

The EMWA Budapest Working Group: A 2-year collaboration to make recommendations for aligning the ICH E3 guideline with current practice and developing clinical study protocol guidance

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Abstract

International Conference on Harmonisation (ICH) E6 and ICH E3, developed nearly 20 years ago, are the current regulatory guidance documents for developing clinical study protocols (CSPs) and clinical study reports (CSRs). Ambiguity in the guidelines, and recent public disclosure requirements mean that review and revision of these guidelines is warranted. In May 2014, EMWA assembled a group of experts, called the Budapest Working Group (BWG), and initiated a 2-year collaboration with a variety of stakeholders to review the two guidelines. The resulting recommendations should address the needs of the widest possible community; incorporate developments since the guidelines were first issued; and facilitate responsible clinical trial data sharing. In this first of three planned open-access publications, we explain the objectives of this project, present our 2-year project plan, and report on progress to date.

Keywords: Budapest Working Group, Clinical study report, Clinical study protocol, ICH E3, ICH E6, Regulatory guidance, Reporting, Responsible clinical trial data sharing

Nearly two decades have passed since the International Committee on Harmonisation (ICH) issued regulatory guidance documents for developing clinical study protocols (CSPs) and clinical study reports (CSRs), respectively ICH E6 and ICH E3. Since then, the evolving context of global pharmaceutical research and development and their

applications means that review and revision of these guidelines is now required.

Public disclosure and transparency of clinical trial data

Despite the global drive towards public disclosure of clinical trial results,¹⁻³ underreporting of trials registered on the US FDA's <http://www.ClinicalTrials.gov> occurs.⁴ For the 53 new medicines approved by the European Medicines Agency (EMA) in 2009–2011, nearly three-quarters of the related results were disclosed within 1 year of trial completion or regulatory approval, and nearly 90% by 31 January 2013.⁵ Voluntary publication of trial data, combined with publication of summary clinical trial results on the EMA's EU Clinical Trials Register (<http://www.clinicaltrialsregister.eu>), has undoubtedly enhanced public disclosure and transparency in the EU. The EMA policy on publication of clinical data for medicinal products for human use, effective 1 January 2015,⁶ will strengthen this trend by mandating stepwise disclosure of clinical data submitted under the centralised marketing authorisation procedure in the EU.

Current guidance for developing clinical trials and reporting results

The topics for inclusion in a CSP are described in Section 6 of the ICH Guideline for Good Clinical Practice E6 (ICH E6)⁷ and more recently in the SPIRIT (Standard Protocol Items: Recommendations

for Interventional Trials) initiative,⁸ and the 2014 EU Clinical Trials Directive No. 536⁹ (effective May 2016) Annex I section D, both of which provide a more extensive list of contents. The regulatory and ethical basis for writing CSRs is grounded in Section 5.22 of the ICH E6 guidelines, and authoring guidance is given in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3).¹⁰ Although ICH E3 and ICH E6 were developed simultaneously and were issued in 1995 and 1996, respectively, certain sections of the two documents conflict and some parts of ICH E3 are ambiguous. As a result, information necessary for reporting a clinical trial may not be adequately captured at the beginning of the study and the guidelines are often interpreted when the results are reported. Brevity in current E6 guidance means there is potential for developing more detailed interpretational CSP guidance that will better support CSP preparation as well as subsequent clinical study reporting.

Since 1995, there have been isolated and incomplete attempts to clarify reporting guidance for CSRs, both regionally, through EMA's 2004 guidance on adapting appendices for CSRs included in marketing authorisation applications (MAAs),¹¹ and globally, through ICH's 2012 supplementary questions and answers document.¹² Furthermore, a consolidated presentation of updated CSR authoring requirements was published in 2014.¹³ The 2014 EU Clinical Trials Directive No. 536⁹ Annex IV, Section A lists items to be included in publicly posted results summaries which, if integrated into CSR synopsis guidance, could create efficiencies. No formal revision and reissue of the original ICH guidance documents for developing CSPs and CSRs has occurred to date.

