Meeting an End-user Need in a Collaborative High Risk Medical Device Software Development in Accordance with Future European Regulations

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Abstract: Caring for a child in life-threatening distress is very stressful and error-prone for the caregivers. An end-user need for a software that would free the child from human error and support the caregivers in the care of the child has thus emerged. Free from the time-consuming and stressful constraints of calculating constants or medication doses and consulting emergency protocols, caregivers could be more available and focused on the vital care of the child. The extension of the scope of medical devices to software for medical purposes is one of the important new points of the future European regulations. The very important overhaul of the previous classification system with the addition of new rules or updating of old ones reinforces the regulations applicable to software. The impact is considerable for the development and market access strategy of high-risk classified software, and participate in a better security and efficacy of the marketed products, for better healthcare. In this article we propose then to detail the strategy used for the development of a high-risk medical device software intended to be used in pediatric intensive care units.

1 INTRODUCTION

The term "medical device" (MD) as defined by the European Medical Device Regulation (MDR) 2017/745 (EUR-lex, 2017a) may refer to an instrument, apparatus, equipment or software intended by its manufacturer to be used in humans. Medical devices (MDs) are particularly difficult to characterize because of their extreme diversity (pair of glasses, hip prosthesis, dental implant…). This variety is expressed through the very nature of the MD, its complexity, its applications, its uses, its users and the environment in which it is used. MDs may be used for the diagnosis, prevention, control, treatment and/or mitigation of disease or injury. To date, the World Health Organization counts approximately 10,000 categories of MDs. In end and consequently to these particularities, the evaluations of MDs need to be adapted and relevant.

To ensure the health and safety of people, MDR (updated and adopted in 2017 for an application in next May 2021) specify the obligations to be respected in their design, development, manufacture, distribution... MD software is subject to the same regulations as MD, however, the characteristics and functionalities they provide often lead to additional regulations. Indeed, it is necessary to ensure the cybersecurity, to guarantee the protection of personal data, sometimes to set up a user manual in electronic format... In order to precisely determine the applicable regulations, the process must be carried out on a case-by-case basis, as each MD software has its own characteristics and functionalities.

Unlike drugs, the regulations relating to MDs (traceability, classification, marking) do not require a Marketing Authorization. The placing on the market of MDs is conditioned by obtaining the CE mark, which is a stage in the development of the product.

This unavoidable step requires sufficient proof of safety and performance obtained through clinical investigations for Class III and implantable devices. The regulatory steps to perform interventional clinical trials using high-risk MD software that don't get yet CE mark are cumbersome, time-consuming and expensive. In order to collect quickly clinical data and without requiring such steps, we have chosen to conduct a first clinical investigation in two phases in order to validate the use of a software calculating doses and offering support algorithms in different clinical situations of pediatric intensive care: a first non-interventional one followed by a simulation.

2 CONTEXT

2.1 Future European Regulations

The world of MDs within the European Union (EU) is going through an important period in its history. Technological advances, the need for harmonization of practices within the EU and massively publicized scandals such as the poly implant breast prosthesis affair have led the various member states to reposition themselves at the regulatory level. The European Directive 93/42/EEC (EUR-lex, 1993) will give way to the MDR 2017/745 common to all member states. This new text aims to unify all MD players under a single regulation, which is more comprehensive in the current technological context. In particular, this new regulation aims to improve traceability and transparency at the European level, but also to be able to monitor notified bodies more closely.

2.2 Specificities of High-risk MD Software

Not all MDs present the same level of risk in terms of their use. The classification is based on the destination of use and the potential risk of the MD for the patient but also the healthcare staff and any other person likely to use the device. The risk class of the MD and the justification of the classification rules shall be applied in accordance with Article 51 and Annex VIII of the MDR 2017/745. This level of risk, estimated by the application successively of 22 rules and 80 criteria, makes it possible to identify 4 classes for MDs, in order of criticality: I, IIa, IIb and III. The classification rules are generally stricter in the regulations than they were in the directives, which will lead to a change of class for many MDs and some will be classified as high-risk devices. The class is very critical because it determines the applicable

requirements and the effort for a manufacturer is incomparable between a Class I and a Class III.

