Chapter 6
Ambient Assisted Living as Medical Devices: A European Perspective

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6.1 Introduction

The World Health Organization describes health technology as 'the application of organized knowledge and skills in the form of devices, medicines, vaccines, procedures and systems developed to solve a health problem and improve quality of life' (Sixtieth World Health Assembly 2007). This definition includes generically all types of technologies used to save human lives.

Among health technologies, the sector of medical technologies has been in outright development for several years with increasing levels of innovation. Currently, we can find more than 500,000 medical technologies on the market. Due to their particularities and comprehensiveness, medical technologies provide a vast range of options for ambient assisted living (AAL) and tailors perfectly into the AAL industry.

AAL emerged in 2007 as a response to the challenges posed by the ageing population. With age, we experience a natural decrease in functional capacities, with distinct tendencies for each individual, according to social and health contexts. It is consensual that the monitoring and management of these capacities benefit from the adoption of new behaviours supported by technologies that promote active ageing (World Health Organization 2002). In this context and as evidenced in other chapters of this book, AAL has become increasingly important (Broek et al. 2009) by resorting to novel devices and interactions, aiming to promote autonomy and independence of the elderly (Sánchez-Pi and Molina 2009; Wichert and Eberhardt 2011).

AAL intends to address needs of older adults and respective major diseases, by meeting the specific individual needs, which might include the access of the

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caregiver to up-to-date clinical information, so that the right care at the right time can be delivered (e.g. continuous home monitoring of physiological parameters). Therefore, AAL combines solutions (e.g. home monitoring), which can easily borderline with medical technologies, with implications on regulatory and legal frameworks that guarantee the safety of users. Current tendencies are highly based on eHealth tools that represent a significant portion of the medical technology innovation, including more and more AAL solutions, with prompt applicability in ageing.

At this point, AAL cannot be dissociated from medical technologies as they provide devices that can greatly foment the independence of the elderly while guaranteeing better life conditions. Moreover, by working in proximity with the populations, AAL can boost innovation in the medical devices sector, during the search for novel strategies that can further increase the quality of life of older persons. By sharing this reality, scientists, developers and project managers of AAL projects face new challenges mainly at the regulatory affairs level, being impelled not only to reach the market but also to guarantee, by legal standards, the safety of users.

This chapter aims to highlight the importance of development and integration, as soon as possible, of a regulatory strategy concerning AAL solutions that guarantees the safe and sustainable development and commercialization of products that can fall under the umbrella of medical technologies.

6.2 Translational Challenges on Medical Devices Development

Basic research is of utmost importance to predict and understand the principles and mechanisms of processes and to characterize, at the micro level, the impact of novel strategies in humans. However, many times, the findings of basic research do not become real outcomes in clinical practice, due to a lack of efforts and channels to transpose the acquired knowledge to the resolution of concrete challenges (Mensah 2018). This can be a consequence of the particular functioning and metrics of the academia, but there are also cases in which the involved institutions do not plan research adequately, at a scientific and regulatory level, or never managed to see their research firmly funded. Either way, basic research becomes inconsequent.

This is particularly evident in AAL where most of the developments aimed the design, development and evaluation of prototypes (i.e. proof of concept). In contrast, evidence-based medicine is supported on statistical and clinical significance, and new developments are required to show they are able to make a difference and are cost-effective.

The concept of translational medicine was first mentioned in the 1990s – but only gained consistency in the early 2000s – as a consequence of the urgency to optimize product development processes and transform laboratory findings in useful clinical tools. Despite the multiple available definitions, translational medicine is globally recognized as a multidisciplinary branch of biomedical research that intends to transfer the knowledge collected from basic research to clinical practice – from bench to bedside – with the aim of improving the success of prevention, diagnosis

and treatment of human diseases (Gannon 2014; Mirvis 2009). In the process, laboratory findings are integrated within clinical research, and results are applied in the discovery of novel treatment strategies, in a continuous bidirectional flow of information.

Translational medicine can be divided in four stages that fill the gaps detected in the translation process: T1, translation to humans; T2, translation to patients; T3, translation to practice; and T4, translation to population (Waldman and Terzic 2010).

According to the principles of translational medicine, basic research must be carefully planned and supported according to future perspectives. At this stage, scientists must be aware of the demands and challenges – related to technical and regulatory support, costs, good practices and logistics – inherent to the translation of their results to humans, specifically to clinical research of medicines and medical devices. Several aspects must be considered and debated: animal models, stability and mechanism of action, adequacy of design, construction and testing of medical devices and target population, among others. This will determine whether a promising medicine or device will be able to cross 'the valley of death' with sufficient and adequate conditions to be integrated in clinical research and reach market (Waldman and Terzic 2010; Hudson and Khazragui 2013; Westfall et al. 2007).

