and Concomitant Treatments	4.4 Demographic and Other Baseline Characteristics 4.4.1 Demography 4.4.2 Baseline Disease Characteristics 4.4.3 Medical History and Concurrent Illnesses 4.5 Prior, Concomitant [and/or] Post-intervention therapy

ICH E3	CORE Reference	TransCelerate CSR template
11.3 Measurements of Treatment Compliance	10.5 Measurements of Treatment Compliance	4.6 Exposure and Study Intervention Compliance 4.6.1 Exposure 4.6.2 Dose Modification 4.6.3 Compliance with Intervention
11.4 Efficacy Results and Tabulations of Individual Patient Data	11.1 Efficacy Results	5.1 [Efficacy and/or Immunogenicity]
11.4.1 Analysis of Efficacy	11.1.1 Primary Efficacy Endpoint 11.1.2 Secondary Efficacy Endpoints 11.1.3 Other Efficacy Endpoints 11.1.4 Post-hoc Analyses	5.1 [Efficacy and/or Immunogenicity] 5.1.1 Efficacy Summary 5.1.2 Primary Efficacy Endpoint(s)/Estimand(s) 5.1.3 Secondary Efficacy Endpoint(s)/Estimand(s) 5.1.4 Tertiary/Exploratory/Other Efficacy Endpoint(s)/Estimand(s) 5.1.5 Post-hoc Analyses 5.2 Safety 5.3 Pharmacokinetics 5.4 Pharmacodynamics 5.5 Genetics 5.6 Biomarkers 5.7 Immunogenicity 5.8 [Health Economics] OR [Medical Resource Utilization and Health Economics] 5.9 [Other Analyses/Results] 5.10 Interpretation on the Validity or Limitations of Study Results
11.4.2 Statistical/Analytical Issues	11.2 Results of Statistical Issues Encountered During the Analysis	5.10 Interpretation on the Validity or Limitations of Study Results
11.4.2.1 Adjustments for Covariates	11.2.1 Adjustments for Covariates	Section name NOT INCLUDED;
11.4.2.2 Handling of Dropouts or Missing Data	11.2.2 Handling of Withdrawals, Discontinuations or Missing Data	

ICH E3	CORE Reference	TransCelerate CSR template
11.4.2.3 Interim Analyses and Data Monitoring	11.2.3 Interim Analyses and Data Monitoring	Added within the applicable analysis subsection within Section 5 (if applicable)
11.4.2.4 Multicentre Studies	11.2.4 Multicentre Studies	
11.4.2.5 Multiple Comparison/Multiplicity	11.2.5 Multiple Comparison/Multiplicity	
11.4.2.6 Use of an "Efficacy Subset" of Patients	11.2.6 Use of an “Efficacy Subset” of Subjects	
11.4.2.7 Active-Control Studies Intended to Show Equivalence	11.1 Efficacy Results	
11.4.2.8 Examination of Subgroups	11.2.7 Examination of Subgroups	
11.4.3 Tabulation of Individual Response Data	11.2.8 Tabulation of Individual Response Data	
11.4.4 Drug Dose, Drug Concentration, and Relationships to Response	11.3.1 Drug Dose, Drug Concentration and Relationships to Response	5.3 Pharmacokinetics 5.3.1 Summary of Pharmacokinetics 5.3.2 Dose and Exposure 5.3.3 Drug Exposure and Safety 5.3.4 Drug Exposure and Response 5.4 Pharmacodynamics
11.4.5 Drug-Drug and Drug-Disease Interactions	11.3.2 Drug-Drug and Drug-Disease Interactions	5.3 Pharmacokinetics 5.4 Pharmacodynamics
11.4.6 By-Patient Displays	NOT INCLUDED	NOT INCLUDED
11.4.7 Efficacy Conclusions	11.4 Efficacy Results Summary	5.1 Efficacy
12 Safety Evaluation	12 Safety Evaluation	5.2 Safety
12.1 Extent of Exposure	10.6 Extent of Exposure	4.6.1 Exposure
12.2 Adverse Events (AEs)	12.1 Adverse Events	5.2.2 Adverse Events *Frequency of AEs by System Organ Class* *Frequency of AEs by Preferred Term* *Frequency of AEs by Subgroups* *Adverse Events by Severity* *Treatment-related AEs* example subheadings in italics