In the same time and over the last few years, we have seen an increased growth in the use of software (on computers, mobile applications, embedded…) as medical solutions (for diagnosis, monitoring, measurements...) in the field of technologies for health. Digital health technologies Software is digital heath devices including artificial intelligence and machine learning which has the vast potential to improve the ability to accurately diagnose and treat disease and to enhance the delivery of health care for the individual. The new regulation has adapted to this technological evolution and defines software and its various classification rules. The definition of MD clearly includes the software (section 2.1, chapter I of the MDR 2017/745) and precise that software shall also deemed to be an active device. MD software is software that is intended to be used, alone or in combination, for a purpose as specified in the definition of a MD in the MDR. However, software for general purposes, even when used in a healthcare setting, or software intended for life-style and well-being purposes are excluded from this definition. A software controlling a device or acting on its use, i.e. interacting with the device, is classified in the same class as the device; a software independent of the device is classified as such in application of point 3.3, chapter II, Annex VIII of the MDR 2017/745. Rule 11 of Annex VIII was introduced into the MDR and is intended to address the risks related to the information provided by an active device. It describes and categorizes the significance of the information provided by the active device to the healthcare decision (patient management) in combination with the healthcare situation (patient condition). It states that software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as class IIa, except if such decisions have an impact that may cause:
- death or an irreversible deterioration of a person's state of health, in which case it is in class III; or
- a serious deterioration of a person's state of health or a surgical intervention, in which case it is classified as class IIb.

Performance and safety requirements specific to software are presented in Annex I of the MDR 2017/745. It is specified that devices shall be designed and manufactured in such a way as to remove or reduce as far as possible the risks associated with the possible negative interaction between software and the IT environment within which it operates and interacts (section 14.2 d) and in accordance with the state of the art taking into

account the principles of development life cycle, risk management, including information security, verification and validation. Software shall be designed to ensure repeatability, reliability and performance in line with their intended use (section 17.2).

The evaluation of MD software is well supervised in the new regulation. It requires the generation of consistent documentation concerning the verification and validation of the software. The design, development process and validation must be described. This information shall typically include the summary results of all verification, validation and testing performed both in-house and in a simulated or actual user environment prior to final release (section 6.1, Annex II).

Software qualification, classification and clinical evaluation are also based on guidance from for example MDCG (Medical Device Coordination Group; 2019-11 Guidance on qualification and classification of Software in Regulation (EU)), MEDDEV (2.1/6 Guidelines on the qualification and classification of standalone software used in healthcare within the regulatory framework for medical devices), the manual on borderline and classification in the community regulatory framework for medical devices (July 2016, version 1.22 (05-2019) Court of Justice of the European Union) and IMDRF (International Medical Device Regulators Forum).

3 THE CLINICAL NEED

3.1 Context

Caring for a child in an emergency situation according to the European Resuscitation Council (ERC) guidelines (Maconochie et al., 2015) is very stressful for caregivers who must provide quality care as quickly as possible, while the prognosis is vital.

The severity of the child's condition is determined after analysis of his vital signs (heart rate, blood pressure, respiratory rate…), which depend on his age. The doses of medication to be administered in the emergency room are calculated according to the child's weight. The knowledge of the norms of the constants makes it possible to anticipate the child's decompensation and to prevent cardiac arrest. The latter is infrequent in pediatrics (10 to 15 times less frequent than in adults) and generates extreme stress. Care algorithms are available but the professionals of pediatric intensive care units only use these on a very punctual basis. Therefore, as soon as an exceptional

pathology occurs, they need to refer to the care protocols in order to avoid any errors. Nevertheless, rereading these protocols is time-consuming and this loss of time is deleterious in the patient's care.

The risk of medication errors by members of the paramedical and medical team is high during patient's care due to the stressful nature of the situation, the short period of time in which the calculations must be performed, the lack of experience of some caregivers and the diversity of the patient population (in terms of age, weight and pathology). Medication errors are made at different stages of patient care: when estimating the child's weight, determining its indication, consulting the recommended dose, calculating, making the prescription, preparing and administering it (Hoyle et al., 2012; Kaufmann et al., 2012; Siebert et al., 2019).

The idea of developing a software tool to free oneself from human error by ensuring the calculation of constants and doses of emergency medication but also to accompany the healthcare team in different emergency situations emerged from a nurse of the pediatric intensive care unit of the Besançon University Hospital. The interest of the software tool lies in the fact that it could provide better care for the child and a better quality of life at work.

3.2 The Software Tool

The innovation of the software lies in the possibility of having all the information necessary for pediatric intensive care unit synthesized in an easy-to-use software. The specifications were developed by ISIFC students and the code by Shine Group. The software has been built in full collaboration and understanding of the caregiver's practices and needs. It is intended to be used on a tablet and is considered as a stand-alone software. It offers 4 main functions:

- a **calculation of the standards of physiological constants and medication dosages** used in the care of an emergency situation based on the child's weight and age. It also specifies the amount of energy to be delivered with the defibrillator in the event of an abnormal heart rhythm.

