DNV·GL

Clinical Decision Support Software

Regulatory landscape in Europe from May 26th 2020

2020

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DISCLAIMER AND ABBREVIATIONS

DISCLAIMER

The objective of this white paper is to provide manufacturers of clinical decision support (CDS) software and health institutions using in-house developed CDS software with a high-level regulatory overview of the new European regulations. The scope of this work is limited to stand-alone software. Software which forms an integral part or component of a medical device, but is not considered CDS, is not discussed in this paper, and the interested reader should refer to the specific requirements in the new medical device regulations. The general recommendations published in this white paper are intended as a resource for health institutions and manufacturers in the management of regulatory requirements of CDS software in Europe and do not represent legal advice of any kind. The clinical use of CDS software in the European Economic Area (EEA) requires compliance to applicable regulatory requirements. The recommendations formulated in this paper are in line with the state of knowledge at the time it was published. Future amendments to the regulations, guidelines or other regulatory documents may impact the compliance management of CDS software. DNV GL encourages manufacturers and legal organizations developing CDS software for medical use to seek appropriate knowledge and support for their conformity processes.

ABBREVIATIONS

CDS	Clinical Decision Support
CE	Conformité Européenne
EEA	European Economic Area
IMDRF	International Medical Device Regulators Forum
IVD	In Vitro Diagnostic
IVDR	In Vitro Diagnostic (medical device) Regulation
MDCG	Medical Device Coordination Group
MDD	Medical Device Directive

MDR	Medical Device Regulation
MDSW	Medical Device SoftWare (MDCG definition)
MR/MRI	Magnetic Resonance / Magnetic Resonance Imaging
NGS	Next Generation Sequencing
QMS	Quality Management System
RUO	Research Use Only
SaMD	Software as a Medical Device
UI	User Interface

EXECUTIVE SUMMARY

Clinical Decision Support (CDS) software is one of the fastest growing fields in healthcare, in phase with the global digitalization of healthcare.

CDS software is transforming healthcare delivery with the promise of better workflow efficiency and improved patient safety, and is enabling new knowledge, e.g. in genomic medicine, to be integrated into clinical practice, providing the potential for improved patient outcomes.

CDS software needs to be safe and efficient, conforming to the standards required for other medical devices or pharmaceuticals used in patients care.

In response to previous patient safety breaches and technology progress since the first issue of the former medical device directives, the European Union has recently released a new medical device regulation (MDR, applicable from May 26th 2020) and in vitro diagnostic medical device regulation (IVDR, applicable from May 26th 2022). This update impacts the regulation of CDS software. In general, more stringent requirements apply to software regulated by MDR or IVDR compared with the previous directive. Clinical evaluation and post-market surveillance throughout the device lifecycle are also strengthened in the new regulations.

Health institutions developing their own CDS software, designated as 'in-house' devices in the regulations, must also fulfil specific requirements such as demonstrating conformity to basic safety and performance requirements. This can be challenging for many health institutions which are not familiar with medical device regulatory compliance activities. Manufacturers and health institutions have expressed their concerns related to the new regulation of software in healthcare. As the result of an activity in the BigMed project, this paper attempts to provide an overview of the ruling principles for the regulation of CDS software in Europe, and some general recommendations for manufacturers and health institutions. We also discuss potential effects of this regulatory update for the industry as well as for healthcare providers.

INTRODUCTION

It is widely acknowledged that information technologies are transforming society, and healthcare is no exception. Clinicians around the world rely more and more on digital systems to produce, store, retrieve and analyse patient health data. The amount of collected data expands continually, which can create new insights to improve patient care. However, the amount of health data can also be overwhelming for clinicians. Clinical decision support (CDS) software can address this challenge by providing clinicians efficient ways to retrieve, filter and/or analyse patient data and assist them in the decision-making process. The ability of CDS software to integrate personal patient data with clinical guidelines, larger patient databases, or any other relevant information, unlocks new possibilities to provide safer and improved care.

Safety and quality are paramount in healthcare. Assurances must be in place to ensure that CDS software will not put patients at risk. The medical device industry, akin to pharmaceutical, is one of the most regulated sectors worldwide. In Europe, manufacturers must demonstrate that their device(s) satisfy regulatory requirements before CE marking can be applied and market access granted. Regulatory requirements are tailored to both the intended use of the device (i.e. its medical purpose) and patients' safety risk. In May 2017, the European Commission released new regulations, replacing previous directives, to come into effect in May 2020 for medical devices (Medical Device Regulation, MDR) and May 2022 for in vitro diagnostic medical devices (In Vitro Diagnostic Medical Device Regulation, IVDR) respectively [1, 2]. Among the most significant changes is the requalification of software (referred interchangeably in the literature as software as a medical device – SaMD, or medical device software - MDSW[1]), which includes CDS software. Therefore, manufacturers of CDS software need to integrate these new requirements to demonstrate conformity of their products and gain access to the market. In addition to this, hospitals or other health institutions will also have to demonstrate conformity of their in-house developed CDS software.

This white paper was prepared through a collaboration between Oslo University Hospital and DNV GL within the Norwegian national research initiative project BigMed (www.bigmed.no). It addresses concerns raised by hospitals partnering in BigMed and other hospitals about the implementation of MDR/IVDR in Norway [3]. As a result, this paper aims to improve the regulatory awareness for manufacturers and health institutions which require guidance on conformity management of CDS software as medical device or in vitro diagnostic medical device. The paper presents an overview of relevant requirements and guidance documents. Finally, it highlights some of the challenges that manufacturers and health institutions may encounter, and it provides some general recommendations for compliance management.

[1] SaMD is a widely used terminology used by US Food and Drug Administration, the International Medical Device Regulators Forum (IMDRF) or in the literature, whereby MDSW is the terminology used in this paper and by the Medical Device Coordination Group in Europe.

THE NEED FOR CLINICAL DECISION SUPPORT SOFTWARE

TRENDS

Health professionals rely on evidence and experience to make appropriate clinical decisions for their patients. Digitalization of healthcare has expanded the amount of health information relevant for a single patient beyond manageable levels, effectively ensuring that a normal single person is unable to process this large amount of data. Combined with the growing need for healthcare, patients' increasing expectations of speed of delivery, and the pressure on currently available resources; major efficiency improvements of care delivery processes while preserving patient safety are required.

As a response, CDS software is being widely adopted, with the promise of better and safer care. CDS software can integrate guidelines, clinical pathways, evidence-based practice, healthcare databases and patient information to provide medical evidence and recommendations to guide therapy decisions for a specific patient. CDS software can for instance provide diagnostic support, alerts and reminders, patient management software and workflow assistance. In some cases, CDS software may be considered as medical devices (i.e. medical device software). Examples below illustrate the variety of CDS software.

