

eCOA Systems and CE Certification

Introduction

Electronic clinical outcome assessment (eCOA) systems can generally be described as electronic systems incorporating software built as mobile applications or interactive technologies (web or voice) to enable the capture of COA data within the context of clinical research. As such, eCOA systems rarely fall under the scope of what the European Union (EU) describes as requiring *Conformité Européenne*¹ (CE) certification, more commonly known as the “CE Mark.”

On May 26, 2021, the EU began fully implementing the *Medical Device Regulation (EU) 2017/745*² (MDR). This regulation was developed to ensure medical devices are marketed consistently across the EU member states, ensure minimum quality and safety standards for patients and users, and ensure that data generated from such devices in clinical investigations are reliable and robust. There is contention as to the applicability of this regulation to eCOA systems, such as mobile device applications (apps). Some clinical trial sponsors require eCOA providers to have a conformity assessment performed on their apps, and as such be certified with a CE Mark.

The motivation for this selective requirement appears to be that these sponsors consider eCOA apps to be classifiable as “software as a medical device” (SaMD), which can generally be described as software intended to be used for one or more medical purposes and these purposes are performed without the software being integral to or driving the function of a medical device. While it is true that certain eCOA apps may fall under the classification of SaMD, eCOA apps typically used in clinical trials do not.

Per the Regulation (EU) 2017/745²:

“It is necessary to clarify that software in its own right, when specifically intended by the manufacturer to be used for one or more of the medical purposes set out in the definition of a medical device, qualifies as a medical device, while software for general purposes, even when used in a healthcare setting, or software intended for life-style and well-being purposes is not a medical device.”

Currently, there are no publicly accessible reference publications or consensus-developed documents that delineate how different types of eCOA systems are classified within the above framework. There is an evident need to develop an appropriate classification scheme for eCOA systems with regards to CE certification and to educate the clinical research community of the actual intentions of the relevant regulations. The European Medicines Agency (EMA) regulations place the burden of proof upon system developers to determine the intended use of the system. The goal of this document is to develop understanding of the regulation and what is involved in CE certification, provide a tool to facilitate determination of when eCOA software can be considered SaMD and hence whether CE certification is necessary.

Manufacturers doing business in the EU must determine if they meet the requirements for CE certification. However, while the focus of this manuscript is the current EU regulation, this general requirement is not limited to the EU; see Appendix 1 for list of countries requiring CE marking.

Terminology and Definitions

The below table details relevant terms and definitions to provide a common understanding of the issues being addressed in this paper.

Term	Definition	Source
CE Mark	<i>“Conformité Européenne.”</i> “By affixing the CE marking to a product, the manufacturer declares on his sole responsibility that the product is in conformity with the essential requirements of the applicable Union harmonisation legislation providing for its affixing and that the relevant conformity assessment procedures have been fulfilled. Products bearing the CE marking are presumed to be in compliance with the applicable Union harmonisation legislation and hence benefit from free circulation in the European Market.”	Official Journal of the European Union, C272/1 26 July 2016. Information from European Union Institutions, Bodies, Offices and Agencies. European Commission: The ‘Blue Guide’ on the implementation of EU product rules 2016 ¹ .
Clinical Investigation	“Any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device.”	European Union Medical Device Regulation (EU 2017/745 (MDR), Article 2 (45)) ²
COA	Assessment of a clinical outcome can be made through report by a clinician, a patient, a non-clinician observer, or through a performance-based assessment. Types of COAs include: • patient-reported outcome (PRO) measures • clinician-reported outcome (ClinRO) measures • observer-reported outcome (ObsRO) measures • performance outcome (PerfO) measures In clinical trials, COAs are intended to provide evidence regarding clinical benefit (i.e., how patients feel or function in their daily lives as a result of the treatment).	National Institutes of Health BEST (Biomarkers, EndpointS, and other Tools) Resource ³ .

