Medical Devices: Definition and Clinical Testing

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Abstract

Similar to drugs, medical devices need to be approved before being CE-marketed. Clinical data, so-called preclinical data, have to be obtained and gathered, and a technical file has to be compiled including a clinical evaluation. In some cases, clinical trials have to be conducted before the approval of the medical device due to lacking of clinical data. This chapter defines medical devices: it describes the regulatory context of approval, the most important parts of the technical file, and the ways and methods of clinical testing required to get the medical device approved and on the market.

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Regulatory Requirements

In Europe, medical devices and in vitro diagnostics (IVDs) are regulated by the EU guidelines Medical Device Directive (MDD, 93/42/EEC), the IVD 98/79/EEC, and the AIMD 90/385/EEC. The MDD and the AIMD are now replaced by the Medical Device Regulation (MDR) 2017/745 from May 25, 2017. The MDR will be in force from May 26, 2020 on. The same applies for the IVD; it will then be replaced by the IVDR.

National law is governed by the EU Directives. In order to regulate national differences and laws, national regulations differing from European member state to member state are in force (Fig. 1).

Objective of the MDD being still in force during the transition phase and the newly established MDR is to ensure a free movement of goods through a standardized regulation of medical devices in Europe (MDR, Articles 2 and 4). Furthermore, the safety of medical devices shall be fulfilled by standardized EU requirements (MDR, Article 3 and Annex I). At the moment, during the transition phase regarding the MDR, the MDD is still in force. Therefore both, the MDD and MDR, will be referenced in this chapter.

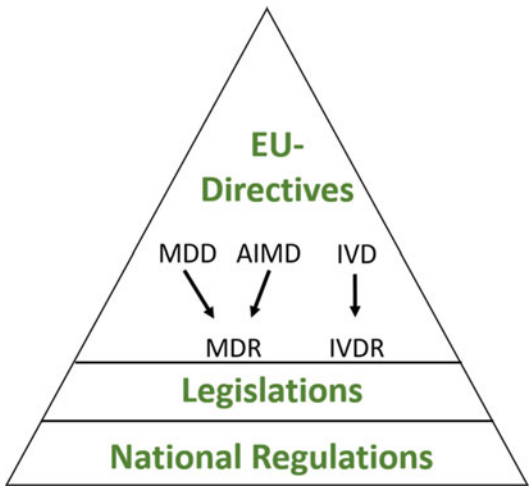

Fig. 1 Dependencies of the European laws to regulate medical devices

Medical Device Definition

In order to ensure a standardized understanding for the definition of medical devices, the MDR defines a medical device (MDR, Article 2). According to the MDR, medical devices are instruments, devices, implants, reagents, materials, and software that are intended to fulfill a medical purpose as defined by the manufacturer or by their intended use. This can be a single or a combined device.

The medical purpose includes diagnoses, monitoring, therapy or relief, prophylaxis, and prognosis of diseases. Furthermore, treatment of injuries or disabilities is also addressed as medical purpose.

This includes the treatment or relief of pain. For example, an active cupping device may contribute to pain reduction and to an improved physical effect (Teut et al. 2012; Lauche et al. 2013; Cramer et al. 2011). At the same time, it fulfills its medical purpose to concomitantly improve and treat an injury (in the sense of pain). The skin is dragged into the cupping device by means of the mechanical impact, and this increases the blood circulation and supply with nutrients of the affected tissue (Li et al. 2017; Cramer et al. 2011; Larsson et al. 1999). During this procedure, the effect is not produced by medications or immunological medicines since only mechanical energy activates endogenous functions resulting in a medical and therapeutic effect.

There is a legal distinction between the effect of drugs and medical devices. Drugs have a pharmacological, pharmacodynamics, immunologic, or metabolic effect, while medical devices act in a mechanic, physical, chemical, or physicochemical way.

In order to define a medical device, it is important to distinguish between the medical impacts of a product. Like a drug, the main effect of a medical device can be in- or outside of the human body. It is important that the main effect on the body is not caused by pharmacological, immunological, or metabolic drugs (MDR, Article 2).