The translation process itself begins with the transfer of basic research to humans with the objective of assessing clinical effect and viability – T1 translation (Fig. 6.1). This is a critical step involving the collection of the first clinical insights of the device prototype in feasibility/pilot trials conducted in humans (healthy or with disease). The evidences of clinical effect in humans must then be confirmed in patients treated in controlled environments during pivotal clinical trials – T2 translation. At the end of this stage, researchers will have insights about the clinical application, efficacy/performance, safety and the implications of the treatment to patients. Entry in the market will happen at this stage.

Next, research will be focused on the best strategies to apply clinical research outcomes to define recommendations for routine clinical practice – T3 translation. At this point, research is no longer conducted in controlled environments but is rather implemented in 'real-world' conditions, among a variety of uncontrollable

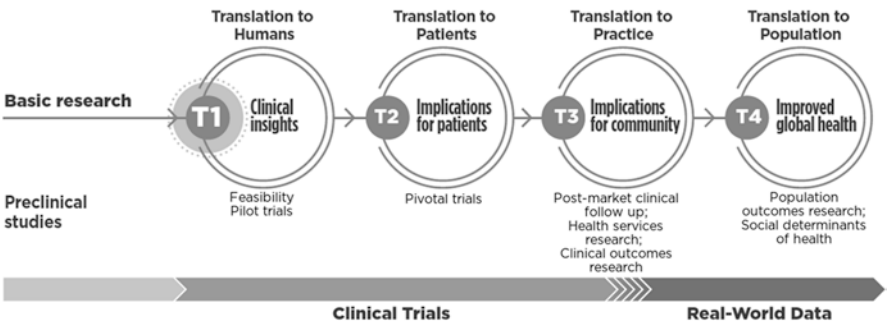

Fig. 6.1 Stages of translation medicine (T1 to T4)

and unpredictable factors. Main implications of the technology for the community will arise from this stage as a result of therapeutic use trials and health outcomes research.

But, considering the ultimate goals of translational medicine, the process cannot be closed with the translation of results to patients: a global approach regarding whole populations is mandatory (Mirvis 2009). Outcomes must be integrated in the search for factors and interventions that affect the daily life and health of a population – T4 translation. This can be achieved through cost-benefit evaluations, surveillance studies and policy analysis. The major objective of this stage, and of the whole translation process, is to improve global health through the integration of the research outcomes collected during basic research and stages T1, T2 and T3. Improvements can arise from both the generated clinical outcomes and from policy development in the sequence of the translation process.

Like in pure medical devices development, in AAL the success of the translation of knowledge – from laboratories to clinical/assistance practice, with the aim of improving the health of populations – depends on a solid and continuous communication between academic researchers and health technologies industries. Their philosophies and expectations are distinct, but cooperation is the only channel that guarantees the bidirectional flow of data that is essential for the successful process that transforms an AAL concept into a valuable therapeutic tool. Also, AAL will benefit from a process that gives preponderance to the new reality of T3 and T4 stages, since being close to the populations and learning with them are in its own genesis.

6.3 Medical Devices Qualification and Classification

Since 2017, the European Union is crossing a transition period in terms of medical technology regulation with the publication, on 5 April 2017, of two new European regulations that revoke Council Directive 93/42/EEC concerning medical devices (MDD) (European Council 1993), Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the member states relating to active implantable medical devices (European Council 1990) (both directives, as amended by Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 (European Parliament and European Council 2007)) and Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices (IVDD) (European Parliament and European Council 1998). Regulation (EU) 2017/745 of the European Parliament and of the Council, of 5 April 2017, on medical devices (MDR) (European Parliament and Council of the European Union 2017) will repeal MDD and AIMDD, as from 26 May 2020, while regulation (EU) 2017/746 of the European Parliament and of the Council, of 5 April 2017, on in vitro diagnostic medical devices (IVDR) (European Commission 2017) will repeal IVDD, as from 26 May 2022. During this transition period, both sets of legislation will apply to medical technologies in Europe. While new legislation is

ready to be followed by scientists, developers and manufacturers, guidelines for its application are still unavailable. In this context, this chapter will follow, whenever possible, the articles of the new legislation.

Besides providing a definition of medical device, MDR establishes the aims, requirements and results that must be achieved in this field and creates a new legal framework regarding medical devices entry into force in all member states on 26 May 2017 with expected date of application as from 26 May 2020.

According to Article 2(1) of MDR, a medical device is defined 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':

- New models of service delivery and care that contribute to greater self-reliance for older adults and greater support for informal carers;
- Diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease;
- Diagnosis, monitoring, treatment and 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 (European Parliament and Council of the European Union 2017).