eCOA	<i>“Electronic Clinical Outcome Assessment (eCOA): An eCOA is a quantifiable measure used as a measure of how patients feel or function that is derived from a digital measure. The clinical meaning is established de novo. Clinical outcomes can be assessed through a report by a clinician, a patient, a non-clinician observer or through an active performance-based assessment or passive monitoring of patient behaviour or performance.”</i>	EMA/219860/2020 Human Medicines Division. Questions and Answers: Qualification of Digital Technology-Based Methodologies to Support Approval of Medicinal Products. 1 June 2020 ⁴
Medical Device	<i>“Any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one of more of the following specific purposes:</i> • diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease, • diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability, • investigation, replacement or modification of the anatomy or physiological or pathological process or state, • providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, <i>And which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.”</i>	Official Journal of the European Union L117/1, Legislation. Volume 60, 5 May 2017 ¹
SaMD	Software as a Medical Device (SaMD) <i>“Software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device.”</i>	International Medical Device Regulators Forum (IMDRF) ⁵

Software	<i>“a set of instructions that processes input data and creates output data.”</i>	Medical Device Coordination Group (MDCG) 2019-11; Guidance on Qualification and Classification of Software Regulation (EU) 2017/745 - MDR and Regulation (EU) 2017/746 – IVDR ⁶
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Governing Regulations

MDR² makes specific reference to software being considered an “active device”, which is one that depends on a source of energy other than the human body. In addition, section 2.5 of MDR² defines an active device that is intended for use in the diagnosis and monitoring of disease as *“any active device used, whether alone or in combination with other devices, to supply information for detecting, diagnosing, monitoring or treating physiological conditions, states of health, illnesses or congenital deformities.”*

Much of MDR² focuses on aspects of safety for patients using such devices, such as design, function, accuracy, use, emissions, contamination, and potential exposure to harmful substances. When assessing how eCOA systems may be classified within the scope of MDR², the critical factor is the intended use.

Intended Use

The intended use by the manufacturer is a key determinant of whether software can be classified as a medical device. In the case of eCOA software, the eCOA Consortium concludes from an in-depth analysis of the regulations that the creator and licence holder of the COA should be considered the manufacturer of the COA and the eCOA system software implements a given COA in a digitized form.

MDR² allows for the potential classification as a medical device if the system is used for one or more specific purposes (see ‘Medical Device’ in the *Definitions and Terminology* table above). Of those specific purposes for which software systems might be considered a medical device and thus fall in-scope for CE certification, only “diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease” or “diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability” might apply to eCOA systems. By way of example, COAs such as the *Structured Clinical Interview for DSM 5 (SCID 5)* or the *Mini International Neuropsychiatric Interview (MINI)* have been used as an aid to support the diagnosis of mental health conditions, but these assessments are not intended to be used in isolation to diagnose medical conditions. When using these COAs in paper format, there is no question that they do not require CE certification as they are not software. If they were to be completed using electronic formats, would that software meet the requirement for CE certification? The eCOA software systems are simply recording responses as entered by the clinician,

making these comparable to simple electronic forms and consequently meeting the definition of software rather than SaMD.

An eCOA system might be used in clinical trials to monitor the status of a disease or condition. In the context of a clinical trial, some eCOAs might be used to establish if criteria have been met that might require clinical site staff to make a determination about a trial participant's safety. An important example of this would be a measure used to assess suicidality, for example the *Columbia Suicide Severity Rating Scale* (C-SSRS). A scale such as the C-SSRS is, in effect, designed to support prospective assessment of the potential for harm, and an electronic implementation of the C-SSRS would not itself determine any action or treatment; the scale only helps inform the intervention pathway. Another example (MDCG 2021-24 p44) is software for electronic diaries that record insulin dose. This is not considered a device unless the data are automatically analyzed and results of that analysis directly alters the patient's treatment.

eCOA software deployed in clinical trials is not used for disease prognosis, nor is it used to directly benefit an individual trial participant. However, the eCOAs used in the context of a clinical trial might generate data that are generalizable and could help us to better understand and predict disease course, whether in response to a treatment intervention or under naturalistic conditions.