- **assistance during resuscitation** in emergency situations such as cardiac arrest. The software provides real-time details of the "defibrillatable" or "non-defibrillatable" cardiac arrest care algorithm, with the ability to switch between the two depending on the situation. It indicates the treatment administration times and informs the team leader of the course of action to be taken. When a treatment must be administered, a visual and audible signal appears on the tablet. This way, the care team knows

how long the child has been in cardiac arrest, how long resuscitation has been underway and at what time the treatments were administered. This quick access to the application requires neither reading nor assimilation of the algorithm. The delays between each step of the care are very precise. An integrated stopwatch makes it possible to respect them.

- a **guidance in the treatment procedures** is provided to the team during various emergency situations. The size of the MDs to be used according to the weight or age of the child or videos explaining the gestures can also be consulted.

- a precise **traceability** is carried out as soon as a medicine or a gesture is performed. All procedures are listed in a care sheet that can then be printed and integrated into the patient file.

This information is obtained in a reliable, quick and simple way based only on the age and weight of the child provided by the user. If the patient's weight is not known, it will be calculated theoretically according to the recommendations of the ERC. The software has 7 tabs: vital constants, defibrillatable cardiac arrest, non-defibrillatable cardiac arrest, admission to emergency room, desaturation, supra-ventricular tachycardia and actions (Figure 1). Inserts at the top of the screen prompt to enter the patient's age in months or years and weight if known. There is also an insert with a stopwatch that starts automatically at the beginning of a cardiac arrest care but it is possible to start, stop and reset the stopwatch. Buttons corresponding to the medical procedures performed or medications administered are located at the left of the screen.
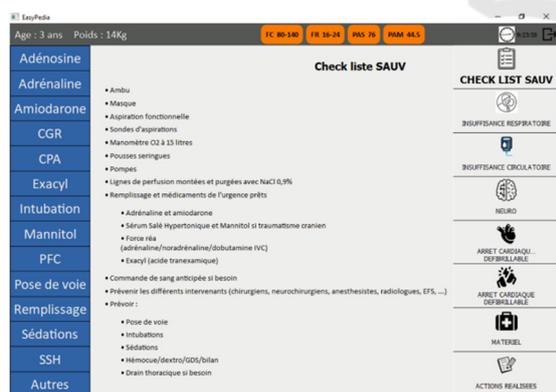
Figure 1: Software homepage.

The information provided has been reduced to the bare minimum so as not to overload the user with information. All the recommendations indicated are those issued by European learned societies such as the ERC. Updates are possible and have already been considered with Shine Group in order to adapt it to

the evolution of the ERC recommendations. The language of the software may also need to be modified to adapt to different computer media or because of technological developments.

This software is an **active MD** allowing a calculation of the values of theoretical physiological constants according to patient's age and weight. The physician will then be able to make an integration and request a quantity of medication to be administered. According to the MDR 2017/745, this software is intended to **provide information which is used to take decisions with diagnosis or therapeutic purposes and may present an immediate danger to the patient's life, such as resulting in death**. It is therefore classified as **Class III**. This class has been determined using rule 11 of Chapter III of Annex VIII of the MDR 2017/745.

Preliminary tests have been carried out with the software using 50 fictitious patient age/weight combinations in order to calculate constants and dosages. Any deviation from the theory was considered as an error. The software made no calculation errors, while the caregivers made between 1 and 11. It takes less time than caregivers to perform calculations (time saving up to 10 min and 29 s).

The proof of concept completed with this first version of the software, the next step was to design a clinical trial in order to acquire a first set of clinical data that will:

- considerate real life data in order to comfort the need and qualify/quantify the errors to avoid;
- allow upgrading the software that will be introduced onto professional's view.

This will participate in building the CE mark file.

3.3 Design of the Clinical Investigation

A regulatory manufacturer responsible for the long and cumbersome procedure for obtaining the CE mark has not yet been identified. As the ambition of the project team is to quickly assess the interest of the software in the care of the child in vital distress, a pilot prospective, descriptive, comparative, and monocentric study has been designed.

The study entitled "Care of the child in vital distress: evaluation of paramedical uses and benefits of a software tool" comprises two phases, a first in real situation then a second in simulation. It will allow to obtain precise information on the errors encountered in the care of pediatric emergencies. The impact of the software on the reduction of errors in simulation, both on dose calculations and on the care of cardiac arrest will also be evaluated. It is planned to last 30-months (in real conditions and in simulation).

