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Review

Comprehensive review on current and future regulatory requirements on wearable sensors in Preclinical and Clinical testing

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Abstract: Background: medical devices are designed, tested and placed on the market in a highly regulated environment. Wearable sensors are crucial components of various medical devices: design and validation of wearable sensors, if managed according to international standards, can foster innovation while respecting regulatory requirements. Material and methods: the purpose of this paper is to take into consideration the upcoming EU Medical Device Regulation 2017/245 and the current and future IEC and ISO standards that set methods for design and validation of medical devices, with a focus on wearable sensors. Risk classification according to the regulation is described. The international standards IEC 62304, IEC 60601, ISO 14971 and ISO 13485 are reviewed to define regulatory restrictions during design, pre-clinical validation and clinical validation of devices that include wearable sensors as crucial components. Results: current and future regulatory restrictions are described, and an integrated method for design planning, validation and clinical testing is proposed. Discussion: application of this method to design wearable sensors should be evaluated in the future in order to assess its potentially positive impact to fostering innovation and to ensure timely development.

Keywords: Medical Device Regulation; wearable medical sensor; medical device; accessory

1. Definition of medical device

Wearable health technologies offer great promise for reducing healthcare costs and improving patient care and that of their family. Wearable technologies entered in various biomedical applications, including tracking, recording, and monitoring of biomedical signals in the form of various accessories such as smart watches, patch, socks, and t-shirt which allow data transfer between the device and smartphone or other device (e.g. computers or healthcare units) [1–3]. By now all these technologies are becoming more popular among healthcare stakeholders. Associations for patient advocacy already consider them important tools to improve therapy involvement despite their widespread adoption is blocked by problems which developers should, ideally, resolve in near future [4]. Furthermore, the use of smart textiles and stretchable electronics is becoming very popular in healthcare monitoring technologies.

The European Union (EU) Medical Device Regulation (MDR) (Council Regulation 2017/745 [5] of 5 April 2017 concerning medical devices) repeals the existing directives on medical devices: Medical Device Directive 93/42/EEC (MDD) [6] and Active Implantable Medical Device Directive 90/385/EEC (AIMD) [7]. The new regulation will enter in force on 25 May 2020 after a transition time of three years; it has significant impacts on manufacturers, due to the burden of implementation of new regulations for new devices and ensuring that legacy products meet new requirements.

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According to the EU MDR, the Medical Device definition is described below.

"Medical device" means 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 following products shall also be deemed to be medical devices:

- *devices for the control or support of conception;*
- *products specifically intended for the cleaning, disinfection or sterilization of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.*

This definition can be commented in view of applicability to wearable sensors. The data collected and the intended use define if a wearable sensor is a medical device or is part of a medical device. In fact, wearable sensors may be used to collect physiological data, movement data, location data and others. Not all data collected from wearable sensors are useful for disease monitoring or diagnosis, so not all of them shall be compliant to MDD requirements.

In some cases, commercial wearable sensors are used in applications that resemble the medical application and is usually defined as "wellness", "self-enhancement" or "self-tracking". These devices are not designed and validated as medical devices, since their intended use cannot be included in any of the features of the Medical Device Definition. So, these devices are designed to be electrically safe but they have no data integrity and accuracy requirements other than commercial expectations. If data from a commercial wearable sensor are later included in a medical device, for example if these data are used as input data for a diagnosis software, the manufacturer of the medical device is using the data under his own responsibility in an unforeseen use of the sensor. In this case the end user of the data, not the supplier for the wearable sensor, shall prove that the quality of the data collected from the sensor is sufficient for a medical grade use. Medical device designers may approach this aspect by treating the commercial (non-medical) wearable sensor as a black box. This approach presents multiple difficulties, both legal and technical, and should be discouraged wherever possible.

2. Definition of component of medical device and of accessory of medical device; their classification

The current MDD-AIMD directives [6,7] and the upcoming MDR [5] regulation provide significant information regarding parts of a finished medical device and accessories.

In both, 'accessory for a medical device' means an article which, whilst not being itself a medical device, is intended by its manufacturer to be used together with one or several particular medical device(s) to specifically enable the medical device(s) to be used in accordance with its/their intended purpose(s) or to specifically and directly assist the medical functionality of the medical device(s) in terms of its/their intended purpose(s).

This definition may well apply to a wearable sensor which may not by itself be a medical device with a well-defined medical purpose, but that is used to collect information that is used as input data for subsequent diagnosis or therapy management by a medical device or by a medical-grade software.