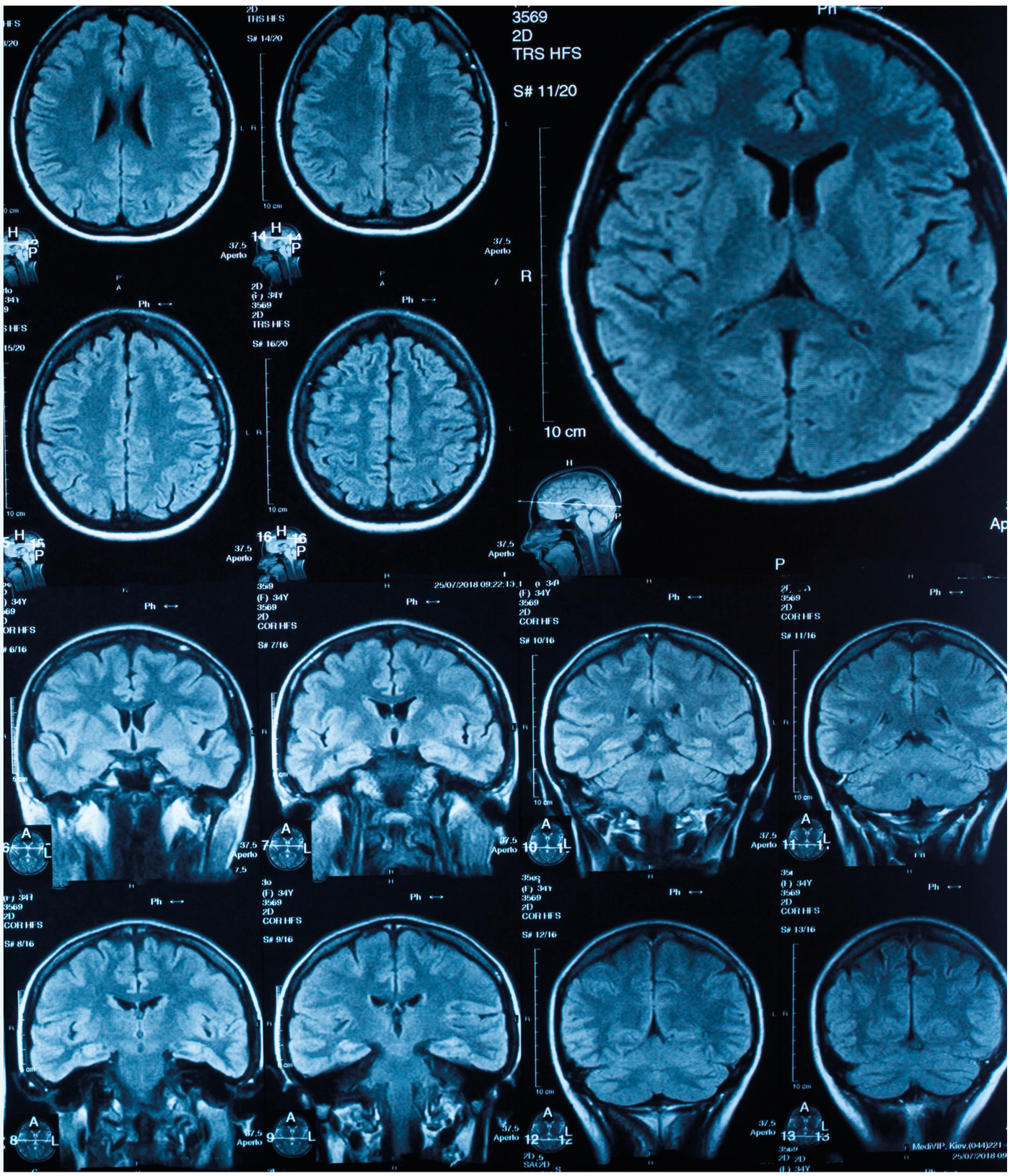
1

Example: Radiology

A CDS software for comparing patient brain MR images with patient and control participant image database to provide indication of early onset neurodegenerative disease.

Clinical studies show that morphometric measurements of the brain (e.g. grey matter thickness in specific areas of the brain), are predictors of early onset neurodegenerative diseases such as Parkinson's or Alzheimer's [4-8]. However, subtle morphometric changes are hardly detectable from the traditional radiological examination of a single patient's MR images. The CDS software in this example normalises patients' 3D MRI datasets (after anonymization of the metadata and "defacing"[2]) and compares the voxel-base morphometry measurements of each patient to a large database of patients and control subjects in order to compute a probability index for Parkinson's and Alzheimer's disease. The clinician uses this information in conjunction with clinical data of the patient to decide on the treatment or follow-up strategy.

[2] Defacing is a process that modify pixel intensity in the facial area to remove the possibility to visualize facial anatomy when using 3D model rendering of a dataset. Hence, a 3D dataset cannot any longer display a facial reconstruction of the patient after defacing.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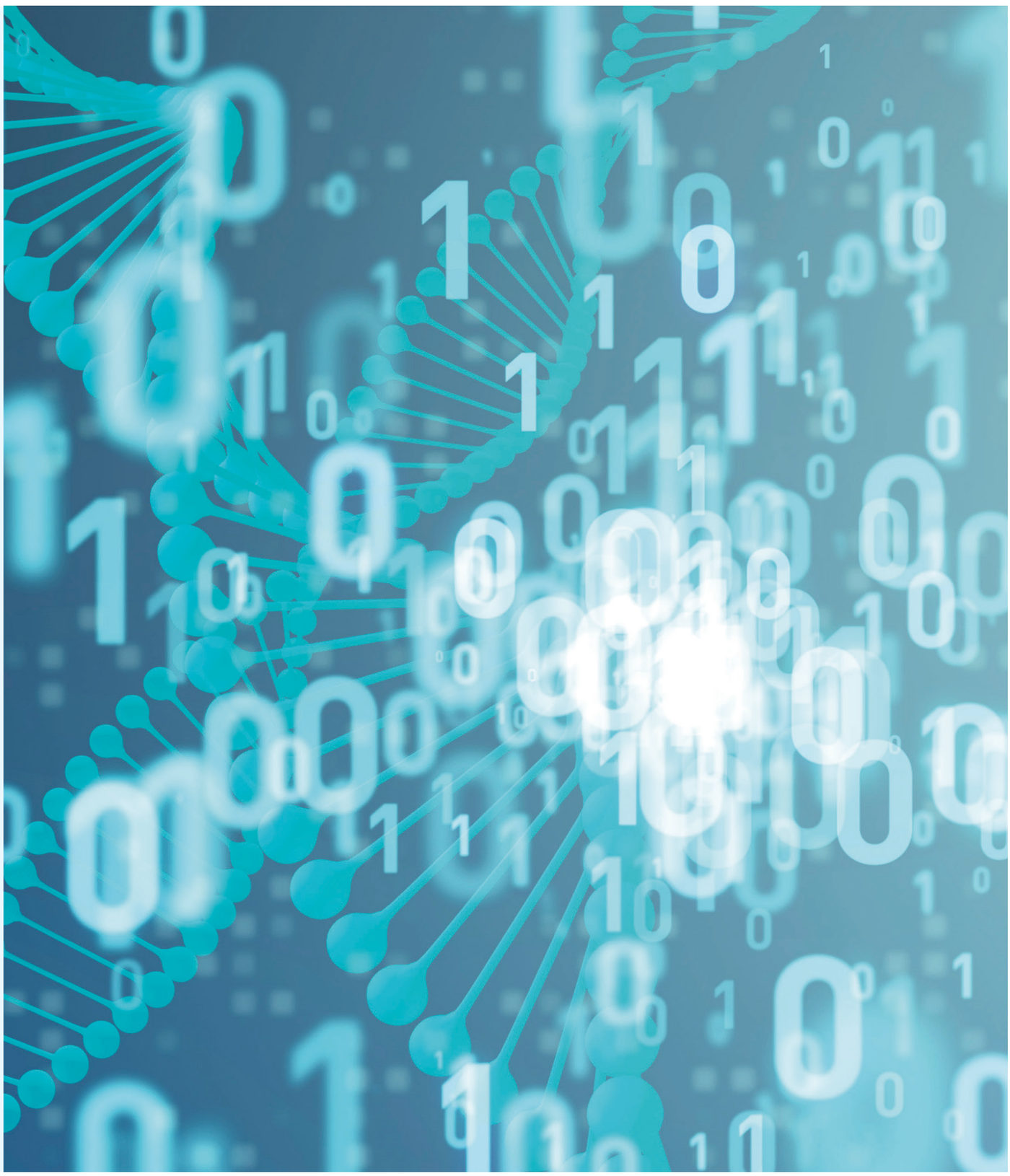
Example: Next Generation Sequencing

A CDS software for prioritization of genetic variants in NGS-based diagnostics of patients with a rare inherited disease.