ICH E3	CORE Reference	TransCelerate CSR template
12.2.1 Brief Summary of Adverse Events	12.1.1 Brief Summary of Adverse Events	5.2.1 Safety Summary
12.2.2 Display of Adverse Events	12.1.2 Most Frequently Reported Adverse Events	5.2.2 Adverse Events
12.2.3 Analysis of Adverse Events	12.1.2 Most Frequently Reported Adverse Events 12.1.3 Categorisation of All Adverse Events	5.2.2 Adverse Events
12.2.4 Listing of Adverse Events by Patient	NOT INCLUDED	NOT INCLUDED
12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events	12.2 Analysis of Deaths, Other Serious Adverse Events, and Other Clinically Meaningful Adverse Events	Section name NOT INCLUDED; redundant
12.3.1 Listing of Deaths, other Serious Adverse Events and Other Significant Adverse Events	12.2.1 Deaths, Other Serious Adverse Events, Discontinuations due to Adverse Events and Other Adverse Events of Special Interest	Section name NOT INCLUDED; redundant
12.3.1.1 Deaths	12.2.1.1 Deaths	5.2.2.1 Deaths
12.3.1.2 Other Serious Adverse Events	12.2.1.2 Other Serious Adverse Events	5.2.2.2 Serious Adverse Events
12.3.1.3 Other Significant Adverse Events	12.2.1.3 Discontinuations Due to Adverse Events 12.2.1.4 Other Adverse Events of Special Interest	5.2.2.3 Discontinuations and/or Dose Modifications Due to Adverse Events 5.2.2.4. Adverse Events of Special Interest 5.2.2.5. Other Significant Adverse Events
12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events	12.2.2 Narratives of Deaths, Other Serious Adverse Events, and Other Clinically Meaningful Adverse Events	NOT INCLUDED
12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events	12.2.1 Deaths, Other Serious Adverse Events, Discontinuations due to Adverse Events and Other Adverse Events of Special Interest	Section name NOT INCLUDED; redundant

ICH E3	CORE Reference	TransCelerate CSR template
12.4 Clinical Laboratory Evaluation	12.3 Clinical Laboratory Evaluation	5.2.3 Clinical Laboratory Evaluation
12.4.1 Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value	12.3.1 Individual Laboratory Measurements by Subject and Abnormal Laboratory Values	Section name NOT INCLUDED; topic covered in sections below
12.4.2 Evaluation of Each Laboratory Parameter	12.3.2 Evaluation of Laboratory Values	
12.4.2.1 Laboratory Values Over Time	12.3.2.1 Laboratory Values Over Time	5.2.3 Clinical Laboratory Evaluation
12.4.2.2 Individual Patient Changes	12.3.2.2 Individual Subject Changes in Laboratory Values	
12.4.2.3 Individual Clinically Significant Abnormalities	12.3.2.3 Individual Clinically Meaningful Laboratory Abnormalities	
12.5 Vital Signs, Physical Findings and Other Observations Related to Safety	12.4 Vital Signs, Physical Examinations, and Other Observations Related to Safety 12.4.1 Vital Signs 12.4.2 Physical Examination Findings 12.4.3 Other Observations Related To Safety	5.2.4 Other Safety Evaluations 5.2.4.1 Vital Signs 5.2.4.2 Electrocardiograms 5.2.4.3 Physical Examination Findings 5.2.4.4 Safety Observations Related to [Medical Device OR Device/Drug Combination Product] 5.2.4.5 Other Observations Related to Safety
12.6 Safety Conclusions	12.5 Safety Results Summary	5.2.1 Safety Summary
13 Discussion and Overall Conclusions	13 Discussion and Overall Conclusions 13.1 Discussion 13.2 Conclusions	6 Conclusions
14 Tables, Figures and Graphs Referred to But Not Included in the Text	14 Tables and Figures	Tables and Figures
14.1 Demographic Data	14.1 Demographic Data	Demographic Data
14.2 Efficacy Data	14.2 Efficacy Data	Efficacy Data
14.3 Safety Data	14.3 Safety Data	Safety Data
14.3.1 Displays of Adverse Events	14.3.1 Displays of Adverse Events	Displays of Adverse Events

ICH E3	CORE Reference	TransCelerate CSR template
14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events	14.3.2 Listing of Deaths, Other Serious and Clinically Meaningful Adverse Events	Listing of Deaths, Other Serious and Clinically Meaningful Adverse Events
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events	14.3.3 Narratives of Deaths, Other Serious Adverse Events and Certain Other Clinically Meaningful Adverse Events	Narratives of Deaths, Other Serious Adverse Events and Certain Clinically Meaningful Adverse Events
14.3.4 Abnormal Laboratory Value Listing (Each Patient)	14.3.4 Data Listings (Each Subject) for Abnormal Clinically Meaningful Laboratory Values, Vital Signs, Physical Examinations and Other Observations Related to Safety	Data Listings (Each Subject) for Abnormal Clinically Meaningful Laboratory Values, Vital Signs, Physical Examinations and Other Observations Related to Safety
15 Reference List	15 Reference List	7 References
NEW	9.3.4 Stopping or Suspending the Study 9.4.3 Avoidance of Bias 9.5.1.2 Secondary Efficacy Measurements 9.5.1.3 Other Efficacy Measurements 11.3 Pharmacokinetic, Pharmacodynamic and Other Analyses Results 11.3.3 Other Endpoints 14.4 Other Data	

