mantrasystems

Mastering the MDR

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About the author and Mantra Systems Ltd

Mantra Systems Ltd delivers a completely new form of medical device regulatory support. Unlike any other consulting company, we have a team of specially-trained medical doctors who apply their clinical acumen and industry expertise to your medical device compliance challenges. With the new MDR focusing heavily on clinical evidence, our knowledge will provide the support you need to ensure your devices meet the requirements of the MDR.

This White Paper is part of a series written by Dr Paul Hercock, the CEO & founder of Mantra Systems Ltd. Paul is dual-trained in medicine and law. He spent 14 years working for the NHS as a front-line clinician and then obtained a Graduate Diploma in Law with distinction from Nottingham Law School. While at law school, Paul established a medical device start-up. He then went on to specialise in providing medical and regulatory support to multi-national medical device companies from across the industry.

Leveraging Paul's expertise, Mantra Systems comprises an infrastructure of specially-trained medical doctors that apply their clinical knowledge to provide support services to medical device manufacturers working to achieve compliance of their medical devices with the MDR.

Introduction

The purpose of this document is to outline a structure for medical device manufacturers working towards compliance with the new Medical Device Regulation (MDR). It serves as a commentary on the MDR and does not constitute formal advice.

The medical device sector is one of the most tightly regulated market sectors in the world. It is essential that all operatives within the medical device sector, especially medical device manufacturers, have a thorough understanding of the MDR and what their responsibilities are.

On 26th May 2021 the Medical Device Regulations (EU) 2017/745 will formally replace the Medical Devices Directive 93/42/EEC (MDD) after a four-year transition period, extended by one year due to the COVID-19 crisis. The introduction of the Medical Device Regulation, commonly known as the MDR, sees the largest overhaul of medical device legislation in decades.

The MDR describes a detailed regulatory environment around medical device design, construction, manufacturing, marketing, surveillance, senescence and oversight. However, the MDR itself is 175 pages of legal text, making it a difficult and demanding instrument to work with directly. After reading this White Paper, you will better understand how to work with the MDR and how to start building an MDR compliance strategy.

MDR structure overview

The full text version of the MDR is 175 pages long. It is an extensive legal text that covers all aspects of medical device regulation. It is imperative that all medical device manufacturers become familiar with the contents of the MDR.

It begins with an untitled introductory section that places the new legislation in context and details what is and is not in scope of the MDR. Specifically, the MDR applies to:

- Products that are a combination of devices and medicinal products, on a case-by-case basis
- Products made from non-viable tissue of human origin
- Some products that may claim a non-medical use but that are sufficiently similar to other medical devices in terms of function and any risks that they generate
- Software that is specifically designed for a medical purpose.

The MDR does not apply to in-vitro diagnostic medical devices, products containing viable cellular material, blood products, purely medicinal products (e.g. drugs), cosmetics, or food.

After the introduction, the MDR text moves on to the substantive sections that contain the legislation. This comprises the **Chapters** that each contain multiple related **Articles** outlining the law itself. The chapters are followed by a series of **Annexes** that detail specific procedures and requirements that are necessary in order to comply with the law contained within the Articles. In other words, very loosely, the Chapters can be thought of as stating "what to do", while the Annexes act as a binding guide as to "how to do it".

How to work with the MDR

This document outlines a basic structure for working with the MDR. Working through each section in order will allow you to begin constructing an MDR compliance or transition strategy for your products. The stages to MDR compliance are:

- Confirm that your product is a medical device and determine what risk classification applies
- Ensure that you as a manufacturer meet MDR base requirements
- Design and implement MDR compliance systems - QMS, PMS, PMCF, Vigilance, risk

management

- Identify what Annex I GSPRs apply to each product
- Perform a gap analysis and clinical evaluation
- Address gaps and ensure ongoing data collection - clinical investigations
- Ensure that all required technical documents have been completed

If you have any questions about any of the content in this document, please contact a member of our team: contact@mantrasystems.co.uk, 0114 386 3349.

What is a medical device? How to determine risk classification.