To be qualified as medical device, a health technology must first comply with Article 1 of MDR, which defines the subject matter and scope of the regulation – describing which product categories are included/excluded from the scope of the regulation – and must also comply with the definition of medical device. If a health technology passes the scrutiny of Article 1, it can be qualified as medical device by resorting to a simple yes/no algorithm (Fig. 6.2). Accordingly, a health technology that has a medical purpose, as described in medical device definition, can be either a medicine or a medical device. It is important to highlight that the developer has the obligation to validate this medical purpose, with proper scientific data. It is not acceptable to identify the medical purpose based only on the assumption that the technology will be used in medical environments or applied by health professionals. At this point, if the principal mechanism of action is pharmacological, metabolic or immunological, the product will probably fall under the scope of medicines´ regulation; if this is not the case, it can be qualified as a medical device. Again, the

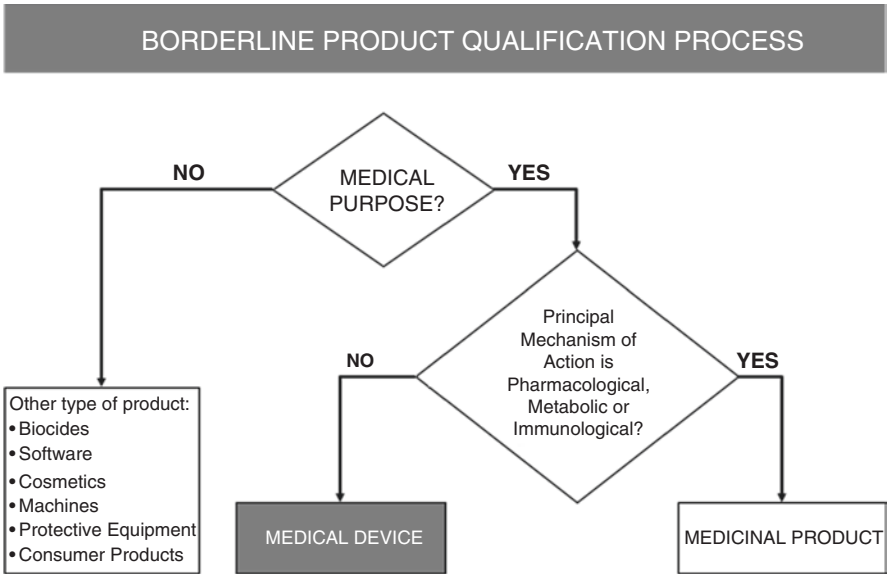

Fig. 6.2 Basic decision flowchart for qualification of a health technology as a medical device

developer must support the principal mechanism of action of the technology with adequate scientific data. Sometimes, it is not clear from the outset whether a given product is a medical device or other product with similar characteristic like biocides, protection equipment, cosmetics, software and medicines. These products – called borderline products – must be carefully analysed, case-by-case, as their classification might be difficult (Medical Devices Expert Group on Borderline and Classification 2018). This issue will be addressed below in the chapter.

The pathway for the development of a medical device, from concept to market, presents particularities that distinguish it from other health technologies (Fig. 6.3).

Three main entities can be identified in this process: manufacturers, competent authorities and notified bodies (when a third party is required).

Competent authorities adapt EU regulations to national realities, designate and supervise notified bodies (described later in the chapter) in member states and are involved in vigilance and market surveillance of medical devices.

Manufacturers develop, qualify and classify their medical devices – classification will define the course of development of the products – and must ensure that they are developed and manufactured in conformity with the general safety and performance requirements, set by Annex I of MDR (European Parliament and Council of the European Union 2017):

- General requirements (Chapter I of Annex I of MDR). Focuses on risk management associated with the design and manufacture of medical devices. As a general principle, a medical device must be designed and manufactured in such a way that guarantees that it has adequate performance during normal conditions

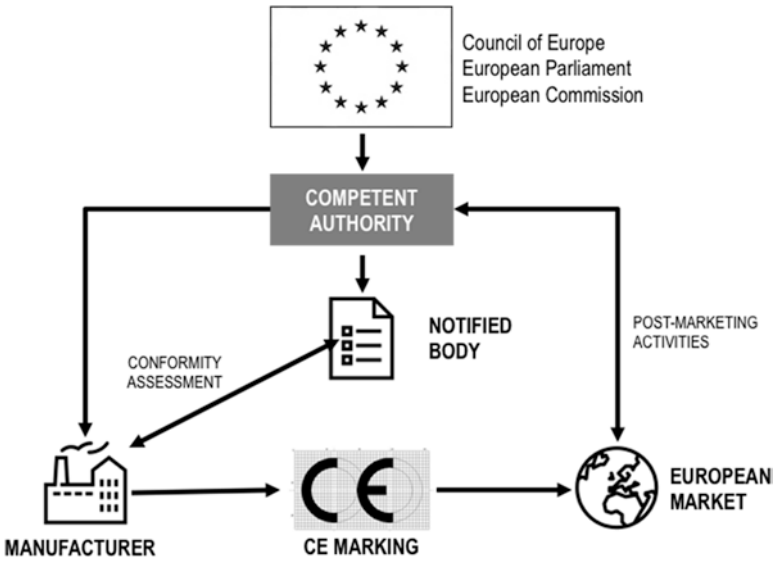

Fig. 6.3 Entities involved in the CE marking process of medical devices in Europe

of use, is suitable for the intended purpose, is safe and effective and does not compromise the clinical condition of the user. As far as possible, the risks associated to the use of the medical device should be reduced, without compromising the overall benefit-risk ratio. For this, manufacturers shall establish, implement, document and maintain a risk management system that evaluates the acceptability of the involved risks and shall inform users about any residual risk.