3.3.1 Phase 1: Non-interventional Study

This first part of the study will allow to describe precisely the number and type of errors in real life situations when treating a patient in vital distress aged 0 to 15 years old in the pediatric intensive care unit of the Besançon University Hospital. Errors will be classified according to their degree of seriousness, i.e. whether or not they endanger the child. They will be collected by a dedicated observer trained to identify these errors, i.e. a caregiver in addition to the usual team and who will not intervene in the care. Fifteen patients will be included over a period of 1 year.

3.3.2 Phase 2: High-fidelity Simulation Tests

Simulation is an active and innovative pedagogical method based on experiential learning and reflective practice that allows to maintain theoretical and practical skills but also to develop cohesion between team members (Brock et al., 2013). The purpose of health simulation is to recreate scenarios or technical learning in a realistic environment with, as a double objective, the immediate feedback of experience and assessment of prior learning. These are clinical and/or professional situations, simple or complex, usual or exceptional, which are used as a support for the construction of the scenarios. High-fidelity simulation provides healthcare professionals with a sophisticated mannequin that reproduces patient's physiological reactions to train how to react to critical situations as close to reality as possible. This type of simulation will be used in our study to evaluate the effects of using our new software on the number and type of care errors, non-technical skills, anxiety and the feeling of self-efficacy of caregivers faced with a scenario unfolding in a life-threatening emergency.

Ten expert teams of caregivers in caring for the child in vital distress (intensive care units and specialist mobile emergency units) and 10 non-expert teams (pediatric medicine and pediatric emergencies) will take part in the simulation tests over a period of 4 months. Each team will be composed of 3 caregivers (a senior physician and two paramedical staff). The expert and non-expert caregivers will be randomly assigned to one of the 10 expert and non-expert teams. For each team, 2 simulation sessions will be scheduled 2 months apart, one without the help of the software and one with the help of the software (order determined by drawing lots).

A software training session will precede the first simulation session and then each session will be divided into two distinct phases: the briefing will specify the framework of the session and its objectives and then the scenario development. Scenarios will be built by physicians and paramedics with extensive experience in simulation and not taking part in the tests. During both sessions, teams will be asked to care a cardiac arrest according to 2 scenarios of comparable difficulty but nevertheless different in order to avoid their memorization. The scenarios will be guided by the trainer who will adapt their evolution according to the learner's reactions. Caregivers will be asked not to share the scenarios so as not to bias the sessions for future caregivers. A single debriefing will take place after the second simulation session and will follow the PEARLS (Promoting Excellence And Reflective Learning in Simulation) framework to analyze the practices and make a synthesis (Eppich & Cheng, 2015).

For each session, an external observer will collect care errors and evaluate the effectiveness of teamwork by determination of the TEAM (Team Emergency Assessment Measure) score (Cooper et al., 2010). After each session, an evaluation of the anxiety and feeling of self-efficacy of caregivers will be carried out using visual analog scales.

In order to initiate this clinical study, funding is required. The clinical study protocol has been submitted in September 2020 to the "APPARA" (Appel à Projets PARAmédical) call proposed by the interregional clinical research and innovation grouping (GIRCI-Est, France) whose objective is to support projects aimed at validating innovative nursing or paramedical care methods. Funding has been obtained and will allow this non-interventional phase coupled with simulation tests to start in the first months of 2021. It is a necessary preliminary step to the design of a larger, controlled, randomized, multi-center trial involving more patients and caregivers.

3.4 Usability and End-users

Usability is the degree to which a product can be used by identified users, to achieve defined goals effectively, efficiency and satisfaction, in a specified context of use. This notion of usability is important to consider in the healthcare field because non-usable tools can waste time, lead to errors in use or even not be used, which can create a risk for both patients and professionals. In order to prevent these errors, the MDR 2017/745 integrates this notion in the demonstration of conformity, which includes reference to harmonized standards with one dedicated to the usability process (International Electrotechnical Commission 62366:2015, International Organization for Standardization or

ISO, 2015). The standard is based on two types user interface evaluation:

- formative evaluation conducted throughout the user interface design and development process. The aim is to validate during development that the user interface is usable in a correct way. This evaluation will continuously feed the design input data, it is likely to modify the user interface specification by revealing new possible user errors, new dangerous situations…
- summative evaluation conducted after the device's design has been completed, it provides tangible evidence of the safe use of the device.