The term ‘medical device’ is defined in Article 2 MDR as:

"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 or more of the following specific medical purposes:

- 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 of a 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,

...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." The definition also extends to:

- devices for the control or support of conception
- products specifically intended for the cleaning, disinfection or sterilisation of [medical] devices

These definitions are comprehensive and serve to address the majority of devices on the market. Working alongside the Article 2 definition, Article 1 considers devices that have a medicinal product as an integral part (e.g. bone cements containing antibiotics), or that administer a medicinal product (e.g. “Epipen” adrenaline syringes for anaphylaxis).

- If a device has a medicinal product as an integral part, it falls under MDR if the action of the medicinal product is ancillary to the action of the device
- If the device merely delivers a medicinal product without altering it, then it falls under MDR

- If the product is placed on the market in such a way that the combination forms a single integral product intended for use exclusively in the given combination, then it falls outside MDR and is subject to Directive 2001/83/EC or Regulation 726/2004.

The first step in working with the MDR is to use these definitions to confirm whether or not a product will be classed as a medical device. The definition in the MDR is broader than that in the MDD, so some products will be drawn into medical device regulation for the first time.

Once a product has been confirmed as a medical device, **the next step is to determine what risk classification the device falls into**. Risk classification determines the conformity assessment procedure that the device must undergo, and forms the basis of constructing and implementing an MDR compliance strategy.

Article 51 states that medical devices are divided into four risk classifications: Class I, IIa, IIb and III.

Class I devices are the lowest risk, with perceived risk increasing progressively through Class IIa, IIb and finally Class III as the highest risk class. With higher risk comes a requirement for a more stringent conformity assessment procedure. Article 51 states that any dispute over device classification must be referred to the competent authority of the relevant member state for them to decide.

The rules for determining the risk class for a device are outlined in Annex VIII. Annex VIII works best when used as a flow-chart in determining the regulatory class of each individual medical device. It is self-explanatory when used in this way, and for this reason is not included in this summary document. It can be found on page 140 of the full-text legislation.

Base requirements for manufacturers

In order for a medical device to be placed into the market, the medical device manufacturer must meet certain base requirements. Additionally, the device must be CE-marked to indicate that it complies with the requirements of MDR. **Chapter 3** of the MDR outlines base requirements for manufacturers, basic rules for CE-marking and specific requirements placed upon 'economic operators' including device manufacturers.

Article 5 begins by stating that a device may only be placed on the market if it complies with MDR when the device is:

"*...supplied, properly installed, maintained and used in accordance with its intended purpose.*"

It also states that all devices must meet the **general safety and performance requirements** (listed in Annex I and detailed later in this document) and must demonstrate this through a structured process of **clinical evaluation**.

Article 10 is an important Article that details base requirements that must be met by all medical device manufacturers themselves. Manufacturers must:

- Ensure that their medical devices are designed and made in accordance with MDR
- Have a risk management system in accordance with Section 3 Annex I of the MDR
- Conduct an appropriate clinical evaluation of all their devices
- Maintain a record of up to date technical documentation
- Have an implemented Quality Management System (QMS)
- Have financial coverage for any potential liability claims against them that may result from use of or contact with their devices.

If MDR compliance has been successfully demonstrated, manufacturers must affix a CE-mark to their devices and must comply with MDR requirements for using a Unique Device Identification (UDI) system. Article 20 simply states that CE-marks applied to products will conform to the general rules for the symbol itself.

Article 15 concludes the discussion on what is required of economic operators such as device manufacturers. It states that every manufacturer must have access to a **person responsible for regulatory compliance**. Most companies will be required to employ their own such person; small manufacturers need not directly employ their own but must have one "permanently and continually" at their disposal. The person responsible for regulatory

compliance must have either:

- Recognised qualification in law, medicine, pharmacy, engineering or other scientific discipline AND at least one year experience in regulatory affairs or medical device quality management
- OR a minimum of 4 years experience in regulatory affairs or medical device quality management.

If you do not have access to a suitably qualified person responsible for regulatory compliance, please email Mantra Systems at contact@mantrasystems.co.uk – our team of specially-trained medical doctors, through our unique framework, can help ensure that the requirement for "permanent and constant" availability is met.

Quality Management System (QMS)

All medical device manufacturers must have in place a **Quality Management System (QMS)** that serves to ensure that devices and business activities are produced and conducted (respectively) to an appropriate standard.