- Requirements regarding the design and manufacture (Chapter II of Annex I of MDR). Describes in detail specific requirements regarding design and manufacture of medical devices and is divided into the following subtopics:
  - Chemical, physical and biological properties;
  - Infection and microbial contamination;
  - Devices incorporating a substance considered to be a medicinal product and devices that are composed of substances or of combination of substances that are absorbed by or locally dispersed in the human body;
  - Devices incorporating materials of biological origin;
  - Construction of devices and interaction with their environment;
  - Devices with a diagnostic or measuring function;
  - Protection against radiation;
  - Electronic programmable systems – devices that incorporate electronic programmable systems and software that are devices in themselves;
  - Active devices and devices connected to them;
  - Particular requirements for active implantable devices;
  - Protection against mechanical and thermal risks;

  - Protection against the risks posed to the patient or user by devices supplying energy or substances;
  - Protection against the risks posed by medical devices intended, by the manufacturer for use by lay persons.

- Requirements regarding the information supplied with the device (Chapter III of Annex I of MDR). Addresses detailed information on label and instructions for use:

  - General requirements regarding the information supplied by the manufacturer;
  - Information on the label;
  - Information on the packaging which maintains the sterile condition of a device ('sterile packaging');
  - Information in the instructions for use.

The manufacturer must create and keep updated versions of all technical documentation that support the evidence of conformity with the general safety and performance requirements described above. Annex II and III of MDR describe in detail the principles of this documentation that can be grouped as follows (European Parliament and Council of the European Union 2017):

- Device description and specification, including variants and accessories;
- Information to be supplied by the manufacturer;
- Design and manufacturing information;
- General safety and performance requirements;
- Benefit-risk analysis and risk management;
- Product verification and validation;
- Preclinical and clinical data;
- Additional information required in specific cases;
- The post-market surveillance plan drawn up in accordance with Article 84;
- The PSUR [periodic safety update report] referred to in Article 86 and the post-market surveillance report referred to in Article 85.

To prepare technical documentation, manufacturers can resort to notified bodies' recommendations since these will be involved in the conformity assessment process, as described below. Currently, recommendations are only available for old directives, but revision is expected soon (Coordination of Notified Bodies Medical 2000).

The list of requirements and documentation described above clearly evidences that manufacturers are responsible for preclinical (design, engineering, laboratory, animal) and clinical evaluation, always under a risk management system. Manufactures are advised to use European harmonized standard to guarantee conformity with the set of requirements applicable to their medical devices. A compilation of the references of harmonized standard is published in the Official Journal of the European Union (European Commission 2017); the most used are EN ISO

13485:2016 (Quality management systems – requirements for regulatory purposes) (European Committee for Standardization 2016), EN ISO 14971:2012 (Application of risk management to medical devices) (European Committee for Standardization 2012), EN ISO 14155:2011 (Clinical investigation of medical devices for human subjects – good clinical practice) (European Committee for Standardization 2011) and EN ISO 10993–1:2009 (Biological evaluation of medical devices) (European Committee for Standardization 2009). Manufacturers are also responsible for CE marking of their medical devices through which they declare that the product meets legal requirements and can be freely commercialized in the European Economic Area.

Depending on the risk classification of the medical device, the process may have the intervention of a notified body selected by the manufacturer.

Notified body 'is an organisation designated by an EU country to assess the conformity of certain products before being placed on the market. These bodies carry out tasks related to conformity assessment procedures set out in the applicable legislation, when a third party is required. The European Commission publishes a list of such notified bodies' (European Commission 2018). Notified bodies evaluate if the medical device is compliant with the high safety, health and environmental protection requirements established in the legislation. As so, they must actuate under the principles of non-discrimination, transparency, neutrality, independence and impartiality assuring confidentiality throughout conformity assessment. If compliance is confirmed, the manufacturer can affix the CE marking in the medical device and proceed to marketing. The life cycle of the product follows with continuous post-marketing surveillance that generates reports to the competent authorities, manufacturer and notified body. Figure 6.4 describes the main stages of research and development process in the medical device industry.