Considerations for the next 20 years and beyond

Regulatory and technical developments over the past 20 years, combined with recent initiatives to enhance the transparency of clinical trial data, mean a review and possible revision of the existing ICH guidelines for CSPs and CSRs are necessary.

Objectives

Review and suggest adaptations to existing guidance text in ICH E3 and develop recommended detailed guidance text for CSPs

ICH E3 is a guidance document, not a template. It should be interpreted flexibly to produce a CSR tailored to the individual study.¹⁰ ICH E3 provides a framework for distilling voluminous study data into comprehensible CSRs that integrate with other

documents in the full dossier submitted to regulatory authorities for review. Although regulatory reviewers may be most interested in the summary and overview documents derived from the CSRs, the dossier must be based on well-prepared individual CSRs. However, some aspects of the ICH E3 guidance are ambiguous. This leads to varying interpretations and, ultimately, different ways of reporting the data.

A *de novo* review of ICH E3, conducted by current end-users, will provide recommendations to minimise ambiguity. The end product should not be a complete rewrite of the ICH E3 guideline because it generally suits its intended purpose. As ICH E3 links to many other guidance documents, including ICH E6 and other industry processes and procedures, the recommendations must anticipate a possible 'domino effect'. Oversight review of the *de novo* review recommendations will ensure appropriate handling of broader issues with collateral impact. Ultimately, stakeholder evaluation and support of the combined *de novo* and oversight reviews will ensure that the final recommendations address the needs of the widest possible community. As CSP guidance must address some CSP components that ultimately feed into ICH E3, a project to develop recommended CSP guidance will also be undertaken.

Consider the increased access to CSPs and CSRs

Historically, the primary audience for CSPs and CSRs comprised investigators, industry insiders, and regulators. The Pharmaceutical Research and Manufacturers of America (PhRMA) and European Federation of Pharmaceutical Industries and Associations (EFPIA) jointly developed Principles for Responsible Clinical Trial Data Sharing, which were implemented on 1 January 2014.¹⁴

In addition, the EU's recently introduced disclosure and transparency policy (EMA policy effective 1 January 2015⁶) increases the traditional audience for CSPs and CSRs. Academic and research groups can request access to datasets to attempt to reproduce study results, or they may perform their own analyses. In anticipation of this change, many pharmaceutical companies created websites for requesting clinical study data and established independent adjudication panels to assess the requests and ensure appropriate disclosure.

Public access to CSPs and CSRs requires, above all, that individual study participants cannot be identified from published information. Developing targeted treatments, which focus research efforts on genetically suitable populations – effectively 'personalised medicine' research – will present

challenges. Patients with rare conditions enrolled in small numbers at a particular site may be relatively easy to identify from their data. If an individual's pre-existing conditions are disclosed, this could preclude their eligibility for health insurance cover in some countries. Potentially, clinical trial data could also be used to influence reimbursement decisions in countries with 'free at the point of access' health-care services or to exclude entire populations from health insurance coverage or state medical aid based on genetic predisposition.

Science and medicine are evidence-based disciplines, where peer-reviewed publication is held in high regard. Cited publications support fact and develop and inform scientific discussion. Professionals, who have Internet, library, and financial resources at their disposal, rarely have difficulties accessing the actual publications from a simple bibliographic reference. To aid transparency and to prevent exclusion of those without institutional resources, the wider audience for CSPs and CSRs must have access to the literature at little or no cost.

Finally, CSRs and CSPs that ultimately progress into a filing within a submission dossier must also continue to meet electronic data standards.¹⁵

Align CSP content and ICH E3 (CSR content)

ICH E6 and ICH E3 are inextricably linked, so a review of one requires a review of the other.

Currently, ICH E6 guidance for CSP development is minimal and open to interpretation. Detailed CSP guidance needs to be developed to improve reporting, optimise reproducibility, enhance transparency, and protect participants.

Currently, study objectives are often not clearly linked to endpoints. This not only raises issues of reproducibility but also confounds statistical analysis planning and reporting.

