How to Meet Regulatory & Compliance Requirements for Capturing eCOAs in Clinical Trials

aparito™

Introduction

The rise of decentralised and hybrid clinical trials has accelerated the adoption of Electronic Data Capture (EDC) platforms to collect and organise data from clinical trials.

The data collected ranges from electronic case report forms (eCRF) documents to readings from medical devices and other instruments. EDC platforms now play a vital role in clinical trials for capturing Clinical Outcome Measures (eCOA) and innovative digital biomarkers emerging through the increased use of digital health technologies.

Advances in digital health technology (DHT), including the use of Machine Learning (ML) and Artificial intelligence (AI) in clinical trial management, have added additional burdens on both providers and consumers of the technology.

Ensuring the reliability, security, and compliance of these systems has gained traction with regulatory authorities. Both the FDA and the EMA have released guidance and regulations to ensure the integrity, reliability, and compliance of technology, for all eCOAs used in clinical trials.

In this white paper, we explore drivers for change in managing quality and compliance in clinical trials and how to ensure you are always audit-ready by using a robust electronic Quality Management System (eQMS).

CSV, CSA and GCP

Computer System Validation (CSV) with the recent move to Computer System Assurance (CSA) and Good Practice (GxP) guidelines are the key frameworks used to ensure the quality of products used in the life science industry. They are also paving the way for using eQMS platforms to manage quality and compliance in clinical trials.

Computer System Validation (CSV)

The FDA regulation 21 CFR Part 11 in 1997 and its associated guidance on the scope and application of electronic records and signatures in 2003, led to the adoption of CSV by life sciences companies. It involves verifying and ensuring the compliance of computer systems used in critical processes like pharmaceutical manufacturing, medical devices, and clinical trials. Key criticisms of CSV are:

- Documentation: It focuses mainly on system documentation. This leads to good documentation that isn't always aligned with how the system operates. Documents get filed to be reviewed when needed rather than maintained as a dynamic document that is regularly updated.
- Long, complex validation tasks.
- A blanket, one-size-fits-all approach to all technology.

This has led to the FDA proposing Computer System Assurance (CSA) in 2022.

Computer System Assurance (CSA)

In September 2022, the FDA released the CSA guidelines. It provides recommendations for implementing risk-based CSA in the pharmaceutical industry.

Key features of CSA are:

- Emphasises the importance of implementing CSA measures to ensure the security, availability, and reliability of computer systems and software used in GxP-regulated activities.
- Promotes a tailored, business-by-business approach based on the risk profile of the software being and focuses on how the system is intended to be used rather than producing lots of documentation.

	CSV	CSA
Risk approach	Focuses on critical functionalities and processes that have the highest impact on patient safety, product quality, and regulatory compliance.	Emphasis on critical thinking, applying automated/unscripted testing and identifying, assessing, and managing related risks.
Process	Lifecycle of a computer system, from design and development to retirement. It involves planning, requirements definition, design, testing, implementation, operation, and maintenance of the system.	Software development processes adhere to relevant standards, guidelines, and regulations specific to FDA-regulated industries. It emphasises compliance with applicable regulations such as 21 CFR Part 11, IEC 62304, and ISO 13485.
Quality	The focus is on comprehensive documentation to show evidence that the system is fit for purpose. Documentation ensures traceability and accountability throughout the validation process.	Refocuses on software quality, new technologies, and reduced documentation through increased use of automation, unscripted testing and QA techniques such as code reviews, testing, and verification.
Change management	Changes to the computer system are carefully managed, following defined change control procedures to ensure that modifications or upgrades to the system do not compromise its validated state and continue to maintain compliance with regulatory requirements.	Continuous improvement is done by implementing feedback mechanisms, monitoring software performance, and conducting post-market surveillance. Aims to identify and address software issues, vulnerabilities, and areas of improvement throughout the software lifecycle.

Table 1: Key Principles of CSV and CSA

GCP

GCP refers to the 'good practice' guidelines and regulations created to ensure that food, medical devices, drugs and other life science products are safe, effective and usable. All regulators such as the FDA, EMA, Medicines and Healthcare Products Regulatory Agency (MHRA) and the International Organization for Standardization (ISO) all define and refer to GxP in their publications. Good Clinical Practice (GCP) is used to manage the conduct of clinical trials.

ICH E6 (R2), is a regulatory guideline, developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). It maps out the requirements of GCP. It outlines the key components to be adhered to in designing and executing clinical trials.

The goal of ICH E6 (R2) is to ensure that repeatable and dependable quality is embedded into the lifecycle -i.e. the design, conduct, monitoring, recording, analysis and reporting of clinical trials- of a clinical trial while safeguarding subject rights.