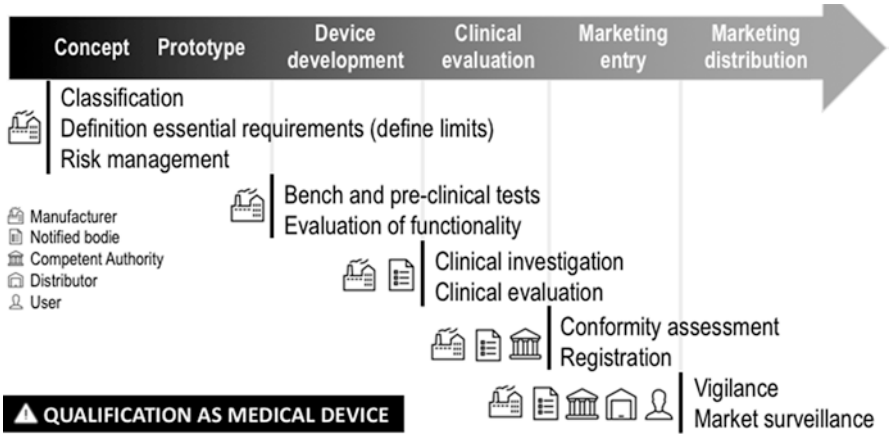

Fig. 6.4 Stakeholder involvement in the research and development process for a medical device

Due to the overwhelming developments on this field, the new MDR introduces updates in the life cycle of the product, giving more importance to the following aspects:

- Premarket procedures (with the creation of the figure of the person responsible for regulatory compliance, implementation of common specifications and deeper scrutiny of high-risk devices);
- Clinical evidence (demanding more clinical data for high-risk devices, publication of clinical and safety data, reinforced equivalence criteria and providing new rules for post-market surveillance);
- Notified bodies (with reinforced designation criteria, unannounced visits and joint audits);
- Post-market surveillance and vigilance (with the introduction of a central database, trend reports, post-market surveillance plan/reports and periodic safety update reports);
- Transparency and traceability (with the registry of devices and economic operators in EUDAMED, development of unique device identifier (UDI), implant cards and adoption of summary of safety and clinical performance);
- Governance, cooperation and oversight (with creation of a medical device coordination group expert panels and expert laboratories).

Qualifying and classifying medical devices – in the early stage of their development – are of utmost importance to distinguish different products while guaranteeing a safe and sustainable development. It is not acceptable to subject all medical devices to similar evaluation procedures, and thus a classification system based on potential hazardous is desirable, to avoid unnecessary procedures. In the scope of AAL, this aspect is fundamental as manufacturers greatly benefit from a harmonized reality that allows the effective development of novel products, with impact on the quality of life of populations.

In the European Union, the classification system for medical devices – defined in Annex VIII of MDR – guarantees harmonized rules and proper development and evaluation. Several criteria are considered in the classification system: duration of use, degree of invasiveness (non-invasive/invasive), type of effect (local/systemic), target organs, use of energy and associated risks.

When analysing AAL solutions, it is expected that several systems fall under the scope of MDR. To classify them in accordance with MDR classification rules is mandatory and a responsibility of the manufacturer. Some aspects must be taken into consideration when dealing with AAL; for example, regarding time of contact, three situations can occur that will have impact in medical devices classification (all of them possible in the scope of AAL): transient use occurs when a medical device is normally intended for continuous use for less than 60 min, short-term use when the medical device is normally intended for continuous use for between 60 min and 30 days and finally long-term use when the medical device is normally intended for continuous use for more than 30 days.

It can be envisaged that the majority of AAL solutions will fall under the category of non-invasive medical devices (Article 2(6) of MDR) – “invasive device means any device which, in whole or in part, penetrates inside the body, either

through a body orifice or through the surface of the body" – but we can easily identify solutions with some degree of invasiveness, such as a continuous glucose monitor. Also, the use of energy in medical devices will increase the risks. Article 2(4) of MDR defines active device as '… any device, the operation of which depends on a source of energy other than that generated by the human body for that purpose, or by gravity, and which acts by changing the density of or converting that energy. Devices intended to transmit energy, substances or other elements between an active device and the patient, without any significant change, shall not be deemed to be active devices. Software shall also be deemed to be an active device'. Many AAL solutions are indeed active devices and many others are software applications; as such, if the manufacturer intends to present a product with medical purpose, it must be classified according to MDR rules dedicated to active devices. Manufacturers can remove the medical purpose from the intended use of a device – stating that the product does not have a medical purpose – but this does not exclude the product from the scope of the MDR, if the definition criteria of medical device are satisfied. Manufacturers must demonstrate, by means of scientific/technical data, that such medical purpose is not achieved.

Under MDR, medical devices are divided in four risk classes:

- Class I (low risk);
- Class IIa (medium risk);
- Class IIb (elevated risk);
- Class III (high risk).