Blue font: New/adapted text in CORE Reference compared to ICH E3

Purple font: New/adapted text in TransCelerate CSR template compared to ICH E3

Appendix 2 Disclosure Requirements in EU-CTR and EMA Policy 0070

	Regulation EU No. 536/2014	EMA Policy 0070
Scope	All IMPs irrespective of marketing authorization status	Centrally authorized products only (approved products)
Clinical trials covered	• Trials conducted in the EU • Non-pediatric trials included in a PIP • Pediatric trials performed outside the EU that are included in a PIP • Pediatric trials involving an IMP • Covered by an EU marketing authorization and sponsored by the MAH whether or not included in a PIP and whether performed in or outside the EU	• Trials submitted to EMA in the context of an MAA, Article 58 procedure, line extension or new indication, regardless of where the study was conducted
Disclosed documents	Clinical trial-related information generated during the life cycle of a clinical trial, including the documents* • Protocol • Assessment and decision on trial conduct • Technical Summary of Trial Results • Lay Language Summary • CSR (main part) • Inspection Reports • Investigator's Brochure • IMPD Section S and Section E • Subject information sheet	Clinical data (CTD modules) including the following clinical reports and individual patient data* • CTD 2.5 Clinical overview • CTD 2.7 Clinical summaries • CTD 5 Clinical Study Reports (CSR main body) • Appendix 16.1.1 Protocol and Amendments • Appendix 16.1.2 Sample Case Report Form • Appendix 16.1.9 Statistical Analysis Plan • Anonymization Report justifying the applied redactions and anonymizations
Platform	EU Portal and EU Database CTIS Ad interim EudraCT database is used	EMA clinical data publication website https://clinicaldata.ema.europa.eu/web/cdp/home
Effective date	Since 31 January 2022, with 3-year transition period	Applicable for applications after 01 January 2015 (new MAAs) or 01 July 2015 (Line extension or New indication); effective since October 2016

Appendix 3 GCP Principles in ICH 6(R2) and ICH E6(R3)

ICH E6 (R2) from 09 November 2016		ICH E6 (R3) – Draft principles as per Explanatory Note 19 April 2021	
1	Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s)	1	Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice (GCP) and applicable regulatory requirement(s).
2	Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.	2	Clinical trials should be designed and conducted in ways that ensure the rights, safety, and well-being of participants.
3	The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.	3	Informed consent is an integral feature of the ethical conduct of a trial. Clinical trial participation should be voluntary and based on a consent process that ensures participants are well-informed.
4	The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.	4	Clinical trials should be subject to objective review by an institutional review board (IRB)/independent ethics committee (IEC).
5	Clinical trials should be scientifically sound, and described in a clear, detailed protocol.	5	Clinical trials should be scientifically sound for their intended purpose, and based on robust and current scientific knowledge and approaches.
6	A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.	6	Clinical trials should be designed and conducted by qualified individuals.
7	The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.	7	**Quality should be built into the scientific and operational design and conduct of clinical trials.**
8	Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).	8	**Clinical trial processes, measures, and approaches should be proportionate to the risks to participants and to the reliability of trial results.**

9	Freely given informed consent should be obtained from every subject prior to clinical trial participation.	9	Clinical trials should be described in a clear, concise, and operationally feasible protocol.
10	All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. This principle applies to all records referenced in this guideline, irrespective of the type of media used.	10	**Clinical trials should generate reliable results.**
11	The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).	11	**Roles, tasks and responsibilities in clinical trials should be clear and documented appropriately.**
12	Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.	12	Investigational products used in a clinical trial should be manufactured in accordance with applicable Good Manufacturing Practice (GMP) standards and be stored, shipped, and handled in accordance with the product specifications and the trial protocol.
13	Systems with procedures that assure the quality of every aspect of the trial should be implemented. Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.		

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Neu-Isenburg, 24 Oktober 2022

Dr. Sabrina Stöhr

Electronically signed by: Dr. Sabrina Stöhr
Reason: final version
Date: Oct 24, 2022 11:25 GMT+2

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Dr. Sabrina Stöhr