A good example may be an actigraph unit that provides information to a medical app, that monitors the sleep/wake cycle to diagnose insomnia or the level of activity [8].

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Accessories are products in their own right and, as a general rule, do not follow the classification of related devices in conjunction with which they are used. Accessories are therefore following both current MDD-AIMD directives [6,7] and upcoming MDR [5] to be classified in their own right.

This implies that, in case of wearable sensors, they will most probably fall in either class IIa or class IIb of the upcoming MDR [5]. In some cases, the sensors may be part of a class III system. The potentially adequate rules may be:

- for wearable sensors intended for monitoring: rule 10, that places active devices for monitoring in class IIa as a general rule and in class IIb in case of monitoring of "vital parameters in dangerous situations"
- for wearable sensors that monitor or manage the performance of a device: rule 9 that classifies these devices in class IIb or class III if the influenced device is implantable
- for wearable sensors that are part of closed loop controllers: rule 22 places devices in class III if they have a "diagnostic function which significantly determines the patient management by the device"; else class IIb as per rule 9

3. Certification path for wearable sensors in Europe

To sell medical devices in the European Union (EU), and even to test these devices in the pre-market phase on human beings, developers are subject to the MDD-AIMD directives [6,7] and the upcoming MDR [5]. For the premarket phase, the safety and traceability requirements apply, together with ethics requirements that protect the participants to clinical trials. For the market phase, manufacturers must obtain (or apply in class I) CE Marking for the product. CE Marking indicates that the medical device complies with the applicable EU regulations and enables the commercialization of the products in all European countries.

The organization that is sponsoring the clinical trial on patients and later is placing the device on the market is responsible for maintaining regulatory compliance, regardless of whether they outsource any or all steps of the manufacturing operation.

CE marking is obtained, for all classes of medical devices except class I, only after a third party, EU-approved organization (Notified Body) has verified that the product complies to all regulatory requirements.

4. Wearable sensors for monitoring VS wearable sensors for feedback control

As said wearable sensors can be used in medical applications with several aims, like parts of devices intended to monitor or treat diseases and impairments. They can monitor different conditions and physiological parameters.

Most classic example of wearable sensors is the photoplethysmogram (PPG), used to measure heart rate using variation of intensity of reflected fraction LED-emitted light, which is correlated with the volume of blood in the illuminated tissue. Recent studies could lead to non-invasive measurements of heart rate variability, which is a useful measurement to assess the autonomic nervous system, using PPG [9]. Heart and vascular system are investigated and monitored due to the high incidence of vascular diseases, with innovative methods enabled by recent improvements of wearable technology, like the auscultation of heart sounds and the use of low energy electromagnetic radiofrequency waves [9,10].

In motion analysis, wearable devices are used mainly to monitor activity status, which is fundamental in rehabilitation phase, to perform gait analysis and to recognize activities, anomalies and accidents [11,12]. The technology of these devices is usually similar to commercial activity trackers one, based on a compound of sensors: Accelerometers, used to measure accelerations and forces [13–15]; magnetometers, designed to understand device orientation; Gyroscopes, which give rotational information. State of the art systems include sensors of all three types, obtaining 9 Degree of Freedoms measurements [9]. Output of these sensors and of possible additional sensors (e.g. altimeter, barometer) are used to classify the tasks performed by the patient.

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Wearable devices can be used to manage systems too, like sensors used to control orthoses, prostheses [16,17] and tele rehabilitation robots, but different technologies are required. The system needs information to properly control the subsequent action and the sensor decision strategy can be different. In case of orthoses and prostheses the principal solutions are wearable surface electromyograph (sEMG). The sensor is composed by dry skin electrodes to collect the electric signal, conditioning circuit, and data processing unit. Myoelectric signals are extremely complex and difficult to use, but machine learning approaches showed it is possible to control prostheses using EMG [18].

In rehabilitation systems, the wearable sensor shall give precise, continuous and reliable information about patient limb position, especially if the device is providing information to a rehabilitation robot that mobilize patient limbs. For this reason, all the solutions seen before can be inadequate. By now the main solution is accelerometer and gyroscope integration with kinematic models, capable of introducing the needed accuracy, but future development in nanosensors and textile electronics could lead to innovative stretch and angle sensors [19].

The accuracy of these systems shall be evaluated depending on what is the main output of the device. In case of activity/pattern recognition the accuracy shall be evaluated comparing the classification output with ground truth obtained via state-of-the-art methods or with preclassified data. On the other hand, if the system output is a measurement, the accuracy shall be assessed evaluating the measurement against a primary instrument. In certain cases, the primary instrument can be a state-of-the art medical device with a measuring function.