Recently it has become far more explicit that directly involving many different types of users, and particularly end-users, at all stages of MD technology and assessment process is crucial. The position of end-users in relation to devices allows them to better judge the performance of the MD concerned, and thus isolate problems encountered in its use. End-users must be involved throughout the design cycle to understand and specify the context in which the device will be used, to specify user and organizational requirements, to produce design solutions, and finally to evaluate the solutions (Shah & Robinson, 2006).

The need for software to help calculate doses and care cardiac arrest in pediatric intensive care units came directly from an end-user, a nurse who regularly encounters errors in the care of the child in vital distress. A work was carried out upstream of the software design to specify its conditions of use: the medical indication (vital distress), the target patient population (children of 0 to 15 years old), the environment of use (emergency room), the user profile (nurse or resident)... The identification of risks related to use (possible errors of use, dangerous situations…), was conducted following the indications of the NF EN ISO 14971 standard (ISO, 2007), relating to the "application of risk management to MDs". Several risks of different levels of seriousness have been identified, such as a typing error, a software failure or a bad calculation formula following an update. This part was accomplished thanks to the ISIFC regulatory and clinical assistance.

A formative evaluation of the software was initiated during preliminary tests of calculations by end-users. The scenarios proposed in the first clinical investigation (described in paragraph 3.3.2) will contribute to this type of evaluation. The ergonomics and organization of the software may need to evolve according to user feedback and in order to adapt to different media: computer, tablet, laptop... Some information in tabs or in the form of tabs may be added or removed to best meet user expectations and ERC recommendations. Similarly, calculation formulas and support algorithms may be modified. The aesthetics of the MD can also be reworked if necessary. This type of evaluation will be pursued throughout the development of the software in particular through clinical trials. The summative evaluation will be carried out on the final version of the software.

4 NEXT CLINICAL VALIDATION STEPS

4.1 Regulatory Approvals

Regulatory proceedings will be initiated in order to start the study in the first months of 2021. This non-interventional study corresponds to a research involving human subjects with minimal risks and constraints (category 3 according to the Jardé law n°2012-300). Thus, a positive agreement from an ethical committee is required to begin the study. The study falls within the scope of the MR003 reference methodology and therefore will not require a request for authorization from the Commission Nationale de l'Informatique et des Libertés for the processing of data from the research.

The study will be registered in the international official web platform ClinicalTrials.gov. On a product point of view, the software will need to be presented to the French ANSM (Agence Nationale de Sécurité des Médicaments et des produits de santé) authority and formalized onto an investigator brochure containing all the data available describing the software and proving a strong level of safety/efficacy in its technical claims.

4.2 Interventional Clinical Study

If the results of the pilot study are consistent with a decrease in errors as a result of staff assistance with the software, the value of the software in the care of the child in vital distress will be assessed in a larger study in real conditions care. Technical regulatory file for assessing CE mark will need also to be strongly constituted and advanced.

The study population will be expanded through the participation of several hospital centers. The patients themselves or the participating centers would be randomly assigned to one of the two following groups: an experimental group with software support and a control group with routinely patient's care in the department. The main objective this time would be to compare the number and type of errors

committed with and without software. Some secondary objectives of the pilot study, i.e. caregiver anxiety and feeling of self-efficacy, could be assessed under real-life care conditions. Other secondary objectives would be added, such as the number of deaths or objectives related to usability.

5 NEXT STEPS FOR BRINGING THE FINAL SOFTWARE TO MARKET

5.1 Development Stages of High-risk MD Software

Bringing a high-risk medical device to market is a highly regulated, complex and time-consuming process, requiring numerous technical studies in order to demonstrate the conformity of the device to established safety standards by the European Commission. Concerning our project, the stages carried out and to come are described by the lifecycle of our software presented in Figure 2.
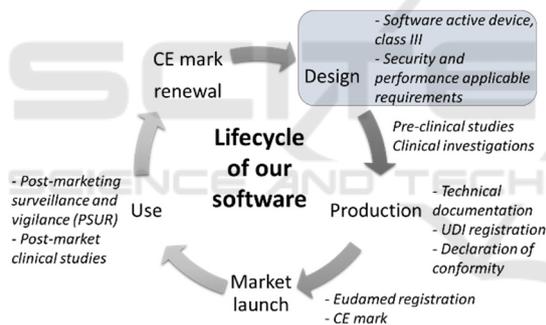
Figure 2: Lifecycle of our software in accordance with the MDR 2017/745 (UDI: Unique Device Identifier; PSUR: Periodic Safety Update Report).