Keeping up with the changing landscape of clinical trials has meant that GCP evolves constantly. The draft of the next version of ICH E6, the ICH E6 (R3) was released in May 2023. It keeps most of the components of previous versions and refines in a few key areas (Fig 1). The goal of ICH E6 (R3) is:

- To provide guidance that applies to different clinical trial designs and facilitate innovation.
- To further advance focus on a proportionate, risk-based approach to the design and conduct of clinical trials.
- Address the complexities of clinical trials in the current global regulatory climate.

The new version also highlights the need to accommodate the nuances and intricacies of evolving clinical research, with increasing complexities deriving from the emergence of novel designs and technologies. Heightened expectations of data systems and records management to ensure data integrity and quality is another key change from the previous version of the guideline.

The focus on technology is evident. In Annex -2, there is emphasis on data acquisition through sources ranging from Electronic Health Records (EHR) and Case Report Forms (CFR) to wearable devices and sensors. The guidelines draws attention to patient interaction through Patient Reported Outcomes (PROs) and Clinical Outcome Assessments (COAs), as well as the consent process, which are now collected via electronic and video options. Annex -2 also highlights how GCP principles can be applied across a variety of trial designs and data sources. For eg. Decentralised Clinical Trials (DCT), pragmatic elements, Real-World Data (RWD), and Digital Health Technologies (DHT).

Section 4 in ICH E6 (R3)- Data Governance- Investigator and Sponsor - aligns with CSV and CSA. The validation of computer systems, along with audit trails, metadata management, backup, disaster recovery, and IT security, are also highlighted, ensuring the integrity and security of trial data.

These changes offer sponsors an opportunity to redefine their clinical technology and data strategy. From digitising Clinical Outcome Assessments, eCOA, to developing new eCOA such as video COA (vCOA) to capture meaningful trial endpoints.

Overarching Principles of ICH E6 (R3)