There is also no requirement that the rationale of the study design is documented. This is best captured when the protocol is being developed. Protocols are usually developed rapidly, so the responsible multidisciplinary team inevitably focuses on producing a final protocol in the shortest possible time. Recording how and why a particular aspect of a study design develops may be a low priority, but if not captured, can lead to reverse engineering when producing the CSR. A requirement to include rationale for design elements in the protocol will increase reporting accuracy and enhance transparency.

Steps must be taken early in the project lifecycle to meet the requirement for disclosure-ready CSRs. Patient identification numbers must not include a centre identifier that could enable individuals to be

identified. Sponsors should be prompted to consider fundamental study set-up issues during protocol design because they lay the foundation for creating a disclosure-ready CSR.

Facilitate clear, fit-for-purpose information sharing

Since ICH E6 and ICH E3 were developed, unwieldy paper-based systems have given way to multiple electronic systems. Information is electronically accessible and shared through professional and social media platforms. Subsequent interpretation and dissemination of resulting insights falls outside the remit of current statutory regulation. Clinical study data must be summarised with absolute clarity and at a level appropriate to support informed interpretation and minimise aberrant claims or criticisms.

To present high-level summary data for regulatory review, detailed data from constituent 'building block' CSRs are typically abstracted and repurposed for regulatory submission summary documents, which include the MAA in Europe, the New Drug Application in Japan and the USA, and the US biologic and device equivalents (Biologic Licensing Application and Product Marketing Application, respectively). The CSR must, however, completely summarise within-study data to allow later simplification. The widespread lack of understanding about this can complicate creation of a CSR. For example, although adverse effects are of ultimate regulatory interest in a submission summary document, the actual numbers of patients experiencing adverse events must first be summarised in the CSR. Ambiguity in ICH E3 guidance about displays of adverse events can lead to CSRs that summarise and report only the numbers of patients experiencing the events without detailing the actual events. This confounds the identification of patterns in event frequencies and compromises the description of individual laboratory abnormalities in the context of adverse events. Upcoming transparency regulations mean that incorrect interpretation of this guideline must come to an end; the guideline must include clear, directive language devoid of ambiguity.

Encourage a streamlined process for disclosure-ready CSRs

Publicly disclosed integrated CSRs will include the CSR text portion (Sections 1–15 in the ICH E3 guideline numbering system), Appendix 16.1.1 (protocol and protocol amendments), Appendix 16.1.2 (sample case report form), and Appendix 16.1.9 (documentation of statistical methods). Patient data listings (Appendix 16.2) will not be disclosed.⁶ The summarised data in Section 14 (tables, figures and graphs referred to but

not included in the text) do not typically include individual patient data, although there are some exceptions, namely, listings of death, other serious, and significant adverse events (Section 14.3.2), narratives of deaths, other serious, and certain other significant adverse events (Section 14.3.3), and abnormal laboratory value listing (Section 14.3.4). The data listings to be included in the disclosed sections should conform to current standards for anonymisation¹⁶ with the understanding that these will inevitably continue to develop. Narratives should be moved to a non-disclosed appendix.

Industry is currently debating a two-step process for submitting and then publishing clinical study results. The two-step process involves producing a submission-ready CSR that may contain data that must be removed after submission to produce the final disclosure-ready CSR. We propose that the CSR should be as disclosure-ready as possible from the outset to safeguard against inadvertent identification of participants, assure optimally timed public disclosure of clinical trial results, and be as cost efficient as possible.

Facilitate – not hinder – the process of licensing medicines

Getting safe and effective medicines to market is in the best interests of all parties. The global population needs medicines and their approval should not be hampered by suboptimal data presentation. Regulatory reviewers appreciate clearly written and well-presented documents; clearly presented information helps them better understand the data and may ultimately streamline the regulatory review processes. Optimisations may include tabulating selected data currently presented in narrative form and increasing the use of graphs over summary tables to illustrate trends.

The Budapest Working Group: Methods for reviewing and developing the ICH E3 guideline and developing CSP guidance

In May 2014 EMWA assembled a group of experts, called the Budapest Working Group (BWG), and initiated a 2-year collaboration with a variety of stakeholders to review the ICH E3 and CSP guidelines (including E6). The roadmap for the BWG and stakeholder reviews resulting in final content recommendations are summarised in Figure 1. Briefly, the project comprises four stages.