For a medical impact on the human body, we already had the example of a cupping device. Medical devices in the human body, which are used for treatment, relief of pain, or therapy of diseases, can be implants (e.g., cardiac

pacemakers, hip or dental implants, etc.) or substance-based medical devices. It is possible to compare them with liquid drugs. Nevertheless, they fulfill the legal definition and effect of a medical device. Liquid herbal cough syrup, for example, can easily be mistaken for a drug. Herbal cough syrup, which lays a protective film over the irritated mucous membranes, carried out by its components, achieves the mitigation of the irritation of the throat by its mechanical impact. Through this protective film, the natural protective function of the mucous membranes is improved, and, thereby, the irritation of the throat and hoarseness is mitigated.

Therefore, herbal cough syrup, with its components, acts in a mechanical way and has no pharmacological, metabolic, or immunological effects.

In order to achieve their effect and clinical performance, medical devices can be supported by pharmacological, immunological, or metabolic drugs (MDR, Article 2). An example of a combined product is bone cement where an antibiotic has been added (drug and medical device). The target of that kind of bone cement is to anchor implants or prostheses directly in the bone (Kühn et al. 2017). This results in the compensation for disabilities or injuries, so the bone cement is defined as a medical device. The addition of the drug (antibiotic) to the bone cement makes the patient feel better and prevents infection (Kühn et al. 2017).

If a product supports the investigation, replacement, or modification of the anatomy or a physiological, respectively, pathological process or condition, it is also defined as a medical device (MDR, Article 2). In addition to the clearly defined medical devices, products controlling, supporting, assisting, cleansing, disinfecting, or sterilizing other medical devices are also defined as such. Examples are sterilizers for instruments used during surgeries or disinfectors of bedpans.

In Vitro Diagnostics as Medical Devices

In vitro diagnostics (IVD) are also defined as medical devices (MDR, Article 2). Often, they are laboratory systems, e.g., devices, kits, etc., supporting the provision of information through in vitro investigation. They investigate samples externally, i.e., outside of the human body (urine, blood, tissue, etc.). IVDs support physical or mental interferences, predispositions of health condition, detect (in-)compatibility, effects of a therapy, or the estimated reaction, and they can assist in the detection or observation of therapeutic measures by obtaining information of the physiological or pathological conditions (IVDR, Article 2).

Simple IVDs, which can be used by patients themselves, are pregnancy tests or blood glucose level tests, for example.

This list of examples and definitions shows that the form and application options of medical devices are extensive. The definition of a medical device according to the MDR means that medical devices must always have a clinical claim to support the patient. During the application of the medical device, the benefit must always outweigh the risk of harm.

Essential Requirements for Medical Devices and the Technical File

It is only possible to place medical devices on the European market if they comply with the strict safety requirements of the European Union. The affixation of the CE conformity mark is the result of fulfilling these requirements (French-Mowat and Burnett 2012).

In Europe, notified bodies (NB) and authorized representatives are responsible for the CE marking process and conformity assessment procedures. The NBs are designated by the respective competent authorities of the respective European member state. They monitor and ensure compliance with regulatory provisions.

It is up to the manufacturer to ensure that their medical device complies with the essential requirements of the relevant EU legislation. The CE marking process comprises the following aspects:

- Checking of applicable directives and annexes
- Selection of the respective conformity assessment procedure/route

- Registration of the medical device at the national competent authority (in Germany DIMDI authorities, e.g., in Switzerland Swissmedic)
- Preparation of the technical file
- Fulfilling the essential requirements
- Preparation of the declaration of conformity
- Submitting it to the NB or to the national competent authority (if applicable in case of Class I medical devices) for certification
- Application of the CE mark and marketing of the medical device
- Implementing vigilance and post-market surveillance actions by monitoring safety, efficiency, and reviewing experience of use and any action required during the product life cycle

Irrespective of the class of the device, all medical devices shall:

- Comply with the essential requirements
- Be object of an evaluation of clinical performance and safety by means of a clinical evaluation and, if applicable, already by a preclinical evaluation or clinical trial
- Fulfill the reporting requirements under the medical device vigilance system
- Have a CE mark

The essential requirements (ERs) can be found in Annex I of the MDD, and the essential performance and safety requirements are detailed in Annex I of the MDR. The latter replace the previous MDD ERs and also define the key aspects to address within the technical file.