Next-generation sequencing is increasingly used to identify the genetic cause of rare inherited diseases [9], but these diagnostics are conducted with a complex laboratory and IT infrastructure. NGS-based diagnostics are performed through a series of steps: DNA is typically extracted from solid tissue biopsies or blood samples, NGS libraries are prepared with methods appropriate for the diagnostic, and samples are sequenced, generating millions or billions of short reads. These are quality-controlled, aligned to reference genomes, and variants unique to the sample are called through a series of complex bioinformatic steps. Every individual, whether healthy or not, has millions of unique genetic variants, most of which have no association with human disease [10]. Hospitals regularly perform complex workflows consisting of both human-guided and automated data processing to prioritize and classify these variants, with the goal of identifying actionable disease-causing variants [10, 11]. In this context, the CDS software uses data from internal and external scientific or research databases, predictive bioinformatics tools, and information about the patient (from the EHR or other sources) to rank these millions of variants by their likelihood of contributing to disease. Clinicians interact directly with the software in an iterative, joint decision-making process, where the CDS functions annotate information onto variants and determine which variants should be presented for clinician review. The clinician uses this information to diagnose the patient and determine appropriate treatment modality.



REGULATORY REQUIREMENTS IN EUROPE

THE NEW REGULATION ON MEDICAL DEVICES AND IN VITRO DIAGNOSTIC MEDICAL DEVICES

In the interest of improving patient safety, and as a response to rapid technology innovation and the globalization of medical device manufacturing processes, medical device regulations are becoming more stringent. In order to promote the European single market and adapt the regulatory framework to the evolution of the medical device industry, the European Commission released new regulations; MDR and IVDR (Regulations (EU) 2017/745 and 2017/746 respectively, published in May 2017) [1, 2]. These replace the former Council Directives 93/42/EEC on medical devices (MDD), 90/385/EEC on active implantable medical devices, and 98/78/EC on in vitro diagnostic medical devices [12-14]. Unlike directives that are translated into the national laws of Member States, regulations apply "as is" (with a few exceptions) in the whole European Union, and associated Member States (including Norway). To facilitate the transition, former directives co-exist with the new regulation during a transition period that ends on May 26th 2020, for medical devices and May 26th 2022, for in vitro diagnostic medical devices. Among the most relevant updates for the qualification of CDS software are the inclusion of the words 'prediction' and 'prognosis' of disease into the definition of a medical device, which extends the range of devices covered by MDR compared to the former MDD definition. Moreover, software is generally requalified to higher risk devices in the new regulations. Qualification and classification criteria for CDS software are reviewed more in detail in following sections.

Manufacturers targeting the European market shall ensure that their devices conform to the applicable regulatory framework prior to CE marking (Conformité Européenne) and market access. The applicability of medical device regulations is governed by the 'intended purpose' of the device. Devices in which the intended purpose is covered by the definition provided in article 2 (chap.1) of MDR or IVDR are governed by these regulations [1, 2] (see MDR and IVDR medical device definitions in textbox pages 16 and 17).

In other words, defining the intended purpose of the device is essential as it impacts on the compliance efforts that the manufacturer needs to provide.

For instance, a software used to monitor heart rate for fitness purposes falls outside the purpose of a medical device, and therefore will not be regulated by MDR or IVDR. However, a software intended to monitor heart rate to predict heart failure would be considered as a medical device.

WHEN IS CDS SOFTWARE REGULATED AS A (IVD) MEDICAL DEVICE?

As a rule of thumb, software that only performs library functions, such as retrieval or archiving of information, are not considered a medical

Qualification precedence from the European court of justice

In practice, the qualification of software may not be obvious. This is illustrated by a previous case of the European court of justice, which opposed the *"syndicat national de l'industrie des technologies médicales"* (snitem) and Philips France, against the French prime minister and the minister of social affairs and health, judged in 2017 [16]. Snitem and Philips France contested the certification obligation for their drug prescription assistance and dispensation assistance software, stated in French legislation [17]. French regulatory requirements were alleged to be more stringent than the medical device directive (MDD), thus breaking European single market principle [12]. The software concerned by this case was a drug prescription software for resuscitation and anaesthesia, which intended to provide doctors information about the correct prescription of drugs, possible contraindications, dosage guidance and possible drug interactions.

The court reviewed in its judgement the definitions provided in the European directives. In the presented case, *"[…] software, of which at least one of the functions makes it possible to use patient-specific data for the purposes, inter alia, of detecting contraindications, drug excessive doses, is, in respect of that function, a medical device […]"* [16]. The court concluded that the software was a medical device in view of European laws and was deemed to be regulated as such as dictated by French legislation.

Medical device definition MDR article 2(1)

`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 disabilty,*
- *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.
[...];

device [15]. However, software that performs analysis, creates and/or modifies information for a medical purpose is likely to be qualified as a medical device.

Considering the requalification of software to higher risk categories in the new regulations, it is likely that software which intends to provide information that cannot be realistically verified by the user, and which impacts on the 'diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease' of a single patient, will be considered as a medical device, and regulated as such.

CRITERIA FOR MDR OR IVDR QUALIFICATION

Former directives and associated guidance documents [12, 14, 18] indicated that CDS software was generally classified as a 'medical device', except when used together with an in vitro diagnostic device for which IVD Directive applied [14]. The new regulation adopts a similar approach, where article 2(1) of MDR and IVDR provide the definition of a medical device and an in vitro medical device respectively, explicitly including software. The two definitions coexist and article 1(4) in the preamble of IVDR provides the conditions for when MDR or IVDR definitions apply for a device:

"Any device which, when placed on the market or put into service, incorporates, as an integral part, a medical device as defined in point 1 of Article 2 of Regulation (EU) 2017/745 shall be governed by that Regulation. The requirements of this Regulation shall apply to the in vitro diagnostic medical device part."

In other words, MDR article 2(1) provides the governing definition of a medical device and IVDR only applies to the IVD (part of the) device.

Still, it can be challenging to know if a CDS software falls under the definition of MDR or IVDR. Indeed, the MDR article 2(1) definition encompasses devices used to "*predict or prognose treatment or alleviation of a disease*", also by "*means of in vitro examination*". The IVDR definition covers devices, (i.e. software in the context of this paper) "*intended to be used in vitro for the examination of specimens […] solely or principally […] for the purpose of providing information […] concerning the predisposition to a medical condition or a disease, […] (or) to predict treatment response or reactions […]*". Although both MDR and IVDR definitions mention in vitro examination, the purpose of the device emerges as the selection criteria for the application of MDR or IVDR. To clarify the interpretation of the regulations, the Medical Device Coordination Group (MDCG) recently released a guidance document about the qualification and classification of medical device software in EU regulations [19].