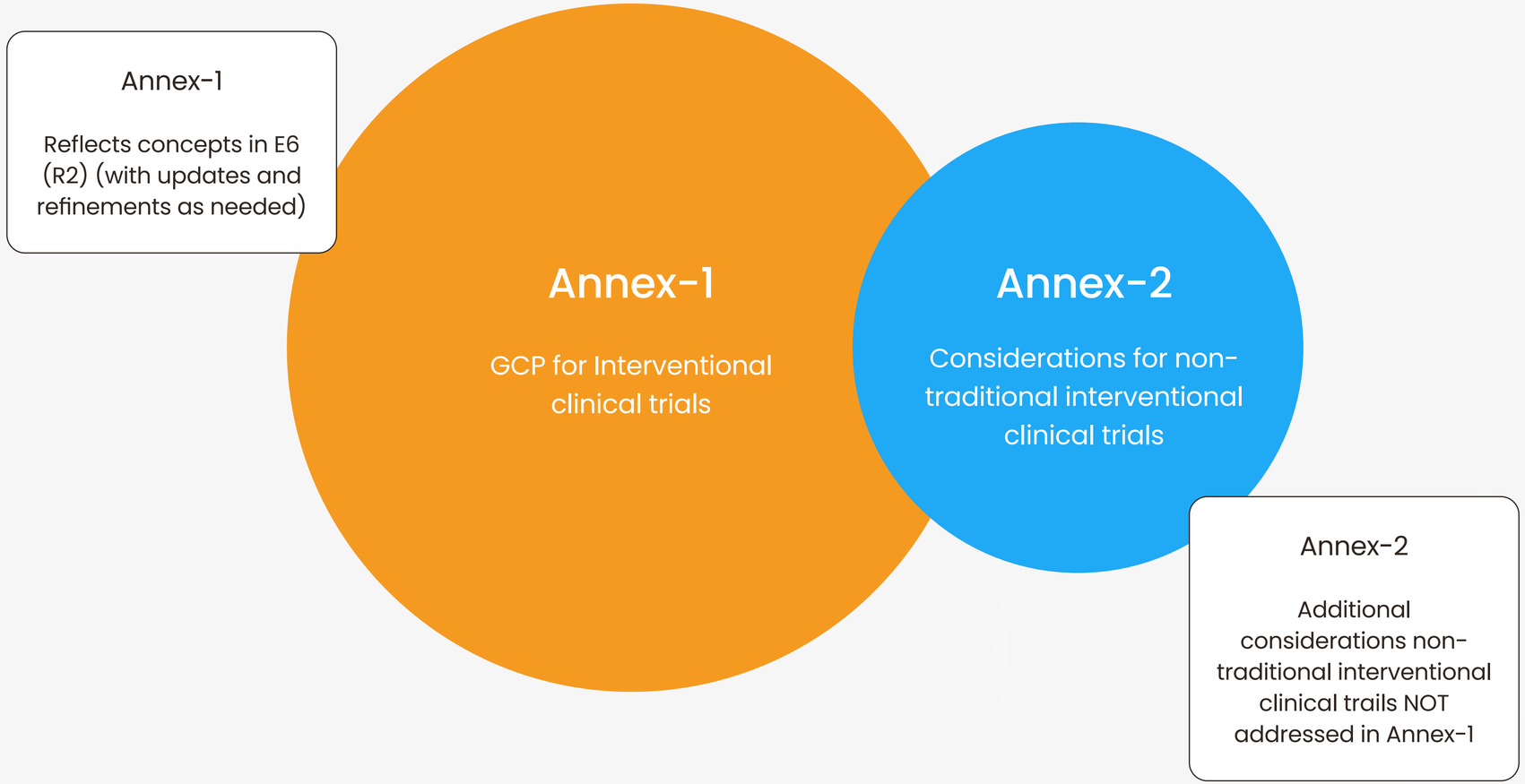

Figure 1: Conceptual Representation of Approach to ICH E6 (R3)

Additional drivers for change in managing compliance and quality

The Pharma 4.0 initiative offers a better understanding of the impact of protocol amendments and the growing impact of ML and AI in drug development and quality management are also driving the change in the way we manage compliance and quality.

- Pharma 4.0: Introduced in 2021 by the International Society for Pharmaceutical Engineering (ISPE), Pharma 4.0 is an initiative to help pharma companies transition into a complete digitisation era based on a 4 part operating model, including resources, information systems, organisation and processes, and culture. It aims to do this through:
- a transformation of the manufacturing workforce towards a more human-centric workflow, embedding best practices concerning health regulations.
- eliminating data silos within organisations, by improving communications between regulators, the industry and stakeholders.
- not focusing solely on IT, but on organisational and cultural aspects, related to processes and resources and aligning both established and innovative industries.

- Better understanding of the impact of amendments: A study conducted by Tufts Center for the Study of Drug Development (Tufts CSDD) in 2022 assessed trends in protocol amendment and the impact amendments have had on clinical trial performance. Sixteen pharmaceutical companies and CROs provided data.
- The prevalence of amendments in phase I – IV protocols has increased substantially (from 57% to 76%) and the mean number of amendments per protocol has increased by 60% to 3.3, up from 2.1.
- Phase I and III protocols saw the highest increases in the mean number of amendments implemented per protocol.
- 77% of the amendments were deemed unavoidable with regulatory agency requests and changes to the study strategy as the top reasons. The most common reason for amendment after change in countries (56.7%), change related to endpoint selection came next (17.5%).

This adds additional complexity to managing, documenting and implementing change while meeting quality and regulatory requirements.

- ML and AI: In May 2023 the FDA shared its view on the increased use of AI/ML throughout the drug development life cycle. Acknowledging that the agency has seen a significant increase in the number of drug and biologic application submissions using AI/ML components over the past few years (>100 submissions in 2021). They've acknowledged that AI/ML is increasingly integrated in areas where the FDA is already engaging, including Digital Health Technologies (DHTs), and Real-World Data (RWD) analytics.

To address these developments, the FDA has accelerated its efforts to create an agile, flexible risk-based regulatory ecosystem and framework that promotes innovation and protects patient safety.

The results (table 2) show that since 2015:

	2015 (n = 836 Protocols)		**2021** (n= 952 protocols)	
	Prevalence	Mean	Prevalence	Mean
Phase I	52%	1.8	67%	3.1
Phase II	77%	2.2	89%	3.3
Phase III	66%	2.3	82%	3.5

[1] https://ispe.org/initiatives/pharma-4.0

[2] https://europepmc.org/article/ppr/ppr699431

Table 2: Amendments in Phase I-III Trial Protocols

Aparito Management Platform - AMP™ our data-driven eQMS

Aparito manages compliance with quality and regulatory requirements through the Aparito Management Platform (AMP™). AMP™ combines quality and management and integrates risk management and data integrity in every component of the platform.

How do we do this?

The AMP™ ecosystem consists of three core components known as The Three Ps - Products, Processes, and Projects. These components ensure that all the quality focus we have on our product and processes feed into all studies on Atom5™.