MDR Article 10 provides detailed requirements about the Quality Management Systems under the new legislation. It states that all manufacturers must establish, document, implement, maintain, keep up to date, and continually improve a QMS that must cover all parts of the manufacturer's organisation, including as a minimum :

- A strategy for regulatory compliance
- Identification of applicable general safety and performance requirements (SPRs)
- Responsibility of management
- Resource management including management of subcontractors
- Risk management
- Clinical evaluation, including Post Market Clinical Follow-up (PMCF)
- Product realisation process
- Verification of UDI assignments
- Set-up and maintenance of post-market surveillance (PMS) system
- Procedure for communications with regulators such as competent authorities and notified bodies
- Process for reporting serious incidences
- Preventative And Corrective Action (PACA) management
- Processes for monitoring and measuring outputs of interventions

The MDR allows for the use of external **harmonised standards** such as ISO standards when constructing elements such as Quality Management Systems. Building a QMS in accordance with ISO 13485:2016 "Quality Management Systems for Medical Devices" will lead to a rebuttable presumption of QMS conformity with MDR standards, although it should be noted that ISO 13485:2016 has not yet been updated for the new legislation.

Post-Market Surveillance (PMS)

A Post-Market Surveillance (PMS) system forms a key part of a manufacturer's Quality Management System (QMS). For every medical device, **Article 83** requires the manufacturer to prospectively plan, establish, document, implement, maintain and update a PMS system for each of their medical devices.

The PMS system must gather, record and analyse relevant data on the safety and performance of the device ***throughout its entire lifetime***.

Article 83 lists a number of important uses for data generated through PMS activities:

- To update the benefit-risk analysis
- To feed improvements to risk management
- To update device design, Instructions For Use (IFU) and device labels
- To update clinical evaluation
- To identify needs for PACAs or field safety corrective actions (FSCAs)
- To update important Technical Documentation

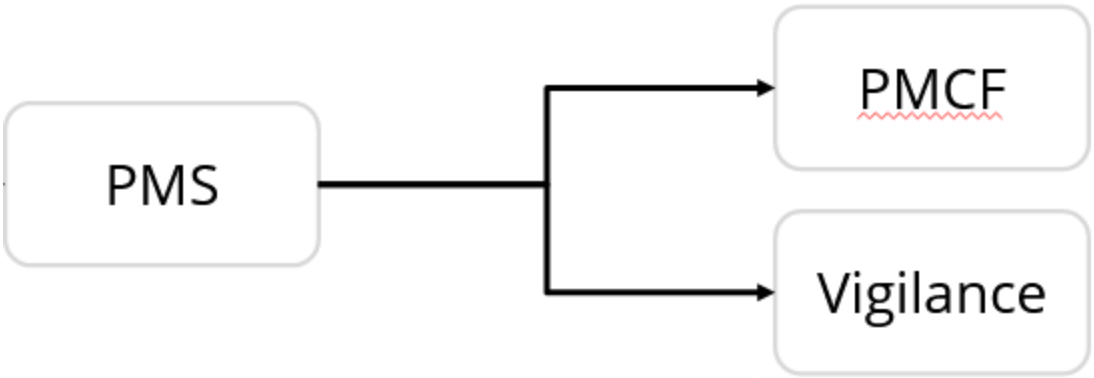
Article 84 states that the PMS system will be based on a documented **PMS plan** constructed around the requirements in **Annex III**, which outlines how to construct the technical documentation that must be produced in relation to the PMS system for every device.

The **PMS plan** must be planned and documented in advance (Article 83) and must contain at least the following aspects:

- A documented process to collect PMS data
- Methods to assess data that has been collected
- Rationale to be applied during risk analysis
- Methods for collecting and investigating product complaints
- Methods for statistical analysis of trends
- Methods for communicating with competent authorities, notified bodies and others
- Methods for tracing devices

What are the elements of PMS?

PMS can be thought of as comprising two major elements: Post-Market Clinical Follow-up (PMCF) and Vigilance:



Post-Market Clinical Follow-Up (PMCF) is a continuous process that involves the proactive collection and evaluation of clinical data relating to the safety and performance of a medical device throughout its entire lifetime. Effective PMCF systems generate **Real World Evidence** that provides data on device performance outside the constraints of a formal clinical trial. PMCF is discussed in detail below.

Vigilance concerns the collection and reporting of data on serious incidents, Field Safety Corrective Actions (FSCAs), and the monitoring of trends of expected side-effects.