In case of wearable sensors intended to provide significant information to feedback loop controlled complex system, the accuracy shall be assessed not only on the output of the sensor, but also on the output of modules which use the sensor information to work.

5. Brief intro to MDR: requirements on safety, performance and benefit, consistent level of quality

Like all medical devices, including accessories, wearable sensors must comply with the Essential Requirements of the current MDD-AIMD [6,7], which are also present in the new MDR [5] with important innovations, especially regarding the obligations of demonstration of clinical benefit. The obligations of the manufacturers can be summarized with three key words: safety, benefit, quality. The demonstration of having fulfilled these obligations occurs through the application of international standards.

For the demonstration of safety, developers of wearable sensors cannot derogate from the application of the ISO 14971 [20] standard, related to risk management, which impacts in particular the design and testing. The result of applying this standard proves that the wearable sensor is free of structural defects that could pose a risk for the patient or compromise the correct functioning, expressed in terms of technical performance.

The ISO 14971 standard poses, in annex C, a list of questions that may be used to identify the device characteristics that are more related to safety in any medical device. Amongst the questions, some are typically applicable to wearables:

C.2.11. Are measurements taken?

In case of wearable sensors, the device typically measures physiological parameters such as movement, pressure, vibration, color shades and a combination of wearable sensors increases the amount of information by for example a time stamp of each event, the orientation in space of the wearable device, absolute location of the sensor, proximity to objects or other sensors, environmental information like temperature, humidity, environmental light, altitude et cetera.

In order to describe risk correctly, developers should be able to define, for each of these parameters, the expected level of sensitivity and specificity of detection and relate the non-compliance to such level of quality to the damage to the patient.

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To correctly relate the device performance to the risk for the patient health, the developers can answer to questions similar to the followings: If the wearable device is not accurate enough, will the patient be actively damaged? Will the patient be diagnosed or cured with a delay?

The answer to these questions shall consider device performance and intended use. If the device measures physiological parameters to define or influence the therapy, it shall have a high-risk profile. In fact, an incorrect measurement can lead to incorrect therapy. If the device is used to directly diagnose a disease or condition the risk profile shall be similar to the case of device that directly control therapy, since the data are not controlled by the physician. If the device is used only to monitor a condition or to inform the diagnosis, the possible error is not automatically propagated to the therapy, leading to a lower risk profile.

C.2.15 Is the medical device susceptible to environmental influences?

In case of wearable sensors, they may be susceptible to specific conditions of the external environment influencing the basic principles of functioning. Mainly the devices may be susceptible to vibrations, other environmental influences as humidity and temperature or protection from dust and water. In case of motion sensors, the devices can be influenced by environmental electromagnetic fields, since most of device use magnetic field information to extract the device orientation in space. This factor shall be considered especially if the device is intended to be used in a clinical setting like a hospital, where machines like MRI devices can influence the magnetic field.

C.2.26 Does installation or use of the medical device require special training or special skills?

In case of wearable sensors, they may require different skills. As part of the usability evaluation, the hazardous use scenario evaluation may enlighten the possibility of improper or impossible use by patients with disabilities, too young or too old, that don't use the wearable for as long as needed to obtain a good amount of data, and so on.

In many cases, a dedicated training may be required for particular wearables or for populations with a low level of medical literacy.

C.2.29 Is successful application of the medical device critically dependent on human factors such as the user interface?

The user interface significant factors may include:

Case, for the handling and grasping of device: is the sensor part of a bracelet or another object that is usually worn for beauty? Is the sensor supposed to be invisible, sticking on the skin?

Indicators for light, audit, haptic feedback should also be considered in their capability to enhance the user experience and on the other hand the potential risk of delivering unclear information to the end user.

For wearable sensors, the main risks may be summarized as follows:

- Electrical hazard: this is particularly applicable for wearables that can be classified as "applied parts" of an electro-medical device. In the state-of-the-art, a very simple example of an "applied parts" of an electro-medical device is an electrode that is physically connected to an ECG (electrocardiogram) monitor. For wearables, an "applied part" could be a bracelet or even an electrode. The appropriate standards include at least IEC 60601-1 [21]; other standards may be applicable in case of wearables that have alarms, are part of closed loop controllers and so on. A detailed discussion follows in paragraph 7.
- Data transfer: the loss or alteration of data may impair the use of the whole wearable device. In particular the developer shall consider this main risk during the design of the device, especially during the communicating protocol definition which can be oriented toward energy optimization but shall guarantee data integrity.
- Hackering of data: clinical data are precious, non-tangible assets. Special regulations apply to the protection of medical device under a cybersecurity point of view. Detailed guidelines are available from FDA (Food and Drug Administration) in both the pre-market [22] and

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post-market phase [23]. It should be noted that the available international standard, while being widely applied, presents significant gaps in the definition of requirements [24].