In the context of this paper, the discussion regarding the qualification of CDS software is limited to stand-alone software, and cloud-based or remote software, where input and output data are transmitted through a network. Consequently, software which is an integral part of another medical device or IVD medical device is not considered hereafter. Specific requirements apply for components of medical devices (including software), which can be found in the regulations.

Any software that processes data (i.e. which is not limited to simple data repository or library function) to generate information for a medical purpose as defined by MDR or IVDR definitions, and for the benefit of patients, is deemed to be regulated by one of these regulations (see

In vitro medical device definition IVDR article 2(1)

`in vitro diagnostic medical device´means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

(a) concerning a physiological or pathological process or state;

(b) concerning congenital physical or mental impairments;

(c) concerning the presdisposition to a medical condition or a disease;

(d) to determine the safety and compatibility with potential recipients;

(e) to predict treatment response or reactions;

(f) to define or monitoring therapeutic measures.

Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices;

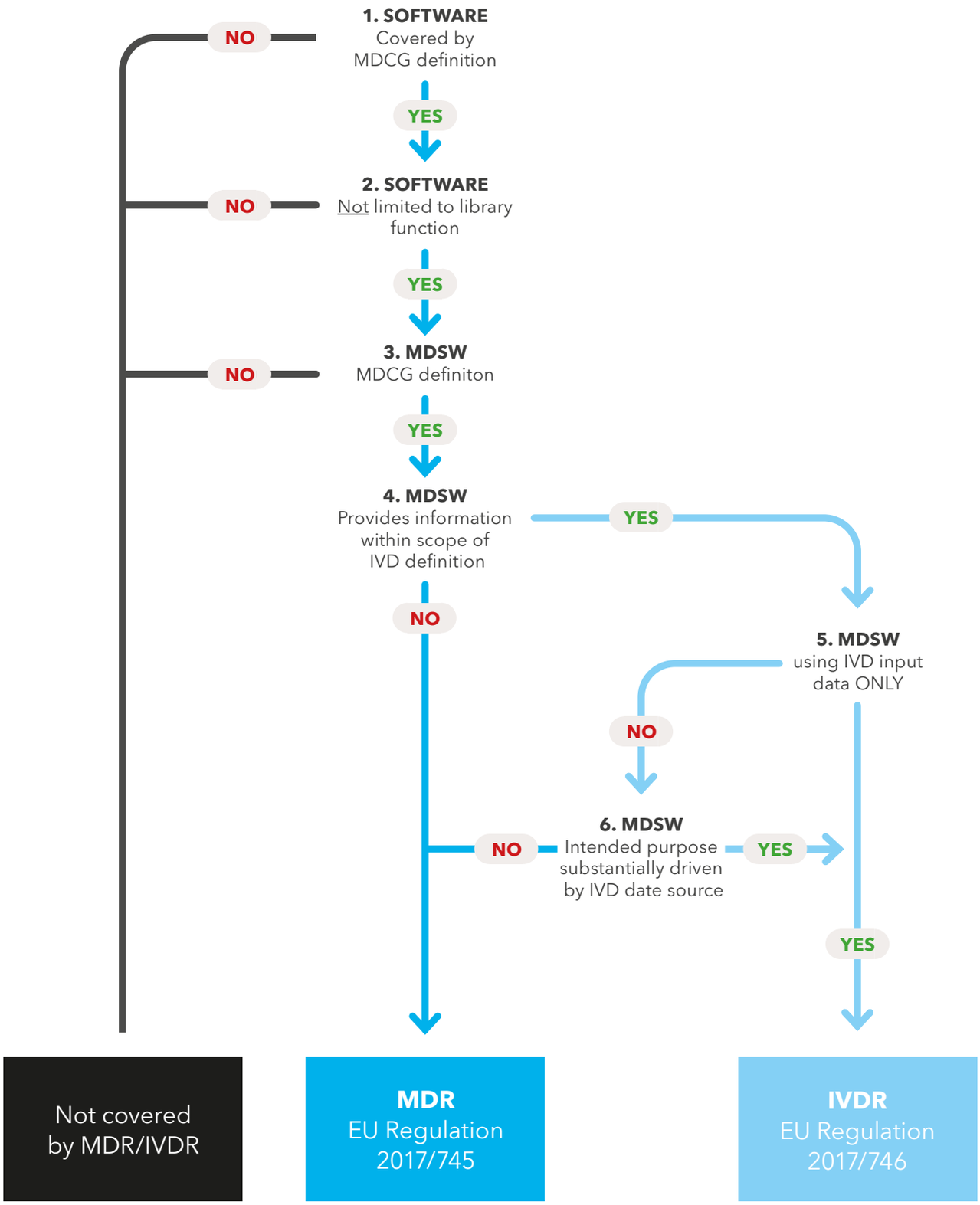


Figure 1: Decision tree to identify appropriate regulatory framework for CDS software (adapted to CDS software from the MDCG 2019-11 guidance [19]).

step 3 in Figure 1, pointing to a medical device software). Hereafter, specific criteria apply for the qualification of the software according to MDR or IVDR. To be regulated by IVDR, the software must fulfil the following conditions (illustrated in steps 4-6 in Figure 1):

i. it provides information within the scope of the IVD medical device definition (step 4) and

ii. it processes only data from IVD medical device (step 5).

iii. When the software processes both data from medical device and IVD medical device, it is regulated by IVDR when its intended purpose is 'substantially' driven by IVD data (step 6).

Some examples are provided in the MDCG guidance document [19]. However, borderline situations may arise for software using several data sources, and specific interpretation of the laws may be required to conclude on the application of either MDR or IVDR. The correct classification of a CDS software is of particular importance, as MDR will apply from May 26th 2020, whereas IVDR applies two years later.

With reference to the preamble of the regulation, it remains the responsibility of Member States to decide case-by-case if a device should be regulated by the provision of the medical device regulations. For borderline product classification, the Commission is entitled to consult the MDCG to deliberate in order to ensure consistent implementation of the law across the Union.

HEALTH INSTITUTIONS DEVELOPING OR USING IN-HOUSE CDS

The regulations allow health institutions to develop and use in-house devices, manufacture and/or modify devices under certain conditions. For clarity, a health institution is designated as "*an organisation the primary purpose of which is the care or treatment of patients or the promotion of public health*" (MDR article 2(36)). This includes hospitals, laboratories and public health institutes involved in healthcare delivery or supporting healthcare systems. Hospitals for instance frequently develop their own CDS software to address specific clinical needs that cannot be addressed with existing commercial software. This is especially true in genomics, where new and fast developing bioinformatics pipelines enable state-of-the-art diagnostics for rare disease or cancer patients. Bioinformatics pipelines, CDS software, or other products are sometimes designated as 'Research Use Only' in hospitals. In diagnostics, RUO devices are not covered by IVDR unless, *"in view of their characteristics, [they] are specifically intended by their manufacturer to be used for in vitro diagnostic examination"* (IVDR article 1(3)). However, health institutions using in-house software to treat or diagnose patients cannot claim exemption to MDR and IVDR. When an in-house CDS software is used clinically for its intended purpose, it is considered to be 'put into service', which in the language of the regulations means that the software, *"other than an investigational device [3] - or other than a device for performance study - has been made available to the final user as being ready for use on the Union market for the first time for its intended purpose"* (MDR article 2(29) – IVDR

[3] See MDR article 2 (44-48) for definitions.

