GxP Lifeline
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Is there a legal requirement to have SOPs for GCP in Europe?

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Before addressing whether there's a European requirement for Standard Operating Procedures (SOPs) for Good Clinical Practice (GCP), we need to consider whether ICH GCP (i.e. as provided by the International Conference on Harmonisation) remains the international standard following the publication of the Clinical Trials Directive (2001/20/EC) and the GCP Directive (2005/28/EC). Why? Mainly because the Clinical Trials Directive did not explicitly mention **ICH** GCP, leading to the perennial question of: which GCP should we be following? So here goes my answer, particularly for those of us affected by European legislation, with a wee bit of context to explain it.

In Europe, the principles of Good Clinical Practice were adopted in July 1996, and became operational in January 1997. These principles were laid down in the community guideline: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), otherwise known as ICH Topic E 6 (R1) Guideline for Good Clinical Practice or ICH GCP. Despite having no uniform legal framework for implementation, **ICH GCP** was largely adhered to within the European Community (EC) as a set of 13 internationally recognised principles for conducting clinical trials. In turn, these were founded in the bioethical principles established in the Declaration of Helsinki. But, its adoption as a regulatory standard was neither complete nor uniform.

In 2001, Directive 2001/20/EC - legislation known as the Clinical Trials Directive - eventually provided a common legal framework across Member States for monitoring and enforcing GCP standards in the conduct of clinical trials. This was followed in 2005 with the GCP Directive (2005/28/EC), which further specified the requirements. However, Directives have to be transposed into national law, in each Member State (within three years of their publication). This created scope for differing interpretations of the intended regulatory requirements, somewhat at odds with the goal of harmonisation.

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Even so, ICH GCP is the cornerstone standard within both the Clinical Trial Directive (Article 1, clauses 2 and 3), and the GCP Directive (Recital paragraphs 1 and 8; Article 1, clause 1a). Far from receiving less emphasis, its principles have been adopted in both Directives, where it must be taken into account by anyone conducting clinical trials with investigational medicinal products. As such, it provides a basic standard for the conduct of clinical trials in a "*set of internationally recognised* ***ethical and scientific quality requirements, which must be observed*** *for designing, recording and reporting trials that involve the participation of human subjects.*"

Is there a European requirement for GCP SOPs?

This then brings me to the question about requirements for SOPs. Even if this requirement isn't explicitly stated in European legislation, the burden to satisfy it exists nonetheless, particularly for sponsors because, according to ICH GCP 5.1.1 they're responsible for "*QA and QC systems with written SOPs to ensure that trials are conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s).*" Likewise, Investigational Review Boards (IRBs) or Independent Ethics Committees (IECs) - as they're better known across Europe - also need to have SOPs for their functions (ICH GCP 3.2.2).

What are the requirements for EU Member States?

As it turns out, in the GCP Directive the requirement for SOPs is emphasised less for sponsors, and more for Member States, since their inspectors need appropriate tools for verifying GCP compliance (Chapter 6, Inspection Procedures, Article 26: "*Member States shall establish the relevant procedures for verification of good clinical practice compliance. The procedures shall include the modalities for examining both the study management procedures and the conditions under which clinical trials are planned, performed, monitored and recorded, as well as follow-up measures.*")

So there you have it: **SOPs are required tools for sponsors to ensure GCP compliance.** For inspectors they're required tools for verifying compliance. As an all-encompassing requirement in the GCP Directive, it often seems to escape attention as the expression of the requirement for SOPs, perhaps because it appears understated. But it's there in Chapter 2, entitled *Good Clinical Practice for the design, conduct, recording and reporting of clinical trials* in Article 2, clause 4: "T*he necessary procedures to secure the quality of every aspect of the trials shall be complied with.*"

I don't know about you, but I think that's all about SOPs. Admittedly, the problem with interpreting law is we can't always see the wood for the trees, particularly when talking letter versus spirit of the law interpretation. What do you think?

Links to the Clinical Trials Directive, GCP Directive and the ICH GCP guideline can all be found on the European Medicines Agency website on the link below.

European Medicines Agency (EMA)

Marie's Blog on the Difference between ICH and WHO GCPs

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