Classification and Inherent Risk

All medical devices are placed into one of the four categories using the classification rules listed in MDD Annex IX. They are also listed in the MDR in Annex VIII.

The categories are:

- Class I (including Is and Im)
- Class IIa
- Class IIb
- Class III

with Class III being the class of medical devices with the highest risk. The classification of the medical device is defined by its intended purpose. Several aspects are important for the classification of the medical device including the duration of contact with the body and application, degree of invasiveness, and local versus systemic effect. The following table provides details for each class (Council of the European Communities. 2007) (Table 1).

Technical File (Technical Documentation)

The essential requirements (ERs) are evidence for the conformity of the medical device with the respective guidelines. These guidelines include detailed requirements for the medical device that must be fulfilled and verified as well as validated in the technical file. Each essential requirement in the checklist of the ERs of a technical file contains each requirement of the MDR. Here, insight in the standards, references, and documented evidence (test reports, drawings, descriptions, etc.) for every single requirement shall be provided by the manufacturers.

In the following, the most important parts of the technical file are described in more detail.

Risk Management

Risk management is an integral part of the ERs and, therefore, of the technical file. The fundamentals of the so-called integrated security are explicitly claimed in the essential requirements of the MDD still in force and the MDR in its transition phase.

A well-working risk management system, similar to a quality management system, is the standard for manufacturers to legally launch the medical device. Therefore, several parts of the risk management annexes are included in the MDD or the MDR.

The standard ISO 14971 “Medical devices - Application of risk management to medical devices” has been enforced as an equal evaluation

Table 1 Examples of product classification

	Classification	Risk	Description	Examples
	General controls			Hospital beds, bedpans
I	Sterile (Is)	Low	Most noninvasive devices that do not interact with the body	Sterile plasters
	Measuring (Im)			Thermometers, weighing scales
IIa	Special controls required: may include special labeling, mandatory performance standards, and post-market surveillance	Medium	Exchange energy with a patient in a therapeutic manner or are used to diagnose or monitor medical conditions. Generally invasive but limited to natural orifices, if hazardous to a patient then it becomes a Class IIb	Powered wheelchairs, hearing aids, ultrasonic diagnostic equipment
IIb	Special controls (as IIa)	Medium	Most surgically invasive/ active devices partially or totally implantable in the body. May modify composition of body fluids	Infusion pumps, ventilators, surgical lasers
III	Pre-market approval is the required process of scientific review to ensure the safety and effectiveness of these	High	Support or sustain human life and are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Device that connects directly with the central circulatory system or CNS or contains a medicinal product	Many implants: vascular and neurological, replacement heart valves, silicone gel-filled breast implants, and implanted cerebella stimulators

of the risks for the manufacturers of medical devices for the authorities and notified bodies.

The requirements of the ISO 14971 are valid for all medical devices, IVDs, and in all phases of the product life cycle. The requirements include the following aspects:

- Risk estimation
- Risk evaluation
- Risk control
- Observation efficiency

Risks can occur anytime in the product life cycle. They are determined at a certain point of the cycle and can be minimized by a measure at a different moment of the product life cycle.

It is necessary to evaluate the residual risks versus the expected benefit before the decision to apply a medical device with a specific intended use in the defined indications for the respective patient population by the defined users (risk–benefit analysis).

The manufacturer is responsible for the risk definition. It needs to be well proved and state of the art.

The decision is based on:

- Public law
- Certain habits
- Values and awareness of the risk

The monitored risks are primarily evaluated based on the relationship with the affected patients or users. Risks which can harm the user or third parties need to be monitored. Furthermore, damage to animals, buildings, belongings, or the environment also needs to be monitored.

Depending on the implemented safety measure, the value of the measure will depend on the minimization of the respective risk. The implementation of a safety measure will reduce the occurrence of the risk a lot more than just a warning sign. On the other side, inherent safety can

eliminate the risk completely or even reduce the severity of the anticipated harm.