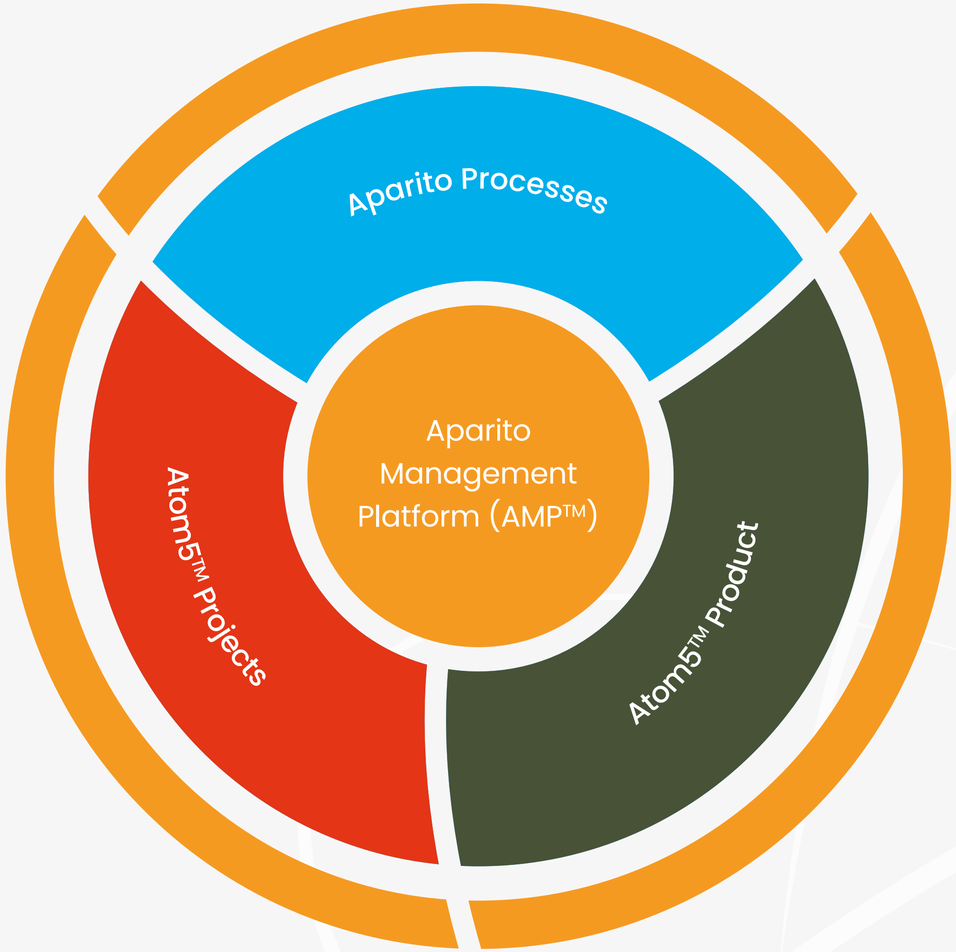

Figure 2: The Three Ps of the AMP™ Ecosystem

Inbuilt tools and features in each of these components:

- Keep CSV/CSA of products streamlined and effective.
- Support Decision -making: Effective CSV and CSA promote informed decision-making. This allows decision-makers to formulate strategies and plans based on data which contributes to strengthening your reputation as a responsive organisation.
- Help manage non-conformities: Helps you swiftly identify and correct potential nonconformities following deviations and complaints diagnosed and recorded in AMP™.
- Incident management: Helps you to log all incidents that arise in the day-to-day operations and filter those that need further investigation as a non-conformity or a CAPA.
- Implement CAPAs: Implementing and tracking action plans for changes and CAPAs necessary for improving processes and reducing risk.
- Manage complexity: Help you efficiently manage the complexity of data and processes with features and tools to track changes such as protocol amendments, ensure data traceability through a digital audit trail, and facilitate the detection of potential errors or inconsistencies in information.
- AMP™ ensures that data quality and data integrity is maintained throughout and keeps your team audit ready by default.

Why choose Aparito and AMP™?

Our experience and in-house expertise ensure that we:

- build our products in line with ISO 27001: 2013 and ISO 13485:2016 certifications
- are well-equipped to manage the rigorous compliance and quality needs of eCOA data capture in the life sciences industry, and can address a crucial challenge faced by the life science industry today – the shortage of resources and experience in the realm of CSV/CSA implementation.

We invite you to strengthen your clinical trials, projects and teams with AMP™ for efficient and comprehensive CSV implementation to help you focus on high-impact drug development, safe in the knowledge you can demonstrate how you meet your regulatory requirements with high data quality and integrity.

Supporting Global Studies with Atom5™

Aparito's eCOA platform is disease-agnostic and scalable, ready for rapid deployment in global trials to support patient data capture in 193 countries and 125 languages.

Designed and built by regulators and clinicians, Atom5™ is 21 CFR Part 11, GDPR and HIPPA compliant, and supports traditional survey-based Patient Reported Outcomes, video eCOAs, wearable integration along with telemedicine, and eConsent via one interface to support hybrid and decentralised clinical trials at scale.

Atom5™ now has an extensive library of validated eCOAs enabling rapid configuration in future studies.

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