- Electro- magnetic compatibility: this is particularly applicable for wearables intended to be parts of medical devices in hospital settings. A detailed discussion follows in paragraph 7.
- Software malfunction. Software malfunction, in terms of bugs, loss of data and/or inadequate performance is a key risk to be taken into consideration. The non-availability of the information provided by the wearable sensor may lead to various levels of consequences, from simple frustration to actual loss of operation of a life-saving device. A detailed discussion follows in paragraph 7.
- Biocompatibility. Most wearable sensors simply come in contact with intact skin. Regardless the very low level of biocompatibility risk, irritation and allergic reactions should be taken into account. The ISO 10993-1 standard [25] provides complete guidance: appropriate test may involve material characterization and, in some cases, some in vitro tests.

6. The relationship between performance and benefit

In case of wearable sensors intended to measure physiological parameters, the link between accuracy and clinical benefit is defined as in more traditional sensors, since devices that provide information to ease diagnosis and monitoring rely on the quality of data. On the other hand, a wearable sensor can introduce different benefits. In fact, it can be less obtrusive in-patient life, improving general quality of life, and in case of motion and gait analysis it can provide real life information, and not information obtained in a simulated environment. Moreover, the possibility to collect information not accessible with other methods, like behavioral and motion data, could enable to evaluate the clinical condition more efficiently [26]. In this sense, once the wearable sensor has been appropriately calibrated to match state-of-the -art accuracy, the relationship between technical performance and clinical benefit is well described by indicators about quality of life and ergonomics.

In case of wearable sensors intended to provide information for a feedback loop complex system the clinical benefit is provided by the output of the complete system. So, the sensor accuracy can directly improve clinical benefit, since it defines the quality of the input in a feedback system which will use the sensor information to plan and complete actions part of a therapy. For example, in a tremor reducing system the device needs an adequate input information to properly distinguish voluntary movement from tremor. So, the high accuracy of the sensor allows to properly reduce the tremor intensity while not suppressing volitional movement [27].

7. Giving proof of safety of a wearable sensor

Proof of safety is achieved by a three steps approach: identify test requirements and methods, test for compliance, assess if risk minimization is acceptable.

Once the standard ISO 14971 has been used to identify the hazardous situations and the international standards have been searched for appropriate safety requirements, a complete set of tests for safety should be available. Prototypes sent to testing shall be significant of the final product.

Typically, the most important requirements will be about electrical safety and electro-magnetic compatibility. These requirements are met by designing the hardware components as per IEC 60601. It should be noted that this standard has a significant number of ancillary documents: the most appropriate to wearable sensors will be IEC 60601-1-2 regarding electro-magnetic compatibility and most probably also IEC 60601-1-6 regarding usability, IEC 60601-1-8 regarding alarms and indicators, IEC 60601-1-11 regarding devices to be used in home settings.

For wearables intended to be part of medical devices that are used to control the parameters they are measuring the IEC 60601-1-10 about closed loop controllers is a core requirement standard. This standard requires that such systems are be stable, reliable, and fault tolerant.

In all wearables, and particularly in the ones used as part of closed loop controllers, software must be designed methodically and validated comprehensively. The standard IEC 62304 [28] provides guidance and it should be noted that this standard is still in the 2006 edition at the time we are writing this article, even if a significant draft is available for consultation.

8. Giving proof of performance of a wearable sensor: input requirements, design outputs and verification as per ISO 13485

ISO 13485 [29] is a very widely applied standards that provides not only guidance on good manufacturing practices, but also guidance on design control for medical devices.

Design control begins with the clear identification of input requirements. Inputs include functional and performance requirements, user needs in terms of ergonomics and of expected benefit, and the definition of those main risks that shall be solved with safe-by-design solutions. Additionally, regulatory constraints are defined.

For wearable sensors, adequate input requirements may be accuracy and robustness of the measurements taken, data transfer policies and standards, choice of adequate power source and power time duration, choice of ergonomics during the wearing phase, for example in terms of shape, weight, aspect and adherence to the skin, and the definition of data security risks and of electrical risks that shall be solved through design. Regulatory constraints may include restrictions on the choice of materials, of suppliers of parts and on use of open source software.