The medical device directive requires the manufacturers to proceed in the following order:

1. Inherent safety: making medical devices inherently safe.
2. Precautions: if this is not possible, risk-minimizing measures have to be implemented.
3. Notes: if this is not possible or if there is insufficient information, then label the remaining risks.

The order of these risk-minimizing measures must be adhered to. It is only allowed to use the next lower measure if it is impossible to use a superior one.

Usability

Usability is a fundamental requirement for medical devices according to Annex 1 of the MDD or MDR. Medical devices need to be manufactured to work under normal conditions of use and fulfill their intended purpose. Medical devices need to be safe and effective and shall not harm the patients or affect the health of the user or third parties (MDR, Annex I).

According to the European standard EN 62366, the usability is defined as interface between the medical device and user. The property of the usability can comprise the efficiency, learnability, and satisfaction of the user (IEC 62366, Section 5.3).

The interface between the medical device and user often results in use errors (incomprehensible operating, false operating, wrong application, etc.). These errors can influence the performance, safety, and complete benefit of the medical device.

Frequent operating functions or the intended context of use are related to a high potential of use error. Deficiencies such as inadequate labeling or ambiguous images can lead to an incorrect application of the medical device (IEC 62366). The context of use of the medical device, e.g., in combination with accessories, can have a significant impact on usability (IEC 62366, Section 5.3).

A laser device for the treatment of pain and wounds can serve as an example for a use error of a medical device. Laser therapy devices are available with different power levels.

The example laser has a power of 30 W and cures skin tissue with a transmitting power of 2 mW. With an additional tip focusing the laser beam, a transmitting power of 22 mW can be achieved. For the application of a laser with a power of 100 W, a transmitting power on the tissue of approximately 10 W is needed. With an additional tip, the laser would be so powerful that the tissue would suffer an extensive damage. The use of such a tip and the focus of the laser beam would bear a potential risk for the patient. By means of usability testings being part of the validation of the medical device, use errors can be identified and corrected, and this finally results in the safe use of the medical device. The use of such a tip in the example above would have been prevented.

Biocompatibility

According to the MDR, biocompatibility of a medical device is defined as biological safety of the device shown by preclinical and general clinical data (MDR, Annex II, Section 6.1). Biocompatibility needs to be tested for all materials of the medical device, which have direct or indirect contact with the human skin or with body fluids of the patient or user. For the evaluation of the medical device's biological safety, this clinical data is analyzed in form of a biocompatibility report and within the clinical evaluation.

Standards, such as the international ISO standards, describe harmonizing and acknowledged procedures which need to show and fulfill specific regulations. The ISO 10993 is an internationally acknowledged standard for the evaluation of the biological safety of medical devices. In Section 3.1 of the ISO 10993-1, the biocompatibility of a medical device or a material is defined as the ability to perform well in a specific application with an appropriate host reaction.

Biological testings of the material of the medical device serve as evidence. With these testings,

the characteristics of the material of the medical device, which are able to influence the biological reaction, are evaluated. The evaluation of the biological safety also considers the impact of soluble chemicals or morphological characteristics, if applicable (ISO 10993, Section 3.1).

According to ISO 10993, biological safety describes the freedom of non-acceptable risks in context with the foreseen use. It can be proved by means of verification testings of the material being in direct contact with human skin or body fluids (ISO 10993-1, Section 3.3).

The final biological evaluation of medical devices comprises the testing of several relevant aspects. This includes the analysis of the material, predicted additives, production-related contamination, packing material, soluble ingredients, and metabolites in the medical device (ISO 10993, Section 4.3).

A complete biological testing of a medical device can be supplemented by additional tests. An additional evaluation like cytotoxicity testings (ISO 10993-5), sensitivity and irritation testings (ISO 10993-10) or testings on hemocompatibility (ISO 10993-4), etc. can become necessary. This depends on the impact, respectively, application, and site of application of the medical device. A cooling pack, which is applied on intact skin, for example, should be tested on cytotoxicity according to IOS 10993-5. Implants that come into contact with damaged skin, tissue, blood, or even mucosa need to be tested on sensitivity and irritation according to IOS 10993-10. Furthermore, a chemical evaluation (ISO 10993-18) is necessary (ISO 10993, Section 6.1.3).