- Stage 1: Existing ICH E3 guidance will be reviewed and recommended updates developed.

New recommended CSP guidance will be developed and then reviewed. These tasks will be performed separately by an EMWA BWG *de novo* review and development team.

- Stage 2: The results of each *de novo* work exercise will be assessed by an EMWA BWG oversight evaluation team to ensure that it meets Good Clinical Practice requirements; transparency/disclosure requirements including responsible clinical trial data sharing; is aligned with the other relevant guidance documents; meets the needs of the international medical writing community; and is globally acceptable and in agreement with industry trends.
- Stage 3: Stakeholders will review the recommendations.
- Stage 4: Comments from stakeholders will be consolidated and integrated into the recommendations.

The outcomes of the stakeholder consultation will form the basis for the second open-access publication originating from this project, which will be published in *Medical Writing* in late 2015. Final content recommendations for ICH E3 and for CSP guidance, agreed by majority consensus with stakeholder parties, are expected to be published in the second-quarter of 2016 in a prominent open-access journal, such as *BMJ Open*. The update and reissue of ICH E3 and the issue of detailed ICH guidance for CSPs including any public consultation processes, are outside the scope of responsibility of the BWG.

Composition of the Budapest Working Group

The BWG collaboration includes professional associations, regulators, and key industry participants with expertise in ICH E3 and ICH E6 guidelines, CSP and CSR templates, and disclosure and transparency issues. In addition to the two main teams (*de novo* review and development team and oversight evaluation team), the BWG also includes a strategist who is working with the partner and stakeholder organisations and an experienced medical writer who is providing administrative support at all stages of the project.

Composition of the de novo review and development and oversight evaluation teams

The E3 *de novo* review team comprises five members:

- Two freelance expert end-users of ICH E3 and ICH E6 (SH and DJ) who have a total of 36 years of regulatory medical writing experience and have written for large and small European, American, and Japanese sponsors,

