A 2026 Joint Summary from the CORE Reference Project and Protocol Development:

Helping regulatory medical writers keep up with modern clinical trials

Introduction

Continuous professional development (CPD) is every regulatory medical writer's responsibility. Not only does this require dedicated care and attention, but it waxes and wanes as day-to-day priorities demand attention.

To help guide medical writers who are just beginning to author clinical trial protocols (protocols) or clinical study reports (CSRs), we have partnered to provide a 2026 snapshot to summarise current key guidance and standards, and to focus on a special topic that is a current pain point for both protocols and CSRs: estimands.

If you are interested in following these topics, subscribe to the Protocol Development newsletters and The CORE Reference Project News Summaries published monthly on LinkedIn.

What guidelines do you need to know?

There are **three** key guidelines that are most applicable to *both* protocols and CSRs:

ICH E6(R3) outlines good clinical practice (GCP) and the R3 revision was adopted on 6 January 2025. An updated consolidated E6(R3) guideline was released on 16 June 2026 that includes Annex 2 (formally adopted on 03 June 2026). The principles and Appendix B (protocols and protocol amendments) are the most relevant sections for medical writers. Annex 1 expands on the GCP principles and provides detailed operational guidance on trial design, conduct, quality by design, data governance, and stakeholder responsibilities. Annex 2 provides guidance on decentralised, pragmatic, and real-world data (RWD) elements.

ICH E8(R1) outlines general considerations for clinical trials, and the R1 revision was adopted on 6 October 2021. At 29 pages, this provides the shortest summary to help orientate medical writers on the general principles of clinical trials, designing quality into clinical trials (i.e., Quality by Design), and on trial reporting.

ICH E9 / E9(R1) are complementary and outline statistical principles for clinical trials. ICH E9 was adopted in 1998, and the addendum on estimands and sensitivity analysis - ICH E9(R1) – was adopted on 20 November 2019. While E9(R1) is the most relevant for the challenging topic of estimands, E9 is important reading for medical writers, generally.

While ICH guidelines remain applicable for many years, regional guidance changes more frequently. For medical writers trying to keep pace with these changes, best practice is to routinely monitor updates in key geographies (e.g., FDA, EMA, MHRA, Health Canada).

Protocol

In 2026, arguably the most influential new protocol-specific guidance affecting medical writers is **ICH M11** (see PD#82)—a common protocol structure and technical specifications document that sets structural standards and common variable definitions. Public examples and implementation experience remain limited as organisations continue to adopt the standard. Medical writers at every stage of their career are adapting to this new template and we are in the exploratory stage of integration into common practice.

CSR

The 2016 Clarity and Openness in Reporting: E-3 based (CORE) Reference remains an essential resource for CSR authors, providing practical guidance and context beyond the ICH E3 guideline. It is evergreen if augmented with an understanding of post-2016 changes in the clinical trials ecosystem. Whether you are developing a CSR for the first time or seeking to enhance consistency and transparency in your reporting, CORE Reference resources should be a key part of your toolkit. Explore the website and follow subsequent updates on the LinkedIn page to keep current.

Special Topic: Estimands

Historically, protocols have used objectives and endpoints to define the purpose of a clinical trial. Endpoints could be well-defined or vague. For example, “Improvement in disease status at Week 24” gives an indication that we would be looking at the improvement of disease at Week 24 compared to baseline; however, the unknown is whether there is a comparison between two interventions; what the disease variable is; how it is measured; and who will be included in the analysis (e.g., all participants who received at least one dose of the intervention, or only participants that received the full intervention?). When developing a CSR where no estimand was defined, writers needed the statistical analysis plan (SAP) to understand how the endpoint was planned to be analysed and then had to provide a summary explanation.

By contrast, an estimand is a statistically measurable and precise description of the treatment effect which reflects the clinical question of interest posed by a clinical trial objective. The estimand framework was developed to ensure alignment between the trial objective(s), design, conduct, analysis, and interpretation of results.

Rather than simply asking "Does the treatment work?", estimands require trial teams to define exactly what treatment effect is being evaluated and under what circumstances.

Every estimand has five attributes:

1. **Treatment** – what interventions are being analysed (e.g., Drug A vs placebo)
2. **Population** – the target patient population (e.g., adults with Indication A or a subgroup defined by a particular characteristic at baseline)
3. **Variable (endpoint)** – the outcome of interest and how it is measured (e.g., change from baseline in Variable X at Timepoint Y)
4. **Intercurrent events (ICEs)** – events occurring after treatment initiation that affect either interpretation or existence of measurements associated with the clinical question (e.g., treatment discontinuation, rescue medication use, death)
5. **Population-level summary** – the summary measure used to compare treatments (e.g., difference in mean change between two groups).

Although the framework may appear complex, it can be viewed as a broader structure that extends beyond a traditional endpoint that explicitly defines the treatment effect of interest and the handling of ICEs. The biggest challenge for teams is the ICE attribute as this can be influenced by medical (e.g., use of rescue medication), statistical (e.g., how different strategies can influence the analysis), operational (e.g., missed visits, intervention supply interruptions), patient (e.g., behaviours that may influence patient participation), and label considerations (i.e., how the product is intended to be marketed). For medical writers, it is important to understand that estimands are not solely a statistical concept. The development of estimands is a cross-functional activity involving for example, clinicians, statisticians, operations, and patient representative team members. Estimands should be discussed early during protocol development. Medical writers are key during this activity and can guide team discussion, ensuring consensus is reached to assure clarity in describing the attributes, and ultimately, inter-document consistency.

In practice, well-defined estimands improve protocol quality by reducing ambiguity and ensuring consistency between the protocol, SAP, and CSR. At the CSR development stage, established estimands make the analysis clearer, thereby reducing the need for interpretation.

Build your understanding of this complex topic by accessing CORE Reference's clear and succinct practical worked example of an estimand.

Take-home message: An estimand defines the exact clinical question a trial is designed to answer. Understanding estimands enables medical writers to support clearer objectives,

more robust protocols, and better alignment between trial design and interpretation of results.