MDR article 5(5)

With the exception of the relevant general safety and performance requirements set out in Annex I, the requirements of this Regulation shall not apply to devices, manufactured and used only within health institutions established in the Union, provided that all of the following conditions are met:

(a) the devices are not transferred to another legal entity,
(b) manufacture and use of the devices occur under appropriate quality management systems,
(c) the health institution justifies in its documentation that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an equivalent device available on the market,
(d) the health institution provides information upon request on the use of such devices to its competent authority, which shall include a justification of their manufacturing, modification and use;
(e) the health institution draws up a declaration which it shall make publicly available, including:
  i. the name and address of the manufacturing health institution;
  ii. the details necessary to identify the devices;
  iii. a declaration that the devices meet the general safety and performance requirements set out in Annex I to this Regulation and, where applicable, information on which requirements are not fully met with a reasoned justification therefor,
(f) the health institution draws up documentation that makes it possible to have an understanding of the manufacturing facility, the manufacturing process, the design and performance data of the devices, including the intended purpose, and that is sufficiently detailed to enable the competent authority to ascertain that the general safety and performance requirements set out in Annex I to this Regulation are met;
(g) the health institution takes all necessary measures to ensure that all devices are manufactured in accordance with the documentation referred to in point (f), and
(h) the health institution reviews experience gained from clinical use of the devices and takes all necessary corrective actions.

Member States may require that such health institutions submit to the competent authority any further relevant information about such devices which have been manufactured and used on their territory. Member States shall retain the right to restrict the manufacture and the use of any specific type of such devices and shall be permitted access to inspect the activities of the health institutions. This paragraph shall not apply to devices that are manufactured on an industrial scale.

article 2(22)). Hence, for in-house CDS software that qualifies as 'medical device' or 'in vitro medical device', health institutions shall comply with the conditions defined in article 5(5) of the regulations (see in textbox for MDR article 5(5)), as summarized also in a recently published factsheet issued by the European commission [20].

The regulator allows health institutions to "*modify and use devices 'on a non-industrial scale' when equivalent ones are not available on the market*" [20]. This requires health institutions to monitor the market to verify that no CE marked product is available for the intended purpose of the in-house device.

This also requires that "*health institutions should have appropriate quality management systems in place; compile documentation on the manufacturing process, the design and performance data of the devices, including their intended purpose; and review the experience gained from the clinical use of the devices and take all necessary corrective actions*" [20].

For health institutions using in-house CDS software within the conditions defined in MDR article 5(5) above, compliance to Annex I general safety and performance requirements needs to be documented accordingly. Health institutions which do not fulfil all the conditions laid down in article 5(5) are subjected to the same requirements as medical device manufacturers, meaning CE marking of the software is required.

In the case of an in-house developed software which qualifies as an IVD medical device, IVDR article 5(5) defines the regulatory obligations of health institutions instead of the MDR article 5(5) above. The most significant difference between MDR article 5(5) and IVDR article 5(5) is the conditional application of a requirement according to the device's class. For IVD medical device of class A, B, or C, health institutions are not required to draw up specific documentation about the manufacturing facility, manufacturing process etc. intended for scrutiny by the competent authority, whereby this clause applies for IVD class D devices and all other medical devices (IVDR article 5(5) recital (g) and MDR article 5(5) recital (f)). Member States may choose to enforce this documentation requirement individually for IVD medical devices class A, B and C, which may create regulatory disparity across the Union.

RISK CLASSIFICATION OF CDS SOFTWARE

As a general principle, regulatory requirements are in proportion with the risk class of the device. The International Medical Device Regulators Forum (IMDRF) have developed a general risk classification framework of software as a medical device based on the significance of the information the software provides and the criticality of the situation or condition of the patient. The significance of the information relates to the intended use of the software to 'treat or diagnose', 'drive clinical management' or 'inform clinical management' [21]. The regulations adopt a similar approach as IMDRF, where the consequence on the patient's health or condition indirectly resulting from the device's failure governs the classification of devices into rising risks categories following the rules outlined in Annexes VIII of MDR (class I, IIa, IIb, III) and IVDR (class A, B, C, D) respectively.

Rule 11 of MDR Annex VIII and rule 3 of IVDR Annex VIII are particularly relevant for CDS software. Rule 11 is a new rule introduced

with MDR (see text box), which specifically addresses the classification of software. Software can be classified as class I, IIa, IIb or III, as illustrated in Figure 2.

Rule 11 states that software which is *"intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as class IIa"* or higher. Following this definition, it may be difficult to know when a software is classified as Class I, if any in that case. IVDR rule 3 is relevant for CDS software regulated by this regulation. For instance, software used for human genetic testing is classified as a Class C device (IVDR Annex VIII rule 3 recital (i))

With the introduction of more stringent MDR/ IVDR, software is generally reclassified to higher risk category devices [19]. This requires more documentation and compliance efforts from software manufacturers, especially related to clinical evaluation, post-market surveillance and periodic safety update report throughout the product lifecycle. For example, manufacturers of software that provides predictive or prognostic information were not automatically regulated under the previous directives. This software will most likely have to undergo CE marking as a medium- or high- risk device according to these new regulations, while such software was not automatically regulated as a medical device by the previous directives.

MDR Annex VIII rule 11

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 detoriation 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 surgical intervention, in which case it is classified as class IIb.*

Software intended to monitor physiological processes is classified as class IIa, except if it is intended for monitoring of vital physiological parameters, where the nature of variations of those parameters is such that it could result in immediate danger to the patient, in which case it is classified as class IIb.

All other software is classified as class I.