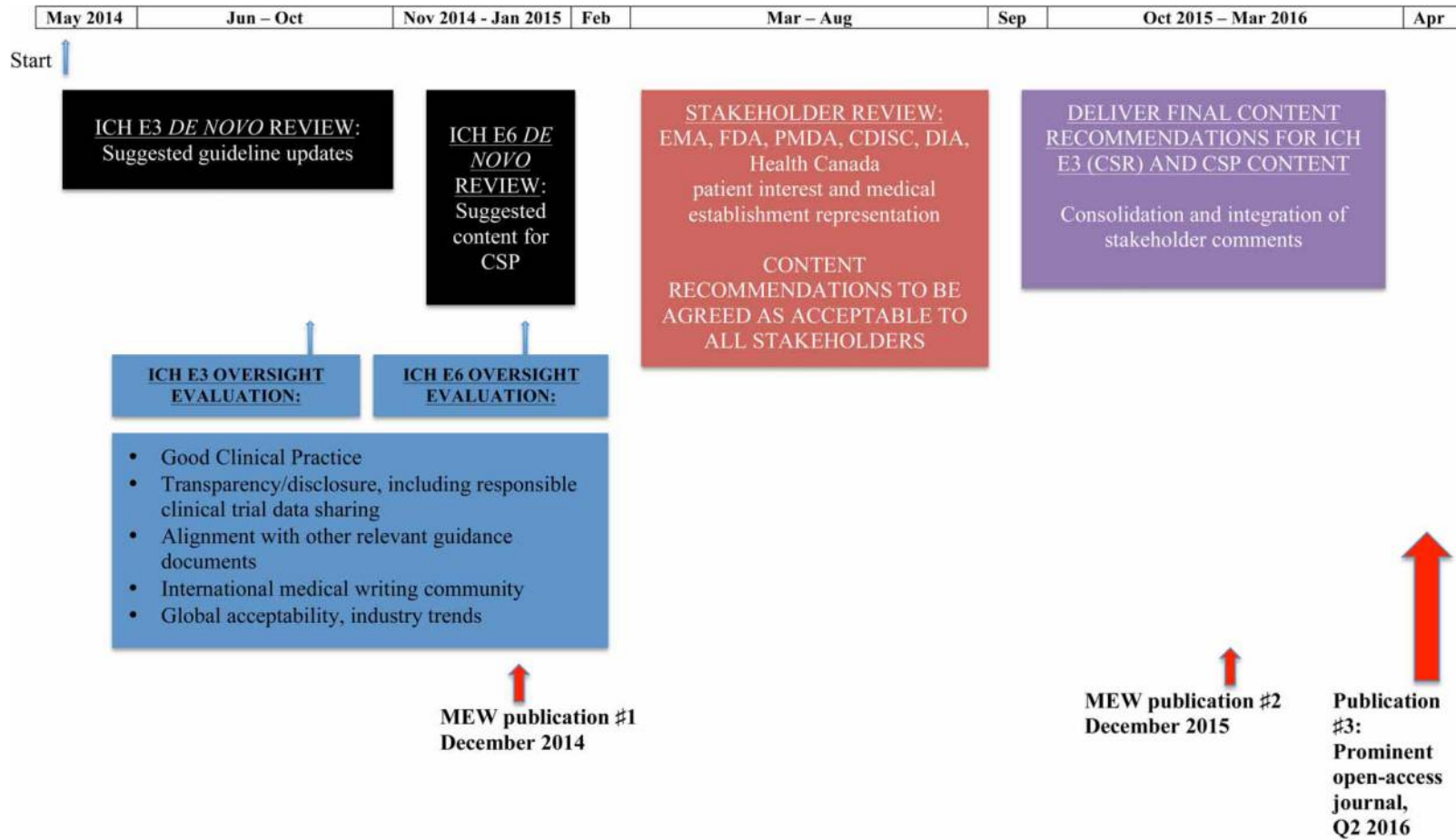


Figure 1: A 2-year roadmap for the EMWA Budapest Working Group *de novo* review and oversight evaluation; stakeholder review; and developing final content recommendations of the ICH E3 (clinical study report) guideline; and developing recommended clinical study protocol guidance. CDISC, Clinical Data Interchange Standards Consortium; CSP, clinical study protocol; CSR, clinical study report; DIA, Drug Information Association; ICH E3, ICH guideline for clinical study report (CSR) authoring; ICH E6, ICH guideline for Good Clinical Practice, including guideline for CSP authoring; EMA, European Medicines Agency; FDA, (US) Food and Drug Administration; MEW, *Medical Writing*; PMDA, Pharmaceutical and Medical Devices Agency (Japan).

Table 1: Composition of the Budapest Working Group

Name	Affiliation(s)	<i>de novo</i> Team Member	Oversight Review Team Member	Position in Budapest Working Group	Focus of Expertise in Budapest Working Group
Sam Hamilton	Sam Hamilton Medical Writing Services Limited (UK) EMWA Vice President	■ E3	■ CSP	Chair Project manager ICH E3 <i>De novo</i> reviewer ICH E3 Oversight reviewer CSP guidance	ICH E3 and CSP guidance end user Project management Association perspective – Europe
Debbie Jordan	Debbie Jordan Limited (UK) EMWA member	■		<i>De novo</i> reviewer ICH E3 and CSP guidance	ICH E3 and CSP guidance end user
Vivien Fagan	Quintiles (UK) EMWA member	■		<i>De novo</i> reviewer ICH E3 and CSP guidance	CSR and CSP reviewer
Anna Shannon	Quintiles (UK)	■		<i>De novo</i> reviewer ICH E3 and CSP guidance	ICH E3 and CSP guidance biostatistical sections end user
Graham Blakey	consult2deliver (UK) EMWA member	■		<i>De novo</i> reviewer ICH E3 and CSP guidance	ICH E3 and CSP guidance pharmacokinetic sections end user
Tracy Farrow	PPD (UK) EMWA member		■	Oversight reviewer ICH E3 and CSP guidance	Global transparency and disclosure perspective
Walther Seiler	Bayer (Germany) EMWA member	■ CSP	■ E3	Oversight reviewer ICH E3 Project Manager CSP guidance <i>De novo</i> developer CSP guidance	Global CSP and CSR templates perspective
Aaron Bernstein	Synchrogenix Information Strategies Inc. (USA) EMWA Past President AMWA member		■	Oversight reviewer ICH E3 and CSP guidance	International medical writing community Association perspective – US
Art Gertel	MedSciCom, LLC (USA) EMWA & AMWA Fellow Think Tank Fellow		■	Oversight reviewer ICH E3 and CSP guidance	Global strategic perspective Regulatory Ethics
Tania Kotsokechagia	Lexis Comms Limited (UK) EMWA member			<i>Ad hoc</i> support	Administrative/medical writing project support