Outcome assessments, regardless of whether they are completed on an electronic device using software or on paper, are not themselves designed to treat or alleviate disease or injury or compensate for disability or injury. In general, COAs are not implemented for medical purposes in clinical trials. Clinical trial sites do not implement medical treatments based solely on these data; the data informs a statistically driven assessment of the effect of a given study intervention or interventions.

Systems in scope for CE certification

As discussed throughout this article, the content and intent of eCOA apps mean they are not generally considered as SaMD and hence do not require CE certification. There may be edge cases to this default position especially where eCOA systems involve sensor-based wearable devices which are sometimes gathered under the umbrella term of "eCOAs." The wearable device itself almost always requires a CE mark as the device is being worn by a trial participant and evidence of adherence to safety expectations are required. There are also use cases where software applications associated with a wearable sensor could be classed as a SaMD due to the nature of the function it performs. For example, apps have been developed and approved for use that can deliver doses of insulin to persons with diabetes where they are paired to an insulin pump.

A further example could be where a wearable device incorporating an accelerometer is used for movement or activity assessments. The data from the accelerometer may be used in place of the traditional 6-minute walk test (6MWT). In this case, the wearable device itself would be CE marked but the 6MWT recorded by an eCOA app would not require a CE mark.

These types of apps should not be confused with the eCOA apps that present COAs via a mobile device, even though for the purposes of a clinical trial they may be installed on the same mobile device. In that scenario, each individual app provided to a trial participant must each be assessed independently, as apps being presented on a single device does not equate to equivalent CE certification status.

eCOA systems and CE certification scope

At the root of the issue might be clarifying exactly what eCOA systems are and do. eCOAs can be described as digitized formats of COAs that are used to measure and record health-related signs, symptoms, functioning, and experiences. When used in clinical trial research, eCOAs help measure the effects of an intervention or to assess the natural course of a disorder or general health of trial participants. The eCOAs are driven by their underlying software programming.

eCOAs are generally applications loaded onto an electronic device. The electronic device, be it a laptop computer, tablet, or smartphone, is not directly measuring physiological responses for medical purposes. A human (clinical professionals, observers, or participants) records a response in the eCOA system based on what they themselves observe or feel. If we consider COAs that are recorded on paper, the paper assessments themselves are evidently never considered to be medical devices. eCOAs are built either based on pre-existing validated assessments (often having been initially created in paper format) or novel assessments developed to ask specific questions relating to a person's experience of their condition, treatment, or activities. Just as on paper, the goal of most eCOAs is to capture data for use in determining an intervention's efficacy and/or safety. Some eCOAs simply record responses that are transferred to a clinical database. Other eCOA systems incorporate algorithms that operate on the data to guide users through the assessment using conditional logic or to calculate summary fields.

Software is defined in the MDCG 2019-11 Guidance⁶ as *"a set of instructions that processes input data and creates output data."* Input data are provided to the software and acted upon through processing or computation to create the output data. Data can be input through means of human data-input devices (e.g., keyboard, mouse, stylus, or touch screen), speech recognition, digital documents or transmissions from other devices. Data outputs include anything displayed on a screen (e.g., numbers, characters, pictures, graphics), audio, digital documents, haptic buzzing, etc. Medical device software (MDSW) is specifically defined as *"software that is intended to be used, alone or in combination, for purpose as specified in the definition of a "medical device" in the medical devices' regulation or in vitro diagnostic medical devices regulation."* Furthermore, *"Software must have a medical purpose on its own to be qualified as a medical device software. It should be noted that the **intended** purpose as described by the manufacturer of the software is relevant for the qualification and classification of any device."*⁶ If the software is intended to process, analyse, create, or modify medical information and the results of that process are governed by a medical purpose, it may qualify as medical device software.

While eCOA systems incorporate software that processes input data and creates output data, the intended purpose of the software is to facilitate collection of clinicians' and or trial participants' responses to the assessment items, guiding them through the assessment and sometimes deriving response-driven scores. The general intent of most eCOA systems is simply to record response data and transmit that data to a database for storage and eventual analysis. In general, most software driving eCOAs do not have a medical purpose of their own. Thus, most eCOA systems would not qualify as medical device software.