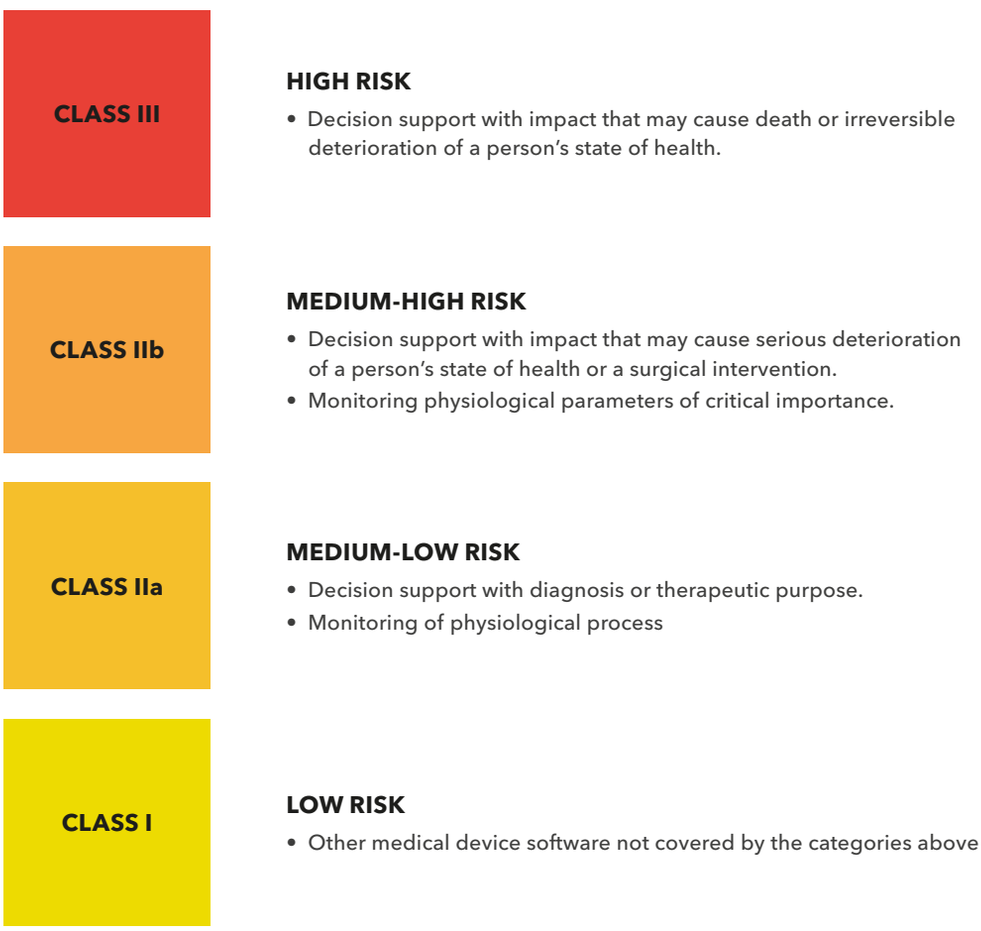


Figure 2: Illustration of the risk classification according to the information provided by the software, adapted from MDR Annex VIII rule 11.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DISCUSSION

CHALLENGES FOR HEALTHCARE ORGANIZATIONS

In response to a recent consultation letter from the Norwegian Ministry of Health and Care Services about the implementation of MDR/IVDR in the country, health institutions in Norway have expressed concerns that the new regulations may negatively impact their activity [3]. Hospitals and labs which provide NGS diagnostics often adapt or develop devices and software, which fall under the definition of 'in-house devices' under the new regulations. The concerns focus on the conditions to be met in article 5(5). For instance, recital (c) requires hospitals using in-house software to justify that their target patients' needs cannot be met by commercially available software on the market. This requirement will almost certainly require hospitals to monitor the market's offering in order to stay compliant. Moreover, manufacturers of CE marked software may claim unfair competition (i.e. in breach of the EU single market principle) in the case a health institution uses an in-house software without being compliant to article 5(5) requirements (i.e. when a similar CE marked software is available). Ultimately, manufacturers claiming violation of the regulations related to the use of an in-house software could file a legal complaint.

There is an urgent need for the MDCG or expert groups to address the challenges posed by open-source software, widely used in genomics and often developed in-house or at academic institutions. Neither MDR/IVDR nor MDCG document provide explicit information regarding the regulation of open-source software and liability issues [1, 2, 20]. Relating to recital (a) of article 5(5), would the distribution of open-source software be considered as the transfer of an in-house software to another legal entity? One could argue that any health institution using open-source code or software should ensure compliance to article 5(5). Ultimately, a commonly used open-source software (without commercially equivalent alternatives) would require each health institution to demonstrate compliance to in-house software requirements.

More generally, some hospitals indicated that regulatory obligations for in-house software will increase their operational costs, either by having to spend significant resources on compliance management or by having to purchase a more expensive commercial alternative [3]. One may say that this cost increase would eventually threaten service offerings for specific patient groups given current budget restrictions in healthcare. However, the aim of the regulations is not to stop hospitals or other health institutions like laboratories from developing in-house software (and other devices) to advance medical research or offering tailored healthcare to specific patient groups, but rather to ensure that in-house devices meet minimum safety and performance requirements. Stricter control of medical device safety and performance is necessary and beneficial to patients, but this may require increased budget allocation for

healthcare institutions in order to preserve patients' access to latest healthcare technology.

POTENTIAL REGULATORY BOTTLENECKS

The MDCG guidance greatly improves the interpretation of the regulations for medical device software, however potential borderline qualification cases remain for CDS software. For instance, the qualification of a CDS software using both IVD and other health data relies on the interpretation of its purpose; "*In the condition where the intended purpose of the MDSW output data fulfils both the medical device and in vitro diagnostic medical device definitions set out in the MDR and IVDR […] a weighting of the data sources based on the significance of the information in relation to fulfilling the intended purpose should be conducted to aid the manufacturer in determining which regulation to apply.*" [19]. For instance, which of MDR or IVDR would apply for a software that combines genotype, phenotype and a variety of other health data such as radiology exams to provide information related to diagnosis or treatment strategies for individual patients? Whether the software provides information 'substantially' driven by the IVD data source or not will determine its qualification according to MDR or IVDR (see decision Step 6 in Figure 1) [19]. This point is critical since MDR applies from May 26th 2020, two years earlier than IVDR. As referred to in the preamble of the regulation (recital 8, page 2) [1], Member States can (and in some cases may have to) decide on a case-by-case basis if a product falls under the scope of MDR or IVDR. However, implementation of the regulations across Member States needs to be harmonized, requiring coordination among competent authorities and actions from the Commission (on its own initiative or by request from a Member State) to solicit the MDCG, supported by technical working groups, to decide case-by-case on the regulation of borderline devices.

The pace of technological development of CDS software, sometimes associated with modification of its intended purpose, requires careful regulatory governance monitoring. Considering the currently limited number of Notified Bodies designated under MDR and IVDR [22], and the eventual need for specific intervention of competent authorities or MDCG related to the regulation of borderline products, manufacturers of CDS software may face substantial delays in their regulatory processes, which ultimately would delay patient access to current and new technologies.

THE NEED FOR CONTINUOUS ASSURANCE

The technical file of a medical device software compiles all aspects of compliance documentation, such as clinical investigation, risk analysis and post-market clinical follow-up to monitor the use of the device. All these aspects have to be aligned to the intended purpose of the device, which also relates to the appropriate risk classification of the device according to the applicable regulation. A major challenge with CDS software is the short product-lifecycle compared with other non-software devices. Frequent software releases are usually launched, with for instance new features or new design. This can create a 'moving target' situation in terms of applicable legislation and classification. For example, a change of the intended purpose can induce a requalification from IVDR to MDR or

reclassification of the software, with the need to update the whole technical documentation according to applicable requirements. In addition, any change that may influence the risk analysis of the device, for instance related to human factors or usability of the software, may require an update of the device's assurance case to maintain conformity. The 'pathway for continuous learning' governing conformity management outlined by the IMDRF partially captures this thinking [23]. However, the high rate of updates of software products argues for continuous assurance management and scrutiny by Notified Bodies and competent authorities, which could challenge the capacity of all stakeholders involved in compliance monitoring.

RECOMMENDATIONS

GENERAL RECOMMENDATIONS FOR MANUFACTURERS AND HEALTH INSTITUTIONS

The regulatory process for medical devices is becoming more challenging with the new European regulations. Manufacturers and health institutions who develop CDS software for clinical use need to carefully qualify and classify their device prior to documenting conformity to all applicable requirements.