To identify the specific risk class of a medical device, the manufacturer is guided by a set of decision algorithms that enable a final classification. In Annex VIII of MDR, 22 rules of classifications are defined. MDD rules were updated; some became more stringent ('up-classification'), and five new rules of classification were created: Rule 11 (software classification), Rule 19 (devices incorporating or consisting of nanomaterials), Rule 20 (body orifice invasive devices intended to administer medicines by inhalation), Rule 21 (devices consisting of substances and introduced into the body via body orifice or skin and are absorbed by or locally dispersed) and Rule 22 (active therapeutic device with an integrated or incorporated diagnostic function). By applying to MDR rules the orientations defined in MEDDEV 2.4/1 Rev. 9 from June 2010 (Classification of medical devices) (European Commission 2010), we can envisage four major groups of rules:

- Non-invasive devices that can be classified from class I to IIb by rules 1 to 4. In the perspective of AAL, several products with these characteristics can have impact on the well-being of populations and on the effectiveness of their healthcare procedures;
- Invasive devices with risk classes from class I to III according to rules 5 to 8. As examples with interest in the context of AAL, we can point out rechargeable nonactive drug delivery systems;
- Active devices with risk classes from class I to III according to rules 9 to 13. In particular, new Rule 11 is dedicated to the classification of software as medical

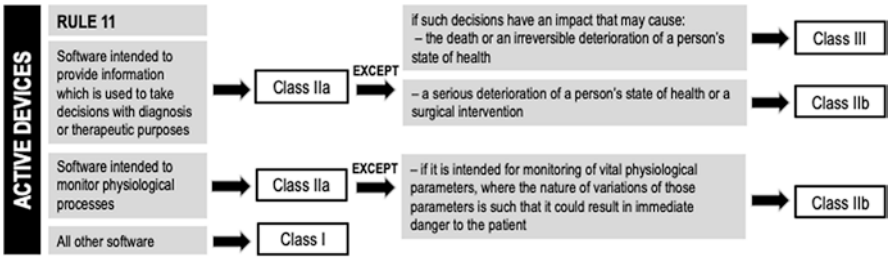

Fig. 6.5 Example of algorithm for application of Rule 11 (software) in accordance with Annex VIII of MDR

device (further described in the next section of this chapter) defining parameters that can classify a software application from class I to class III (Fig. 6.5);

- Special rules that include risk classes from class IIa to III according to rules 14 to 22. New rules 19, 20, 21 and 22 were created as a response to recent innovations within medical technologies. The advent of nanotechnology is well represented in Rule 19 (devices incorporating or consisting of nanomaterials) with possible impact in AAL when nanomaterials are used.

Manufacturers are responsible for propounding a classification for their devices; as such, research teams must be adequately trained to guarantee the adequate planning of the initial stages of development, avoiding wrong decisions that can delay the development process and increase costs and time to access market.

While qualification and classification are of major importance in the first steps of product development, in AAL, developers must be aware that if their technology is qualified as a medical device, the translation to humans needs to be supported with clinical evidence. If quality data on bench and animal tests gives the confidence to advance for research in humans, clinical data to support demonstration of clinical benefit is mandatory to be in conformity with MDR. In medical devices, clinical evaluation is defined in Article 2(44) of MDR as '… a systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer' and Article 2(48) defines clinical data as '… information concerning safety or performance that is generated from the use of a device and is sourced from the following':

- Clinical investigation(s) of the device concerned;
- Clinical investigation(s) or other studies reported in scientific literature of a device for which equivalence to the device in question can be demonstrated;
- Reports published in peer-reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated;
- Clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up.

To perform clinical evaluation of medical devices, manufacturers need to assess sufficient clinical data to verify the safety and performance, including clinical benefits, of the device in evaluation. As set in the definition of clinical data, different sources can be used to gather information for the assessment procedure. In specific cases, and when clinical, biological and technical equivalence can be demonstrated to other device, clinical evaluation can be based on scientific literature. If the technology in question is innovative, equivalence is probably not possible to demonstrate, and manufacturers must generate their own clinical data resorting to clinical investigation. It is important to emphasize that implantable devices and class III devices are always obligated to be subjected to clinical investigation except if they meet the exception identified in Article 61(4) of MDR. In the end, to be in conformity with clinical evaluation requirements, manufacturers must follow Annex XIV (Clinical evaluation and post-market clinical follow-up) and Annex XV (Clinical investigation of the MDR) (European Parliament and Council of the European Union 2017). Manufacturers can guide the clinical evaluation process of their medical devices by applying the guidelines of MEDDEV. 2.7/1 Rev.4 from June 2016 that divide the process in five stages: Stage 0, Definition of the scope of the clinical evaluation; Stage 1, Identification of pertinent data; Stage 2, Appraisal of pertinent data; Stage 3, Analysis of clinical data; and Stage 4, Clinical evaluation report.

In AAL, if a simple or complex innovative solution falls under the scope of medical technologies, its correct qualification and classification determine the regulatory roadmap to follow and the successful pathway to market.