The CE certification process

Processes and controls must be implemented for the entire life cycle of the device – from concept to development to active use and eventual retirement.

There are a number of steps to follow to obtain CE marking for a medical device, which, in the case of eCOA software and applications would be applicable should they be considered as SaMD. As defined in Regulation (EU) 2017/745² *“devices should, as a general rule, bear the CE marking to indicate conformity to this regulation so that they can move freely within the Union and be put into service in accordance with their intended purpose.”* It is the responsibility of the manufacturer to obtain and place the CE mark on the product. Therefore, CE marking can only be achieved with the involvement of the manufacturer, either directly or via an authorised representative. For example, an authorised representative may be engaged if the manufacture doesn’t have an office within the EU.

It is essential to identify the class of medical device for this purpose as this will determine the approach to be followed for achieving certification.

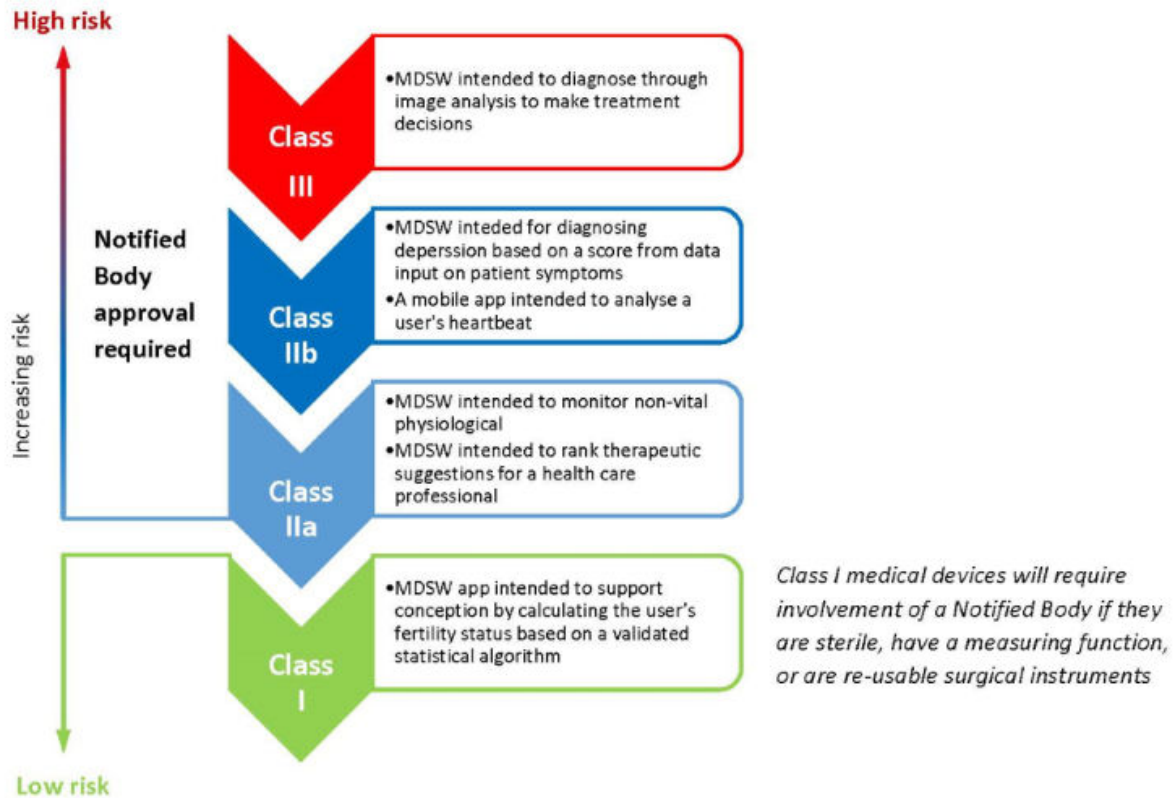
Medical device classification rules are outlined in Regulation (EU) 2017/745 Annex VIII, Chapter III. Rules 1 to 4 cover non-invasive devices and rules 5 to 6 cover invasive devices. Rules 9 to 13 cover active devices, which are devices that require a source of energy to work. Finally, a set of Special Rules (Rules 14 to 22) apply to devices that are both invasive and active or that combine medical devices with an in-vitro diagnostic device or drug. Assessing devices against these rules will determine the device classification which can be summarised as follows:

<i>Class</i>	<i>Description</i>
I	low risk, non-invasive devices
IIa	low to medium risk devices invasive devices that are in place for short periods of time (e.g., up to 30 days)
IIb	medium to high-risk invasive devices that are in place for long periods of time (e.g., longer than 30 days).
III	high risk invasive devices

Based on Medical Device Regulation MDR (EU) 2017/745 Article 51 Annex VIII

As outlined previously, the intended use of an eCOA system would not normally lead to it being classified as a medical device. For all classes of medical devices (or SaMD) the manufacturer is required to have obtained sufficient clinical data to prove the device conforms to safety and health requirement by way of conducting clinical investigation(s).

The below diagram summarizes the classifications of MDSW:



It is the **intended** and not the accidental use of the device that determines the class of the device.
(MDCG 2021-24)

For Class I devices, self-certification via a conformity assessment is considered sufficient, with the manufacturer providing evidence to support requirements relating to their technical documentation, Quality Management System and post-market surveillance plan and report as defined in the Regulation (EU) 2017/745 Chapter 5, Section 2.

Class II and above devices require a notified body to be involved in the certification. The notified bodies are organisations authorised to issue CE certificates on behalf of the relevant health authorities. The notified body will undertake the conformity assessment on behalf of the manufacturer.

Regardless of a device class, the manufacturer is required to provide technical documentation, a risk assessment, and a declaration of conformity which includes details on the design, manufacturing processes, and intended use/operation of the product. Further detail on the documentation requirements can be found in Appendix 2.

To summarise, to obtain a CE mark the manufacturer will need to complete the following steps:

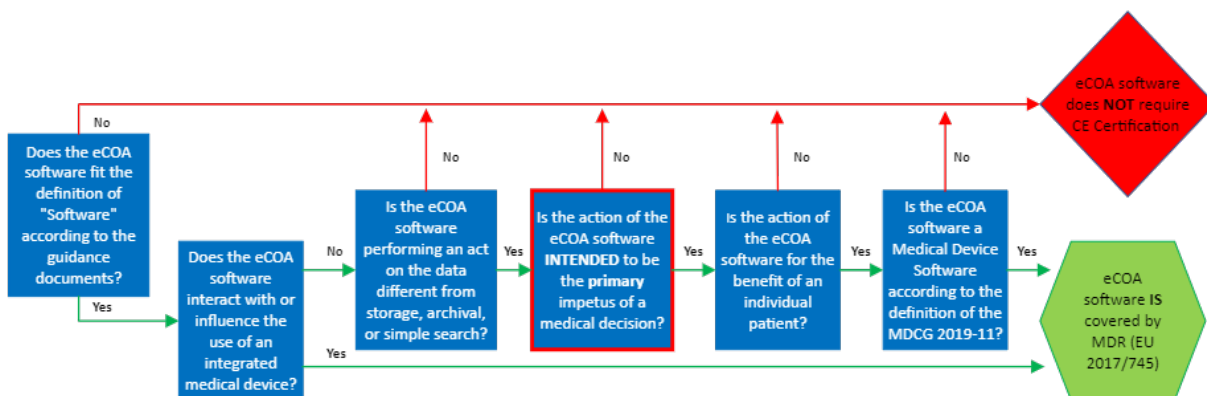
- Confirm the risk-based class for the medical device (i.e., Class I, IIa, IIb, III)
- Prepare the technical documentation to support the certification application

- Undertake the appropriate assessment procedure (obtaining a certificate of conformity from a notified body if appropriate)
- Register with the competent authority (e.g., EMA in the EU).