In the clinical evaluation, the clinical data on the biological safety of the medical device are also used for the evaluation of the clinical safety of the medical device.

Clinical Evaluation of a Medical Device Based on Clinical Data

According to the MDR, the clinical evaluation is a systematic planned process to continuously collect, analyze, and evaluate clinical data of a medical device. This process has the objective to show the clinical safety, clinical performance, and the clinical benefit of the medical device. The intended use of the medical device, as defined by the manufacturer, is confirmed (MDR, Article 44).

The intended use includes information on the application of the product, the user group, patient population, and the application environment. In the clinical evaluation, this information is verified by means of clinical data pertaining to the evaluated medical device or to an equivalent medical device. Furthermore, the respective indication(s) or the field of application of the medical device shall also be verified by means of clinical data. The main focus of the clinical evaluation of medical devices is the evaluation of the risk–benefit–relation of the medical device.

In regard to the risk–benefit ratio, the clinical benefit is defined as the positive effect of a medical device on human health. Such a positive effect shall be confirmed and must be measurable and patient-relevant, including the results of a diagnosis. A positive effect on the treatment or on public health is also defined as a clinical benefit (MDR, Article 52).

The applicable guideline for clinical evaluations is the MEDDEV 2.7/1 Revision 4. If the clinical evaluation report (CER) is written according to this guideline, the manufacturer also complies with the MDD/MDR requirements and the ERs.

Equivalent Medical Device (according to MEDDEV 2.7/1 Rev. 4)

Equivalent medical devices are comparator products to the evaluated medical device. They are equivalent to each other and in some aspects similar. The evaluation of equivalence is done by comparing the following aspects of the medical devices:

clinical/technological/biological

The evaluated and possibly equivalent medical device must be equal in terms of the clinical (intended use, indication, application) and biological (material) aspects. They must be similar in terms of technical parameters. If all of the three aspects are fulfilled, the medical devices can be considered to be equivalent.

In order to show the clinical benefit of a medical device, a cooling pack may serve as an example. The intended use of the cooling pack is the physical transmission of cold on human skin. The

treatment is part of cryotherapy. Cooling packs are often used for the relief of pain, swelling, or sports injuries.

Within these indications, the clinical benefit of the medical device may be assumed. In case of pain or swelling, the benefit of a cool pack can be pain reduction or a decrease of the swelling. If the manufacturer wants to advertise that kind of benefits, these must first be proved by clinical data within the clinical evaluation. Clinical data collected after the marketing of the medical device resulting from post-market surveillance and clinical follow-ups (PMCF), if applicable, are also defined as clinical data (MDR, Article 48).

The clinical performance and safety of the medical device shows its clinical benefit. The clinical performance is defined as the ability to fulfill the intended use of the medical device by means of its technical, functional, and diagnostic characteristics (MDR, Article 52). Clinical safety implies the safe use and application of the medical device.

In our example of the cooling pack, the medical device is able to cool down a specific body area of the patient by its therapeutic effect. The performance specifications and the application conditions of the cooling pack are decisive.

An analgesic effect precipitated by cold starts from the moment the surface of the skin reaches a temperature of 13.6 °C (Bugaj 1975). After the application, cooling packs filled with ice need 20 min to cool the skin surface to 10.2 °C (Bitton et al. 2016).

With these data, the clinical performance and benefit of the medical device can be shown. The literature reveals that by means of cooling down the skin and then reducing the pain. This is the cooling pack's clinical benefit on the patient's skin.

PMS data, data collected from regional safety databases like the BfArM, Swissmedic, or MHRA or data from international databases like the FDA MAUDE database and also the clinical data in related scientific and evident publications, all give insight into the safety of medical devices. In the clinical evaluation, safety databases are used to analyze reportable events, incidents, and recalls related to the medical device. Furthermore, recalls and complaints from the internal manufacturer's PMS data are used for the evaluation of clinical safety. The number of recalls, reportable events, and incidents within a fixed period of time compared to the sales figures of the medical device shows the ratio between events and number of sold devices: if the number of reportable events, incidents, recalls, etc. is low versus a high number of sold devices, the safety of the respective medical device can be assumed.