Design control continues in the design output phase, where multiple options and multiple prototypes are developed and tested against the requirements, to reach a proof of concept prototype and, in later phases, a significant commercial prototype. Design control shall document the different iterations and justify the choices that led to define which was the most adequate, amongst all possible variants.

Later, a significant prototype is subject to regulatory verification and validation, in terms of safety testing and in terms of performance testing. During this phase, the input requirements shall be reviewed and the tests shall give proof that they have been met. For example, SW verification according to IEC 62304 may be used to give proof of software consistent quality, usability testing on real users may give proof of correct ergonomics, accuracy and repeatability testing may give proof of adequate performance.

9. Minimum requirements to access to the clinical phase: ISO 14155

For demonstration of benefit, wearable developers may refer to the ISO 14155 standard [30], related to good clinical trial practices for medical devices.

The result of applying this standard demonstrates that there is a statistically significant relationship between the appropriate technical performance of the device and the actual clinical benefit to the patient.

In order to test the device on human beings, being patients or healthy volunteers, in order to collect information regarding the expected clinical benefit, the developers shall respect legal and regulatory requirements that ensure the highest level of protection of the human being.

Trials that are intended to give proof of clinical benefit shall receive a preliminary approval of an Ethics committee: the approval is based on the review of the risk profile of the device, including adequacy for electrical safety and software reliability. Additionally, the ethics review will ensure that an adequate amount of data is collected for statistically significant results.

For this reason, the minimum requirements to obtain approval include at least giving proof of the device safety and giving proof that, for each participant to the trial, the participation to the study represents a potential beneficial impact on his/her clinical condition.

According to ISO 14155, the principal investigator of the study and the Ethics Committee shall receive a document (investigator brochure) that summarizes the risk- benefit profile of the device under assessment. Part of this document is the proof of safety according to harmonized standards (typically, at least electrical safety as per IEC 60601-1). Additionally, other safety testing may be required: for example, biocompatibility as per ISO 10993 or proof of software verification as per IEC 62304.

10. Giving proof of clinical benefit: pilot and pivotal clinical studies as per ISO 14155

It is no longer sufficient to demonstrate that the wearable sensor "works": accuracy and sensitivity are just the core requirements for the technical performance.

To use the wearable sensor in a clinical setting, developers should also give proof that it obtains, in a statistically significant way, the clinical benefit for which it was designed. In many cases, it will not be possible to gather sufficient clinical evidence in the literature and it will be necessary to perform appropriate clinical studies.

Designers may refer to the ISO 14155 standard, which provides methods for planning and monitoring the study.

The result of the application of this standard allows to demonstrate that the device obtains, in the target population, a clinical benefit that is both demonstrated and significantly higher than the potential risk of use. It is important to note that the clinical benefit can be expressed both in relation to the health (or quality of life) of the individual patient and to a positive impact on the management of the therapeutic path through HTA (Health technology Assessment) indicators.

Firstly, the clinical evaluation is focused on the relationship between technical indicators and clinical indicators. Typically, this relationship is studied in small studies, although adequate for a good statistical evaluation. These studies should include both safety endpoints (often also measured in terms of technical malfunctions) and technical performance endpoints, while clinical efficacy endpoints are hypothesized and tested.

A "pilot" study is normally described as a small-scale study, useful to verify if the project is adequate, to establish its feasibility or to obtain information that allows to determine the size of the sample of the definitive study. A pilot study, in the case of medical software, may be relevant in the case of:

- Need to study usability and “wear-ability” of the sensors
- Need to better define the target population or the time schedule of the study monitoring visits

In pilot studies, although statistical analyzes are still relevant, there is ample flexibility in the design of the study: therefore, often non-randomized studies without control will still be adequate. Furthermore, efficacy endpoints will not always be required, while safety endpoints can not be overlooked.

A "pivotal" study is instead considered a specific study to provide the data necessary for a regulatory approval. A regulatory study aims to gather clinical evidence to confirm that the benefit-risk ratio of the medical device is favorable to the patient. A pivotal study, in the case of wearable sensors for medical monitoring or feedback, must be performed in all cases where the evidence in the literature is not sufficient for CE certification.

In this case, it will be important for the study design to collect statistically significant evidence. A double blind, randomized study may be difficult to design in case of wearable sensors, which makes the choice of endpoints and metrics even more important.

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