6.4 Borderline Challenges of Medical Technologies

Medical technologies are present in our daily life – from birth to advanced ages – making healthcare more efficient and increasing autonomy and quality of life of individuals, with emphasis on elderly populations. As age advances, the number of available products increases exponentially along with the needs that individuals have for them (Fig. 6.6). A plethora of technologies are explored from medical devices, in vitro diagnosis, imaging and eHealth, among many others. This is in good agreement with the objectives of AAL, as evidenced by the large variety of products and services that are being developed to increase the quality of life of population.

Some of these products are difficult to classify due to their patterns of innovation related mainly to the combination/confounding with medical approaches. They can be considered borderline products – a concept in the scope of medical technologies that defines cases where it is difficult to state if a given product is, for example, a medical device, an *in vitro* diagnostic medical device, a software as medical device and a health and wellness software, or cases where the accepted classification rules cannot be promptly applied (Medical Devices Expert Group on Borderline and Classification 2018).

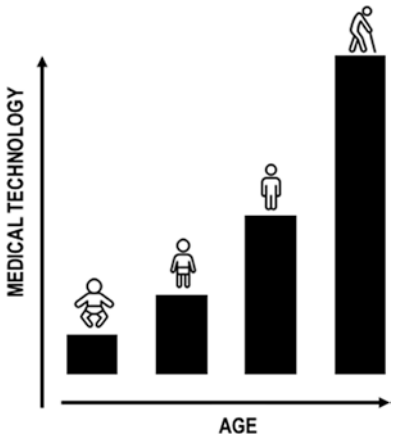

Fig. 6.6 The use of medical technology increases as age advances

Current developments in medical technologies are based on miniaturized, intelligent, low invasive and combination products. Along with this, research strategies consider the demand for personal use products and the particular needs of special populations. Thus, it is expected that borderline products continue to emerge in the scope of AAL, demanding particular attention concerning to regulatory issues, control of quality, safety and performance.

To highlight this tendency, we can focus our attention on some challenging strategies that demand particular analysis. With this problem, several fields emerged inside medical technologies; for instance, eHealth with software and mobile applications are major challenges in AAL systems.

In a time where technologic platforms such as mobile computers, smartphones and tablets are available for most people, different kinds of software are being widely used in healthcare, both with medical and nonmedical purposes. The incorporation of software in medical devices became widespread so that specific regulation was conceived for these particular cases, minimizing the risks associated to this combination. Big challenges began when software was suggested as a medical device, forcing regulators to create adequate tools for proper and convergent control of these devices. According to the International Medical Device Regulators Forum (IMDRF), software as medical device is defined when it is '… intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device' (International Medical Device Regulators Forum (IMDRF) 2013). This implies that the software guarantees a valid clinical association between its output and the clinical condition and provides the expected technical and clinical data (International Medical Device Regulators Forum (IMDRF) 2017; European Commission 2016).

Under the European regulation, it is important to clarify that according to MEDDEV 2.6/1 from July 2016, software 'is defined as a set of instructions that processes input data and creates output data' and stand-alone software '… means software which is not incorporated in a medical device at the time of its placing on the market or its making available' (European Commission 2016). Stand-alone software must have a medical purpose to be qualified as medical device. When used in

healthcare settings, these types of software can run on all types of operating systems and may have several applications, from directly controlling an apparatus (e.g. radiotherapy treatment) to providing support for healthcare professionals (e.g. X-ray interpretation) (European Commission 2016). A myriad of solutions in AAL will fall under the qualification criteria of stand-alone software as medical device. Following decision trees similar to those used in medical devices classification, stand-alone software guidelines allow developers to qualify their technology according to regulatory rules (MEDDEV 2.1/6 from July 2016, decision diagrams) (European Commission 2016) and determine if the developed AAL solution is a stand-alone software as medical device. If so, the life cycle of the ALL solution will be ruled by the regulation applied to medical devices.

These features are well expressed, for example, in a mobile application for processing electrocardiograms (ECGs). Such an application will be classified as stand-alone software as medical device if it uses signal data from an external source that can be received wirelessly, for example, from an AAL system and processes it to an ECG waveform – performing an action on data – for medical benefit of an individual patient. This will provide timely and accurate diagnosis and treatment. This software application will fall under the scope of the MDR and will be qualified as medical device, and its classification will be ruled by Rule 11 of Annex VIII of MDR (Medical Devices Expert Group on Borderline and Classification 2018).

Another example is software developed with the purpose of treating a variety of neurodisorders. The combination of several software applications allows the physician to establish rehabilitation plans based on interactive games and exercises, for cognitive stimulation, and to access patient's progress. Assuming an AAL context and depending on its autonomy, the patient – alone or with the support of a caregiver – can perform the planned tasks at home and the clinician can plan, monitor and assess the patients' progress throughout the treatment plan, at distance in the comfort of its office. Depending on the intended purpose identified by the manufacturer – treatment of disease, injury or handicap – this software can be easily integrated in a AAL solution and should be qualified as medical device and classified by means of Rule 11 of Annex VIII of MDR (Medical Devices Expert Group on Borderline and Classification 2018).