INTENDED PURPOSE, QUALIFICATION AND CLASSIFICATION OF THE SOFTWARE

The intended purpose of the software shall be carefully defined as this governs the regulatory requirements associated to it. For software-containing modules, e.g. library function modules not covered by the medical device definition, or a module that qualifies as a medical device, manufacturers should consider separate or integrated conformity management of these modules. Specific guidance on this topic is provided by the MDCG [19].

Manufacturers shall then identify the risk class of their software and choose the appropriate conformity assessment route, eventually with the assistance of a Notified Body. In case of uncertainty, competent authorities may be required to decide case-by-case on the qualification or classification of a software product. Health institutions only need to classify their CDS software if this is regulated by IVDR, since the application of recital (g) of IVDR article 5(5) is class dependent in the Member State it is developed.

QUALITY MANAGEMENT SYSTEM

Manufacturers of CDS software regulated by MDR or IVDR shall have a proper quality management system in place, including organizational and leadership support procedures. Within the new regulations, manufacturers need to demonstrate continuous improvement of the quality management systems (QMS), and the appointment of a person responsible for regulatory compliance with appropriate qualifications.

COMPLIANCE MANAGEMENT

Annex I of MDR and IVDR set the minimum safety and clinical performance requirements for qualified software, which are summarized by MDCG [24]. A general recommendation is to integrate these requirements early in the development of the software. Manufacturers and developers of CDS software should for instance pay attention to human factors in the design phase. Software features and user interface (UI) design are closely related to human factors such as alarm fatigue, users' work-around strategies and bypass of safety control measures. Users' related errors and bypass strategies directly impact the risk management of the device, which requires manufacturers to consider 'foreseeable misuse' of their software as mentioned in Annex I. Cybersecurity is another important aspect of medical device software.

A recent document issued by the MDCG provides more detailed guidance regarding cybersecurity requirements for software manufacturers [25]. Furthermore, it is expected that manufacturers demonstrate compliance of their device using common specifications and harmonized international standards. Common specifications refer to technical and clinical requirements other than standards to be used to fulfil the regulatory requirements, which will be published by the European Commission. Manufacturers and developers of CDS software shall also consider other regulations such as the General Data Protection Regulation (GDPR) and regulations related to IT environment.

In addition to ISO 13485 and ISO 14971 (QMS and risk management, respectively), several international standards are relevant to CDS software, although full conformity to these standards is not mandatory for the overall conformity assessment. A non-exhaustive list of relevant international standards for CDS software is provided in the next section.

Clinical evaluation and clinical investigation for high-risk devices is strengthened in the new regulations, including collection of patient safety issues and user data throughout the entire lifecycle. The general principles of clinical evaluation for software as a medical device are outlined in IMDRF document [23]. These principles rely on:

- the scientific validation of the clinical association between the information provided by the CDS software and the targeted clinical condition
- the analytical validation about the accuracy, reliability and precision of output data correctly processed from input data
- the clinical validation, which demonstrates the ability of the CDS software to provide accurate, reliable and precise information to achieve its intended purpose.

For manufacturers, clinical evaluation and eventual clinical investigation requirements described in MDR Annexes XIV and XV, and IVDR Annexes XIII and XIV shall be met.

NON-EXHAUSTIVE LIST OF RELEVANT INTERNATIONAL STANDARDS FOR CDS SOFTWARE QUALITY ASSURANCE

The use of international standards is in some cases expected to demonstrate conformity to regulatory requirements. For instance, requirements sometimes refer to “state of the art” methods in the design of the device, risk management or other topics. Hundreds of standards are relevant for medical devices and software.

The list below mentions only some of the most relevant standards for CDS software manufacturers and developers to support their conformity process (www.iso.org).

- EN ISO 13485: 2016: Medical devices – Quality management systems – Requirements for regulatory purposes
- ISO 14971: 2019: Medical devices - Application of risk management to medical devices
- EN ISO 14155: 2011: Clinical investigation of medical devices for human subjects. Good clinical practice

- IEC 80002-1:2009: Medical device software – Part 1: Guidance on the application of ISO 14971 to medical device software
- IEC TR 80001-2-2:2012: Application of risk management for IT-networks incorporating medical devices - Part 2-2: Guidance for the disclosure and communication of medical device security needs, risks and controls
- IEC 82304-1:2016: Health software - Part 1: General requirements for product safety
- IEC 62304:2006/Amd 1:2015: Medical device software – Software life-cycle processes – Amendment 1
- IEC 62366-1:2015/COR1:2016: Medical devices - Part 1: Application of usability engineering to medical devices – Technical Corrigendum 1
- IEC TR 62366-2:2016: Medical devices - Part 2: Guidance on the application of usability engineering to medical devices
- ISO/IEC 15026 (all parts): Systems and software engineering – Systems and software assurance
- ISO/TS 25238:2007: Health informatics – Classification of safety risks from health software

REGULATORY SURVEILLANCE

As discussed previously, the regulatory process of CDS software can be modified as a result of a change made by the manufacturer, health institution or regulator. Regulatory updates and guidelines are published continuously and manufacturers or institutions with regulatory obligations should keep themselves updated.

Guidance documents issued by the European commission and the MDCG can be found here:

https://ec.europa.eu/growth/sectors/medical-devices/new-regulations/guidance_en

RECOMMENDATIONS FOR HEALTH INSTITUTIONS DEVELOPING IN-HOUSE CDS SOFTWARE

Health institutions traditionally have little experience with CE marking of medical device and staying informed of all regulatory requirements of their in-house CDS software will undoubtedly require additional resources.

As for manufacturers, the intended purpose of the in-house software should be precisely defined. This step is crucial as it impacts directly on the qualification of the software as medical device or IVD medical device. Following the qualification of their in-house software as medical device or in vitro medical device, health institutions shall explicitly document how this software addresses a patient group's specific needs better than commercially available software. Non-compliance to this requirement of MDR/IVDR article 5(5) would potentially infringe the single market principle in the European Union and ultimately compromise patient safety. Moreover, the comparison of an in-house developed software to existing commercial software refers partly to the intended purpose, or more specifically, the addressed patient group (MDR/IVDR article 5(5)).

Health institutions shall document the safety and efficacy of their in-house software prior to use in clinical settings. Although health institutions are not formally required to fulfil the specific clinical evaluation requirements in MDR Annex XIV or IVDR Annex XIII, they are expected to collect information to support the documentation of general safety and performance requirements in an evaluation phase of the device.