PMS Reporting

PMS reporting requirements differ according to the risk class of the device in question. For Class I devices, a **PMS Surveillance Report** must be prepared that summarises relevant results, conclusions, and any PACAs, updated as necessary. For all other device risk classes, a more detailed **Periodic Safety Update Report (PSUR)** must be prepared for every device. For Class IIb and Class III devices the PSUR must be updated annually, whereas for Class IIa devices the PSUR must be updated at least once every two years.

Post-Market Clinical Follow-Up (PMCF)

PMCF is a continuous process that comprises the proactive collection and evaluation of clinical data from the use of CE-marked medical devices when used as intended. Effective PMCF systems produce **real world evidence** that demonstrates the safety and performance of a medical device in normal use. PMCF data must confirm the safety and performance of the device ***throughout its entire lifetime***.

Detailed rules for conducting PMCF are provided in **MDR Annex XIV Part B**. It provides a list of documents that must be produced in relation to PMCF activities, along with a guide to the required contents of the documents.

PMCF must be performed in accordance with a method detailed in a **PMCF plan**. This plan must specify how the PMCF system will:

- Confirm safety and performance of the device throughout its expected lifetime
- Identify previously unknown side-effects
- Monitor the rate and severity of known side-effects
- Identify and analyse any emergent risks
- Ensure continued benefit-risk acceptability
- Identify any systematic misuse or off-label use

Each PMCF plan must include detail of data collection methods to be used, a rationale for the methods chosen, and a timescale of PMCF activities, amongst other requirements.

The results of PMCF shall be analysed and periodically documented in a **PMCF Report** that will form part of the CER and technical documentation.

Careful consideration needs to be given to the structure of the PMCF system that will be implemented in relation to each device. Mantra Systems are experts in developing medical device product registries, a powerful and future-proof method of collecting PMCF data that complies fully with MDR requirements. Contact a member of our team today.

Vigilance

A **Vigilance** process is an important component of the PMS system for every medical device. Vigilance concerns the collection of information about product complaints, serious incidents, field safety corrective actions (FSCAs), and the monitoring of trends of side-effects and adverse events.

Serious incidents are unexpected or "new" events that take or threaten life or limb. Manufacturers must report all serious incidents to the relevant competent authority as soon as a causal relationship between the device and the incident has been identified.

Article 87 outlines requirements for a wider response to any serious incident involving a medical device. It places a degree of responsibility on the Member State itself to undertake measures such as a targeted information campaign to encourage doctors and patients to report suspected serious incidents to competent authorities. This may be useful for a manufacturer to know when dealing with the aftermath of a serious incident involving one of their devices.

In the event of a serious incident, a manufacturer may be required to conduct a **Field Safety Corrective Action (FSCA)**. A field safety corrective action (FSCA) is designed to prevent recurrence of a serious incident. If a FSCA becomes necessary, the manufacturer must bring it to the attention of users of the device through a **Field Safety Notice (FSN)**.

MDR Article 89 outlines how to proceed in the event of a FSCA, stating that the process shall include:

- An investigation on the facts
- A risk assessment focused on the event
- Co-operation with notified body and competent authority
- Not making changes to or sampling any devices that are under investigation – they must be supplied for examination "as is".

If an incident is deemed by a manufacturer not to be serious, or it is deemed to be an established side-effect, then it must be captured as part of **Trend Reporting**, rules for which are outlined in **MDR Article 88.** Manufacturers must monitor the rate of known side-effects and report any statistically significant increase in their frequency or severity.

Annex I General Safety and Performance Requirements (SPRs)

The next step in building an MDR compliance strategy is to perform a clinical evaluation for each medical device. Clinical evaluation involves assessing the extent to which conformity with the relevant **MDR Annex I General Safety and Performance Requirements** has been demonstrated by performing a **Gap Analysis**.

In order to perform a gap analysis and subsequent clinical evaluation, it is first necessary to determine which Annex I SPRs relate to a device.

MDR Annex I contains three chapters:

- General requirements
- Requirements regarding design and manufacture
- Requirements regarding information supplied with the device

The general requirements will apply to almost all devices, whereas the other sections must be scrutinised and a judgement made as to which requirements will be relevant. In this section, we give a summary of the contents of each chapter.