The same considerations could not be extended to a mobile application for storing pictures of skin moles, in a smartphone, as no data manipulation occurs, a prerequisite for a software to be qualified as stand-alone software as medical device. If the same application, besides storing pictures of moles, can also assess them with the help of an algorithm that classifies the mole as a melanoma, supporting diagnosis of skin cancer, it can be qualified as medical device and classified according to Rule 11 of Annex VIII of MDR (Medical Devices Expert Group on Borderline and Classification 2018). Applications that just store data and do not perform any action on it, with impact on an individual patient, are generally not medical devices. Healthcare information systems, normally dedicated to manage data, by storing, archiving and transferring, are not qualified as medical devices. However, specific modules of software may be qualified as medical devices (e.g. a medication module) (European Commission 2016).

Another technology of interest is bone-anchored hearing aids. The product comprises a titanium implant and a sound processor that relies on an electric power source. The question is whether the system is an active implantable medical device or only a medical device. The key for the classification is based on the fact that the implanted part (titanium) is not active and that the active element (sound processor) is not implanted. Thus, the system is not an active implantable medical device but rather a medical device as both components are classified as such (Medical Devices Expert Group on Borderline and Classification 2018). While this example is not per se an obvious AAL solution, wireless solutions that can be connected with the sound processor can fall under AAL. If the AAL solution (e.g. smartphone application) is developed with a medical purpose, it will probably fall under MDR with a particularity: if it is commercialized as a single system comprising the implant, the sound processor and the software application, the risk classification will be the highest of the three components, and all parts must comply with the general safety and performance requirements set for that classification.

The difficulties of the development of software as medical device do not end with qualification and classification; challenges also emerge during clinical evaluation. International Medical Device Regulators Forum suggests a three-step process for clinical evaluation of software as medical device:

1. Valid clinical association (Is there a valid clinical association between your software as medical device output, based on the inputs and algorithms selected, and your software as medical devices' targeted clinical condition?);
2. Analytical validation (Does your software as medical device correctly process input data to generate accurate, reliable and precise output data?);
3. Clinical validation (Does use of your software as medical devices' accurate, reliable and precise output data achieve your intended purpose in your target population in the context of clinical care?) (International Medical Device Regulators Forum (IMDRF) 2017).

Borderline issues regarding medical devices and medicinal products, in vitro diagnostic medical devices, cosmetics and biocides are also a topic of concern that deserves careful debate. AAL is not by excellence a field for this type of products, but several examples of borderline questions can be studied in the *Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices* (Medical Devices Expert Group on Borderline and Classification 2018).

The discussion around borderline products is a mirror of the technological advances in the field of medical devices. It gains particular importance in the scope of AAL due to the exponential emergence of products with the specific purpose of increasing the quality of life of the targeted population. Manufacturers must be aware of these challenges, and regulators have the obligation to create guidelines and recommendations to assure sustainable, harmonized and secure development of novel products.

6.5 The Medical Device Regulatory Pillar in the Development of AAL Solutions

In a context of continuous growth and constant innovation, the medical device sector faces big challenges regarding mainly the safety of products. Scientists and manufacturers have the responsibility of creating quality products, according to the market needs, while guaranteeing conformity with regulations and safety for users. eHealth and borderline products add strains to this context, as classification and research demands might be unclear or misinterpreted.

In the scope of AAL, this becomes even more significant as products shall not only fulfil the needs of the target population but also be designed and manufactured in such a manner that utilization poses minimum doubts and risks and guarantees usability. Specific milestones can be introduced in the development chart of a AAL solution. By answering in the initial steps of the project – sometimes already at the initial brainstorming of the concept – to question like 'Does my product have a medical purpose?', 'What type of medical device it is?' and 'What is its inherent risk to the user?', the developer will be armed with data that enables a more efficient research and development process, by ensuring correct application of resources and decreasing the time to market. When developing a medical technology, the developer must have in mind that the four stages (T1, T2, T3 and T4) needed to technology translation from an idea to a product are also answers to regulatory demands. In Europe, MDR, with its demands for safety, performance and post-market activities, obligates the developer/manufacturer to respond to the four translation stages to maintain the product available for the user in a healthcare setting.

These demands can only be attended if all stakeholders actuate under the same base of principles and according to the same rules. A solid, comprehensive regulatory basis must be available, and its application shall be assured and inspected. Thus, competent authorities are obliged to identify the evolution of research and of the market and support/inspect manufacturers during the development and commercialization processes.

The new MDR is introducing changes in the medical technology sector with strict measures to increase transparency, traceability and security while demanding more clinical evidences and the involvement of experts in the evaluation process. This context must be integrated in AAL projects, if a medical purpose is identified, and, by default, project management policies must contemplate regulatory affairs specialists (employed or subcontractor) since this is the best way to ensure the sustainability of the regulatory pillar and the success of the project.

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