Before the market launch of a medical device, it is imperative to define its family and its class according to the regulations in force. The classification will determine the regulatory requirements applicable to ensure that all of those for placing on the market and conformity assessment have been fulfilled. In our case, the software is an active device of class III, which imposes compliance with the strictest regulatory requirements in terms of safety and performance.

This step of design is followed by the clinical evaluation composed of pre-clinical studies and clinical investigations in the case of a high-risk device. Our software is currently ready to start this phase but regulatory approvals are still needed.

A complete technical documentation will then be needed with the obligation to register an UDI (Unique Device Identifier) which improve the security of devices by a better traceability. The completion of the assessments will be marked by the declaration of conformity to the applicable regulatory requirements.

The market launch will be preceded by registration of the software in the new Eudamed European database always with a view to improving traceability and transparency, but above all by obtaining the CE mark. For high-risk MDs, the intervention of a notified body chosen among those appearing on the list of the European Commission will be necessary to assess conformity of the device according to the requirements of the MDR 2017/745 in order to obtain the CE mark.

Once the device is marketed, a surveillance system will be set up to collect, record and analyze data on the quality, performance and safety of the device, during its entire life span. For our Class III device, the manufacturer will draw up and annually make available to the notified body a Periodic Safety Update Report (PSUR), summarizing the results of the analysis of the data from the post-market surveillance system. It will aim to indicate that the risk-benefit ratio is always positive in post-market. This report must also be recorded in the Eudamed platform. Post-market clinical studies may be required to collect these performance and safety data.

5.2 Focus on Clinical Evaluation of High-risk MD Software

Clinical evaluation is a systematic and planned process to generate, collect, analyze and evaluate clinical data on a device on an ongoing basis in order to verify the safety and performance of the device, including clinical benefits, when used as intended by the manufacturer. This evidence complements the pre-clinical evaluation data obtained through laboratory testing and other verification and validation results.

Different types of clinical evaluation are possible: analyze data from the literature, compile data specific to the device, use data from an already marketed equivalent device, carry out a clinical investigation involving the device to obtain unpublished data. The use of equivalence is the simplest solution and is reserved for non-innovative devices. Annex XIV (3) of MDR specifies 3 characteristics that manufacturers must consider when demonstrating equivalence: technical (e.g. conditions of use, properties and algorithms), biological (if applicable for software) and clinical (e.g. clinical condition or purpose,

population and performance). Clinical investigation of software rest on content validity (context of use and concept of interest), construct validity, reliability and sensitivity to change. It is the most difficult path because it is long, risky and expensive. It is nevertheless mandatory for all class III and implantable MDs (Chapter VI, art 61 MDR), including our software, except in special cases introduced in the MDR 2017/745. For example, equivalence can be applied if both manufacturers have concluded an agreement allowing full and permanent access to the technical documents necessary to achieve equivalence, which may severely limit the use of equivalence for clinical evaluations. Equivalence can also be used within the same group or the same manufacturer for range upgrades.

Conformity assessments will require more qualitative clinical evidence and data to demonstrate the performance and safety of a device, the evaluation of adverse side effects and the acceptability of the benefit-risk ratio than ever before. Indeed, notified bodies will be uncompromising in terms of the quality and quantity of clinical data collected.

New documents will be requested for Class III MDs including our software. The Summary of Safety and Clinical Performance Characteristics (SSCP), and the PSUR previously described in paragraph 5.1. The SSCP is particularly useful to fight against the lack of transparency since it will be published to the public on the Eudamed platform. Moreover, the clinical evaluation plan will be submitted to a European expert group for decision upstream of the clinical evaluation.

In conclusion, clinical evaluation is a continuous process initiated for device certification and then constantly updated with post-marketing surveillance.

6 CONCLUSION

We proposed to develop a MD software designed to help paediatric drug preparation and care of cardiac arrest during resuscitation with the aim to significantly reduce the occurrence of medication errors, anxiety and improve feeling of self-efficacy of caregivers. Coupled with a feasibility and usability study, the results of the pilot study will be used to build a pivotal study that will demonstrate the real interest of our software in the care of the child in vital distress. It could have the potential to change paediatric clinical practice in the area of emergency medicine.

However, many steps remain to be taken in order to market a product that complies with the regulations, but our work presented the interest of building the evaluations in parallel to the product development (technical, but also regulatory, business, market point of view), each one feeding the other one.

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