The objective of the clinical evaluation is the comparison of the residual risk(s) resulting from the risk analysis and the clinical benefit of the medical device. The benefits and risks of a medical device can only be assessed in interrelation by "weighing any benefit to health from the use of the device against any probable risk of injury or illness from such use" (Guidance for Industry and Food and Drug Administration Staff 2012). Hence, they are to be understood as relative terms: a balanced consideration based on valid scientific evidence in making risk and benefit determinations, including the critical issue of identifying benefits and residual risks, is essential.

Based on the findings from literature, clinical data, as well as risk analysis, it can be inferred that the probability of a patient experiencing a substantial benefit when using the evaluated medical device outweighs the probability of suffering harm due to a residual risk of the device significantly.

Clinical Trials with Medical Devices

A clinical trial also called clinical investigation is defined as "any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device" (SG5/N1:2007).

Conducting a clinical trial is a scientific process that represents one method of generating clinical data. A clinical trial can be conducted with the medical device in the preclinical stage before the CE marking and marketing of the device if clinical data to the medical device are insufficient to show its clinical safety,

performance, and benefit. To achieve CE approval for specific medical devices, such as long-term invasive applications or implants, clinical trials must be conducted unless the use of existing clinical data can be sufficiently justified. During the pre-approval phase of a medical device and depending on the goal of the clinical trial, various study designs could be useful, ranging from a single-center non-randomized trial to a multicenter, multinational, randomized, controlled trial.

Furthermore, clinical trials can be conducted during the post-market phase of the medical device during the post-market surveillance process. In this case, further clinical data pertaining to the medical device need to be collected to further prove its clinical safety, performance, and benefit or new claims in this context. These clinical trials are conducted as so-called post-market clinical follow-up trials and can include clinical trials according to ISO 14155 or non-interventional studies (NIS) in form of observational studies. Which form or way of collecting further clinical data is chosen belongs on the result of the clinical evaluation indicating which further clinical data is needed.

The overall objective of a clinical trial is the evaluation of the clinical safety and clinical performance of the medical device in question and whether the device is suitable for the purpose(s), user(s), and the population(s) for which it is intended within the claimed indications (ISO 14155).

ISO 14155-1:2009 Clinical Investigation of Medical Devices for Human Subjects – General Requirements details the general requirements for the conduct of clinical trials, and ISO 14155-2:2009 Clinical Investigation of Medical Devices for Human Subjects – Clinical Investigation Plan contains detailed information about the procedure and contents of a clinical trial plan. Clinical trials (also referred to as clinical studies whereas this term rather belongs to drugs than to medical devices) must take into account the respective scientific principles underlying the collection of clinical data along with accepted ethical standards for the use of human subjects. The clinical trial objectives and design are documented in a clinical trial plan.

The following table reveals the differences between clinical studies with pharmaceuticals and medicines (drugs) and clinical trials with medical devices (Chittester 2014) (Table 2):

ISO 14155 also defines the good clinical practice (GCP) standard for clinical trials with medical device. European legislation also explicitly requires compliance with the Declaration of Helsinki defining the ethical principles to be respected when conducting clinical studies or trials on human subjects.

As a rule, all clinical trials need to be approved by Ethics Committees and notified to the competent authorities of involved countries. Other regulatory institutions may need to be involved in the

Table 2 Clinical studies with drugs and clinical trials with medical devices

Drugs	Medical devices
Phase 1:	Pilot:
Aimed at safety and tolerance	Smaller population with disease or condition (10–30 subjects)
Healthy volunteers (20–100 subjects)	Determine preliminary safety and performance information
Determine dosing and major adverse effects	
Phase 2:	Pivotal:
Aimed at safety and effectiveness	Larger population with disease or condition (150–300 subjects)
Small population with disease or condition (50–200 subjects)	Determine effectiveness and adverse effects
Confirm dosing and major adverse effects	
Phase 3:	
Aimed at safety and effectiveness	
Large population with disease or condition (hundreds to thousands of subjects)	
Determine drug–drug interactions and minor adverse effects	
Phase 4:	Post-approval study:
Post approval study	Collect long-term data and adverse effects
Collect long-term data and adverse effects	

regulatory process depending on national law. Only in case of NIS, notification to the competent authority is sufficient, and an Ethics Committee approval is not required.