including pharmaceutical companies, contract research organisations (CROs), biotechnology companies, and academic institutions

- One member (VF) experienced in reviewing CSRs and protocols from a medical writing CRO perspective
- An experienced biostatistician (AS) working for a CRO responsible for statistical authorship and review of CSPs and CSRs
- An experienced freelance clinical pharmacologist (GB).

The E3 oversight evaluation team includes:

- A pharmaceutical company CSR and CSP template expert (WS)
- A CRO transparency and disclosure expert (TF)
- A consultant with expertise in global regulatory standards and industry trends (AG)
- Representation from the American Medical Writers Association (AMWA) (AB).

Teams will remain the same for the CSP project, except for SH and WS who will exchange roles, SH to the oversight evaluation team and WS to the *de novo* development and review team. WS will develop the CSP guidance that will be subsequently reviewed by DJ and VF. The members of the BWG are listed in Table 1.

Status of the review

Oversight evaluation is now complete for the ICH E3 review and is ongoing for the CSP content recommendations. A package of introductory material has been delivered to the stakeholders. The BWG anticipates completing its review and development work in January 2015. Stakeholder review of both documents will begin in March 2015 and will include:

- Regulators in all three ICH regions – EMA, the US FDA, and Japan's Pharmaceutical and Medical Devices Agency (PMDA)
- Regulator outside the ICH region – Health Canada
- Clinical Data Interchange Standards Consortium (CDISC)
- Drug Information Association (DIA)
- Patient interest representation
- Medical establishment representation.

In addition, a number of stakeholders hold cross-organisational positions and contribute expertise and insights from three large pharmaceutical companies; the ICH E3 2012 question and answer working group; and TransCelerate Biopharma Inc. transparency effort.

Declarations

All BWG team members provided their time and expertise on an entirely voluntary basis. EMWA and AMWA generously contributed funding for team meetings throughout the duration of this project. EMWA funded the open-access of this publication.

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Author information

Sam Hamilton, PhD, is a freelance regulatory medical writer with 21 years of experience in clinical and medical writing roles in the pharmaceutical industry. Sam has written numerous protocols and CSRs for all phases of studies for European, American, and Japanese CROs, pharmaceutical sponsors, biotechnology companies, and academic groups over the past 16 years. Sam is currently Vice President of EMWA.

Walther Seiler, PhD, ELS, is a regulatory medical writer with more than 20 years of experience in an international CRO and a global pharmaceutical company. His current responsibilities include the maintenance of his company's templates for CSRs and CSPs.

Art Gertel, BA, BS, MS, PhD, has more than 35 years of increasingly senior-level positions in the pharmaceutical industry and leadership roles in professional organisations, as well as with collaborative efforts focusing on the improvement of the research, development, review, and approval of new therapeutics and diagnostics. He is the Past President of AMWA; a Fellow of both AMWA and EMWA; recipient of AMWA's Swanberg Award; a member of CDISC's Glossary and Protocol Modeling groups, and serves on the Advisory Boards of The International Publication Planners Association (TIPPA) and Hummingbird IRB. Art is a Registered Agent with the FDA, a Senior Research Fellow with the Centre for Innovation in Regulatory Science (CIRS), and has recently established a strategic regulatory consultancy – MedSciCom, LLC.