General requirements

- The device shall achieve the performance intended by the manufacturer, be safe and effective, and any residual risks must be acceptable when weighed against benefits
- Risks must be reduced as far as possible
- A risk management system must be established, implemented, documented and maintained. Paragraph 3 of this section (page 94 of the PDF version of the MDR) contains a checklist that should be used as reference when designing a risk management system.
- The device should maintain intended characteristics and performance when subjected to stresses which can occur during normal conditions of use
- Device must be designed, manufactured and packaged so that it is not adversely

affected during transport and storage.

Requirements regarding design and manufacture

This chapter contains a long checklist of considerations. They should be worked through systematically with each device to see which requirements apply. To help you gain an understanding of the content of this section, we here list a summary of the domains covered. It contains some requirements in the following domains:

- Chemical, physical and biological properties
- Substances and particles (including wear debris)
- Infection and contamination
- Devices incorporating a medicinal product
- Devices incorporating materials of biological origin
- Construction of devices and interaction with their environment
- Devices with a diagnostic or measuring function
- Protection against radiation, whether intended or not
- Electronic programmable systems (including software that is a medical device in its own right under MDR)
- Active devices, and devices connected to them
- Particular requirements for active implantable devices
- Protection against mechanical and thermal risks
- Protection against risks posed to patient or user by devices supplying energy or substances
- Protection against risks posed by devices intended for use by lay persons

As can be seen, this Chapter contains a detailed list of requirements. It is important to go through the general SPRs and identify which requirements relate to a particular device. This information can be applied in two ways:

- If the device is in development, develop a plan for how these requirements will be met and evidenced
- If the device is already in market

- What evidence is there that these requirements have been met?
- What gaps are there and how can they be addressed?

Requirements regarding information supplied with the device

This chapter comprises a further checklist to work through. It contains specific requirements for the device labels, the instructions for use (IFU), and device packaging. As with the other sections, if it is approached as a checklist, this chapter is very accessible.

Clinical evaluation and clinical investigations

Chapter VI of the MDR (starting with Article 61) is a comprehensive chapter that details the rules for performing clinical evaluations and investigations into medical devices, defined in Article 2 as:

***Clinical Evaluation**: Systematic and planned process to generate continuously, collect, analyse and assess the clinical data of a medical device in order to verify safety and performance.*

***Clinical Investigation**: Any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a medical device.*

Clinical evaluation

Clinical evaluation involves the 'bringing together' of all information relating to a medical device and asking the question "can we prove that this device is safe and meets all expectations for its performance?"

The output of the clinical evaluation process will be documented in a **Clinical Evaluation Report (CER)**, an important part of the technical documentation that must be submitted towards the conformity assessment procedure for each device.

Under MDR the objectives of clinical evaluation are:

- To demonstrate conformity with the relevant general safety and performance requirements (“SPRs” – listed in Annex I)
- To evaluate the presence and rate of undesirable side-effects
- To determine the acceptability of the benefit-risk ratio of a device.

All manufacturers must plan, conduct and document a clinical evaluation following the process detailed in **Annex XIV Part A**, which requires that clinical evaluation should include at least:

- A list of identified relevant general SPRs
- Specification of the intended device – its purpose, indications, contra-indications and intended clinical benefits

- Outline of methods for examining clinical safety
- Outline of parameters to be used to assess benefit-risk ratio
- Clinical development plan: show progression from pre-release tests to first-in-man studies to confirmatory investigations, to pivotal clinical investigations and PMCF.

Manufacturers must perform an overall analysis to reach conclusions about the safety and performance of the device, including its clinical benefits. Clinical evaluation must:

- Be thorough and objective
- Account for both favourable and unfavourable data
- Be proportionate and appropriate to the device and its risks

The results of clinical evaluation, and the clinical evidence on which it is based, shall be documented in a **Clinical Evaluation Report (CER)**. This shall support the assessment of device conformity.

The process of clinical evaluation under MDR, and of writing and updating Clinical Evaluation Reports (CERs) to the required standard, is technical and challenging. Making mistakes can prove very costly, financially and otherwise.

Contact Mantra Systems Ltd today: 0114 386 3349 / contact@mantrasystems.co.uk to speak with one of our specialist advisors. We will ensure that your clinical evaluation process is MDR compliant from inception to conclusion.