The essential documents for a clinical trial with a medical device are similar to the ones required for a pharmaceutical study. The term Clinical Investigation Plan or Clinical Study Plan is generally used to refer to the clinical study protocol in case of a clinical trial with a medical device. Inclusion of a section on risk management in the Clinical Investigation Plan is required. Also the inclusion of preclinical data on the medical device is necessary.

Regulatory requirements for clinical trials with medical devices are different to pharmaceuticals, and this has an impact on the design of their clinical trial (www.hra.nhs.uk). There is no legal requirement to demonstrate the efficacy of the device to obtain CE marking. The objective of the clinical trial is to demonstrate the safety and performance (conformity with claims which is the clinical benefit) of a medical device. In a pharmaceutical study, the objective is to demonstrate the safety and efficacy of the medicinal product. One consequence is that case numbers in a medical device trial are usually lower than in pharmaceutical studies. The stage of a clinical investigation which needs to be satisfactorily completed for CE marking may therefore be likened to Phase II in drug development, where evidence of clinical activity of a drug is sought, rather than Phase III. Since efficacy does not need to be demonstrated, randomized controlled trial designs for medical devices are rarely necessary, and, therefore, proof of statistical significance may not be necessary. Interim analysis of study data may be feasible, provided it has been written into the investigation plan.

In comparative pharmaceutical studies, the most robust comparator is a placebo control, which is often applied and generally required by authorities. In a medical device trial, a placebo control is usually not feasible. This is particularly the case with implantable devices, where placebo control groups are simply not possible. However, studies comparing a medical device with standard therapy are possible, although in some cases there may be no standard therapy available which is similar enough to warrant comparison, especially for innovative devices. In addition, the user (usually a healthcare professional) often cannot be blinded to the study intervention.

A specific feature of a clinical trial with a medical device is that product performance may be influenced by the user. Furthermore, the use of a medical device may sometimes be associated with a learning curve for the user, where the outcomes improve with experience.

Another aspect is that adverse events, in particular adverse device effects, may not only concern the study subjects but also third parties, such as users of the device. In contrast, adverse events in pharmaceutical studies are only assessed and monitored for the clinical study subjects.

Due to the wide range of types of device, testing methodologies vary widely. Some performance data might simply require user handling feedback; other data might be more analytical. Medical devices often create large amounts of data that are transmitted, processed, and stored via specific software interfaces. For such data sets, specific monitoring rules have to be established focusing on supervising data processing rather than individual data points.

Conclusion

Medical devices are subject to regulatory requirements in order to ensure their safety and performance. The relation between the clinical benefit experienced by the patient and the residual risk of the medical device is most important. In order to evaluate the benefit and risk of a medical device, several evaluations and appraisals claimed by the European guidelines are necessary.

The ERs applicable for medical devices (MDD/MDR) result in a uniformly accepted system which is necessary for a safe application of medical devices and enabling international trade.

The form of evaluation of clinical data pertaining to a specific medical device depends on its classification. If the ERs for a medical device are fulfilled, a Class I medical device can be marketed without the involvement of a notified

body, and the clinical evaluation is sufficient. The documentation and technical file of Class IIa, IIb, or III medical devices needs to be assessed and approved by a NB. Compliance with applicable standards is essentially required. Each medical device must fulfill these requirements independent on its classification.

The clinical evaluation of medical devices evaluates the clinical safety and performance as well as benefit of the medical device and assesses if any residual risks exist. The ratio between benefit and residual risk is evaluated, and the medical device is only assumed to be safe when the benefit overweighs any residual risk. In this context, scientific evident publications, scientific research, clinical trials and investigations, medical knowledge, PMS data, safety reports, and clinical evaluations of the medical device contribute to the compliance with the ERs. In case of specific (high-risk) medical devices or if no clinical data is available for the evaluated medical device, the manufacturer needs to collect own clinical data in form of clinical trials or later in form of PMCF activities.

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