It is evidently a very significant and resource intensive piece of work for any eCOA system provider to commit to the process of CE certification. Consequently, it is imperative that the expectations for CE marking are based on actual and verifiable application of the applicable regulations.

An eCOA and CE certification Decision Tree

The figure below provides a decision tree that can help to determine whether an eCOA system requires CE certification as a medical device.



Conclusion

At their core, electronic clinical outcome assessment systems perform the same fundamental purpose as paper-based COAs and should be treated as such. Clinical trials often use eCOA systems to collect data that are used to assess treatment endpoints. The overwhelming majority of eCOA systems are not intended to be used as medical software or medical devices. They are not designed to be the primary driver of medical decisions, nor should they be considered as such. Furthermore, eCOA systems are not used to directly benefit individual participants in clinical trials. eCOA systems are designed to collect data from individuals to be aggregated with other trial participant data before being subjected to statistical analyses that allow us to understand how participants feel or function in the context of a clinical trial.

It is evident that eCOA systems rarely fall under the classification that would require CE certification. An eCOA system that does qualify would be the exception, rather than the rule. Simply put, the intended use of most eCOA systems is to capture data and the intended use is pivotal to determining whether CE certification is required.

References

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5. International Medical Device Regulators Forum. Software as a Medical Device (SaMD): Key Definitions. 9 December 2013. <https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf>
6. Medical Device Coordination Group (MDCG) - Guidance on Qualification and Classification of Software Regulation (EU) 2017/745 - MDR and Regulation (EU) 2017/746 – IVDR. <https://ec.europa.eu/docsroom/documents/37581/attachments/1/translations/en/renditions/native>

Appendix 1: Countries requiring CE marking

The below country list is taken from the US Department of Commerce's International Trade Administration website[^]. The list is not definitive, and some countries listed may require additional certifications or markings where country-specific requirements are in place:

Austria	Greece	Norway
Belgium	Hungary	Poland
Bulgaria	Iceland	Portugal
Croatia	Ireland	Romania
Cyprus	Italy	Slovakia
Czech Republic	Latvia	Slovenia
Denmark	Liechtenstein	Spain
Estonia	Lithuania	Sweden
Finland	Luxembourg	Switzerland
France	Malta	Turkey
Germany	Netherlands	United Kingdom

[^] [https://www.trade.gov/ce-marking#:~:text=The%20CE%20marking%20\(an%20acronym,requirements%2C%20which%20ensure%20consumer%20safety](https://www.trade.gov/ce-marking#:~:text=The%20CE%20marking%20(an%20acronym,requirements%2C%20which%20ensure%20consumer%20safety)

Appendix 2: CE Certification checklists

A summary of documentation requirements for Conformity Assessments when obtaining a CE Marking are detailed in the EU's *Technical documentation and EU declaration of conformity website**

Technical documentation package should contain the following detail as a minimum:

- Manufacturer name and address, or those of any authorised representatives
- a brief description of the product
- identification of the product, for example, the product's serial number
- the name(s)/address(es) of the facilities involved in the design and manufacture of the product
- the name and address of any notified body involved in assessing the conformity of the product
- a statement of the conformity assessment procedure that has been followed
- the EU declaration of conformity
- label and instructions of use
- a statement of relevant regulations to which the product complies
- identification of technical standards with which compliance is claimed
- list of parts
- test results

A risk assessment should be included in the technical file that covers possible risks from use of the product and how these risks are mitigated, as well as determining the applicable essential requirements, and how the product complies with these requirements.

EU Declaration of Conformity:

- Manufacturer name and full business address or that of the authorised representative
- the product's serial number, model, or type identification
- a statement, stating the manufacturer takes full responsibility for the product.
- means of identification of product allowing traceability – this can include an image
- details of the notified body which carried out the conformity assessment (if applicable)
- the relevant legislation with which the product complies, as well as any harmonised standards or other means used to prove compliance
- your name and signature
- the date the declaration was issued
- supplementary information (if applicable)

* https://europa.eu/youreurope/business/product-requirements/compliance/technical-documentation-conformity/index_en.htm