Clinical Investigations

MDR Article 62 gives general requirements for all aspects of performing clinical investigations under the MDR, specifically regarding how an investigation is designed, authorised, conducted, recorded, and reported. Article 62 also lists some common-sense conditions necessary before a clinical investigation may be conducted. It is worth reading this part of Article 62 in detail (page 57 of the PDF version of the MDR) but it is possible to condense the contents into the following principles:

- Get appropriate approvals first
- Treat subjects fairly, especially if they are vulnerable
- Obtain informed consent

- Ensure that anticipated benefits outweigh any risks for subjects
- Protect any data obtained during the investigation
- Don't induce participation through undue influence
- Minimise pain, discomfort or fear for participants

MDR Article 63 outlines specific requirements for obtaining informed consent from subjects whose data is used in an investigation. For anyone already familiar with the principles of obtaining informed consent there is really nothing new here. Essentially, the requirements are that information given to a subject shall:

- Be given by an appropriate person
- Enable the subject to understand the investigation, what it is for, and what it might mean for them
- Guarantee protection for the subject if they refuse or later withdraw consent
- Be comprehensive, clear and understandable
- Include, where available, the EU-wide clinical investigation identification number

MDR Annex XV outlines the requirements for performing clinical investigations in accordance with MDR. Conformity to the requirements in this Annex will help to ensure that the results of clinical investigations will be admissible for assessments under MDR. Annex XV contains three chapters:

- General requirements
- Documentation regarding application for clinical investigation
- Other obligations of sponsor

General requirements

- Conduct clinical investigations in accordance with recognised ethical principles.
- Methods shall be
    - In line with standards in the field
    - Appropriate to the device
    - Documented in a Clinical Investigation Plan (CIP)

    - Designed to address all relevant device features
- End-points of the investigation shall address the intended purpose, clinical benefits, performance and safety of the device
- Investigators shall have access to technical and clinical data regarding the device

Documentation regarding application for clinical investigation

This section lists what must be included in an application to perform a clinical investigation, in each following documents. It can be used as a simple checklist to ensure that documents are appropriately structured. We will cover this in more detail in the in-person training.

- Investigator's Brochure (IB) – document for principal investigator outlining investigators responsibilities in conducting the study
- Clinical Investigation Plan (CIP) – study protocol
- Other information

Other obligations of sponsor

- Ensure that serious adverse events occurring during the clinical investigation will be reported to the sponsor by investigators in a timely manner
- Keep documents such as IB, CIP and others for at least 10 years after clinical investigation has ended; 15 years if implantable device
- Appoint independent monitor to oversee the conduct of the investigation and its accordance with CIP
- Prove that the investigation was conducted in accordance with requirements of good clinical practice
- Prepare a clinical investigation report

Technical documentation

MDR Annex III contains a list of technical documentation that is required for submission in support of a device in order to demonstrate conformity. As with Annex I, this Annex functions best as a 'ready-reckoner' that can be used to ensure that all important/relevant aspects have been covered. The specific requirements for technical documentation relating to PMS are covered separately in Annex III.

Technical documentation should include:

- Device description and specification, including any variants and accessories
- Complete set of labels, packaging labels and transport packaging
- Instructions for use
- Design and manufacturing information
- Demonstration of conformity with general safety and performance requirements (SPRs) in Annex I, including
    - A list of those that apply, and an explanation of why others don't
    - Methods used to demonstrate conformity with them
    - Any harmonised standard (ISO standards) or CSs applied
- Benefit-risk analysis and risk management
- Product verification and validation
    - Engineering and pre-release tests
    - Evaluation of published literature relating to the device
    - Software validation, as relevant
- Clinical Evaluation Report (CER)
- PMCF plan and PMCF evaluation report (as in Part B of Annex XIV, see below)
- Occasional further information depending on the device.

Drafting many of these technical documents requires the input of a suitably trained doctor, available through Mantra Systems. Contact our team today.

Conclusion

This concludes our commentary on how to build a compliance strategy in accordance with the MDR. We hope that this document has served to make the MDR easier to work with as an instrument. Throughout the year we will be running a number of exclusive training sessions that will build upon this foundation and lead to a detailed understanding of all aspects of the MDR and how to work with it.

To see the full scope of training available at Mantra Systems, and to find out how to register for a place, please visit www.mantrasystems.co.uk/mdr-training for more details.

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For further information on these and our other services please visit our website www.mantrasystems.co.uk.