In summary, health institutions developing in-house CDS software should consider the following actions where relevant:

- Gain insight and spread knowledge among relevant staff members about the new regulations
- Define the intended use of the in-house developed software for qualification purposes
- Consider a request to competent authority for borderline device qualification, and classification for IVD medical devices
- Perform market surveillance of available CE marked software on the market, eventually in collaborative networks. Evaluate if the needs of specific patient groups at the health institution would be met by commercially available software above
- Apply appropriate quality management systems procedures throughout the software lifecycle
- Evaluate the safety and performance of the software prior to its clinical use to support the documentation of Annex I requirements
- Ensure that the conditions of article 5(5) of the applicable regulation (MDR or IVDR) are met during the period the in-house software is 'put into service'
- Ensure documentation of Article 5(5) and Annex I requirements for eventual inspection by competent authorities
- Consider relevant international standards to support documentation to Annex I requirements

METHODS AND LIMITATIONS

Hospitals are often at the forefront of technological and clinical research development, such as in NGS in rare diseases or cancer. Partners in the BigMed project consortium have acknowledged the importance of regulatory requirements in the adoption of developing technologies in precision medicine. The introduction of updated MDR and IVDR has triggered some concerns among stakeholders of the consortium. As a result, DNV GL, as one of the partners, conducted semi-structured interviews with three partners in the consortium with the aim of understanding the clinical needs for CDS software in relation to the new regulations. Findings highlighted the initial concerns of health institutions and the need for an overview of the regulatory landscape for CDS and in-house developed software. In the same period (spring-autumn 2019), the Norwegian Ministry of Health and Care Services issued a consultation letter to a broad range of stakeholders regarding the implementation of MDR and IVDR in Norway. Stakeholders' responses, in particular from other health institutions in the country, supported our findings [3].

A review of the applicable requirements in the regulations, guidelines and scientific literature was conducted to analyse the findings and address the main concerns. We extended our discussion to potential challenges that may arise related to the practical implementation of the regulations. Finally, high-level recommendations were assembled for manufacturers and health institutions which develop CDS software for clinical use.

This paper does not aim to provide an exhaustive list of recommendations or actions for manufacturers and health institutions. Instead, it aims to address the general concerns about the implementation of the regulations, discuss challenges and improve regulatory process understanding.

CONCLUSIONS

The use of CDS software is growing rapidly, with the potential to provide better and safer care to patients, whilst in parallel significantly improving care delivery efficiency. CDS software, like all other devices that provide information that impact diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease of patients, are likely to be regulated by MDR or IVDR. With the reclassification of software to a higher risk device class in Europe, manufacturers will need to put more efforts in to prove and maintain the conformity of their software throughout its lifecycle. The compliance management of CDS software can be challenging, driven by rapid technology development and a growing integration of multiple data sources. This white paper highlights some potential challenges identified. With the development pace of CDS software, a better alignment between manufacturers, Notified Bodies and competent authorities is needed to manage the modifications of existing and introduction of new CDS software, which argues for continuous compliance monitoring solutions. Moreover, competent authorities in collaboration with the European Commission and MDCG, may have to statute case-by-case for qualification and classification of borderline software while ensuring harmonized implementation of the regulations among Member States.

The new regulations also introduce regulatory requirements for health institutions developing in-house CDS software. This is a concern for hospitals, which will likely need to allocate specific resources to manage medical device compliance, whilst already being under economic pressure.

REFERENCES

1. *Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.* European Union. Official Journal of the European Union L117, 60 2017.
2. *Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.* European Union. Official Journal of the European Union L117, 60 2017.
3. *Høring om gjennomføring av forordning 2017/745 om medisinsk utstyr og forordning 2017/746 om in vitro-diagnostisk medisinsk utstyr.* 2019 [cited 2019-11-29]; Available from: https://www.regjeringen.no/no/dokumenter/horing-om-gjennomforing-av-forordning-2017745-om-medisinsk-utstyr-og-forordning-2017746-om-in-vitro-diagnostisk-medisinsk-utstyr/id2652683/.
4. Gupta, Y., K.H. Lee, K.Y. Choi, et al., *Early diagnosis of Alzheimer's disease using combined features from voxel-based morphometry and cortical, subcortical, and hippocampus regions of MRI T1 brain images.* PLOS ONE, 2019. 14(10): p. e0222446.
5. Avants, B.B., C.L. Epstein, M. Grossman, et al., *Symmetric diffeomorphic image registration with cross-correlation: Evaluating automated labeling of elderly and neurodegenerative brain.* Medical Image Analysis, 2008. 12(1): p. 26-41.
6. Rosen, H.J., S.C. Allison, G.F. Schauer, et al., *Neuroanatomical correlates of behavioural disorders in dementia.* Brain, 2005. 128(11): p. 2612-2625.
7. Burton, E.J., I.G. McKeith, D.J. Burn, et al., *Cerebral atrophy in Parkinson's disease with and without dementia: A comparison with Alzheimer's disease, dementia with Lewy bodies and controls.* Brain, 2004. 127(4): p. 791-800.
8. Fischl, B. and A.M. Dale, *Measuring the thickness of the human cerebral cortex from magnetic resonance images.* Proceedings of the National Academy of Sciences of the United States of America, 2000. 97(20): p. 11050-11055.
9. Boycott, K.M., M.R. Vanstone, D.E. Bulman, et al., *Rare-disease genetics in the era of next-generation sequencing: Discovery to translation.* Nature Reviews Genetics, 2013. 14(10): p. 681-691.
10. Eilbeck, K., A. Quinlan, and M. Yandell, Settling the score: *Variant prioritization and Mendelian disease.* Nature Reviews Genetics, 2017. 18(10): p. 599-612.
11. Richards, S., N. Aziz, S. Bale, et al., Standards and guidelines for the interpretation of sequence variants: *A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.* Genetics in Medicine, 2015. 17(5): p. 405-424.
12. *Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, Amended by Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007.* OJ L 169, 12.7.1993, p. 1, (12.7.1993) 1993, amd 2007.
13. *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.* OJ L 189, 20.7.90: p. 17-36 1990.
14. *Council Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998*

on in vitro diagnostic medical devices. OJ L 331, 7.12.1998, p. 1, (12.7.1993) 1998, amd 2011.
15. Thorogood, A., S.B. Touré, J. Ordish, et al., *Genetic database software as medical devices.* Human mutation, 2018. 39(11): p. 1702-1712.
16. *Judgment of the Court (Fourth Chamber) of 7 December 2017 Syndicat national de l'industrie des technologies médicales (Snitem) and Philips France v Premier ministre and Ministre des Affaires sociales et de la Santé. Request for a preliminary ruling from the Conseil d'État (France). Reference for a preliminary ruling — Medical devices — Directive 93/42/EEC — Scope — 'Medical device' — CE marking — National legislation making drug prescription assistance software subject to a certification procedure laid down by a national authority. Case C-329/16, in Judgment ECLI:EU:C:2017:947,* C.o.J.o.t.E. Union, Editor. 2017, InfoCuria.
17. *Article L. 161-38 of the Social Security Code (JORF of 15 November 2014, p. 19255; decree No 2014-1359).* 2014.
18. *MEDDEV 2.1/6. Guidelines on the qualification and classification of stand-alone software used in healthcare within the regulatory framework of medical devices.* European Commission, DG Internal Market, Industry, Entrepreneurship and SMEs, Directorate Consumer, Environmental and Health Technologies, Unit Health technology and Cosmetics. 2016.
19. *Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR.* MDCG 2019-11, 2019.
20. *Factsheet for healhtcare professionals and health institutions.* European Commission, 978-92-76-03182-6: 2019.
21. *"Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations.* International Medical Device Regulators Forum (IMDRF), IMDRF/SaMD WG/N12FINAL:2014, 2014.
22. *Software as a Medical Device (SaMD): Clinical Evaluation.* International Medical Device Regulators Forum (IMDRF), IMDRF/SaMD WG/N41FINAL:2017, 2017.
23. *Summary of safety and clinical performance - A guide for manufacturers and notified bodies.* MDCG 2019-9, 2019.
24. *Guidance on cybersecurity for medical devices.* MDCG 2019-16, 2019.

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