

Consultation response: MHRA Regulation



Submitted to
Medicines & Healthcare
products Regulatory Agency

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The Medicines and Healthcare products Regulatory Agency (MHRA) invited views on possible changes to the regulatory framework for medical devices in the United Kingdom (UK). We want to develop a future regime for medical devices which enables:

- Improved patient and public safety;
- Greater transparency of regulatory decision making and medical device information;
- Close alignment with international best practice, and;
- More flexible, responsive and proportionate regulation of medical devices.

The PHG Foundation welcomes the review and has provided the response below.

Q1.1 Do you think the scope of the UK medical devices regulations should be expanded to include the additions suggested above?

Yes

Q1.2 Please set out what (if any) further amendments you would like to make to the scope of the UK medical devices regulations.

We welcome the suggested additions to the definition of medical devices. In particular, the expansion of software to include IVD software, and devices that provide information to predict treatment response or reaction are necessary additions to the remit of medical device regulation to keep abreast of technological developments whilst ensuring patient safety. More needs to be done to encourage more entities to become approved bodies and prevent the impending bottleneck, which risks undoing all the welcomed changes in the proposal.

Q1.3 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 1.1-1.2, including any impacts on you or other stakeholder groups.

As of July 2021, there were only three Approved Bodies (ABs) in existence in the UK. The EU's transition to the EU MDR may also be a reason why so few EU Notified Bodies are applying for AB designations. The proposals mention tightening turnaround time frames for conformity assessments; more stringent requirements for ABs; and the innovative routes to market, which are all welcome from a patient safety perspective but may further increase pressure on ABs if no amendments are made to encourage relevant entities to apply for AB designations. We encourage amendments to Chapter 5 proposals that mitigate any bottleneck whilst maintaining safety standards.

Q1.4 Should we make clear that 'intended purpose' is to be construed objectively and that key materials such as a manufacturer's technical documentation may be used as evidence of intended purpose?

Yes

Q1.5 Please set out the reasoning for your reply to question 1.4, including your views on the materials that should be taken to evidence intended purpose, and any implementation considerations and expected impacts of any proposed changes.

As we discuss in our report, [Algorithms as Medical Devices](#), we agree that 'intended purpose' should be construed objectively and key materials, including manufacturer's technical documentation should be used as evidence of intended purpose.

Objective assessment enables regulators to evaluate the primary function of a device and the risks it poses to consumers. This should include assessment of claims about the device that are used in marketing and the media. A subjective approach risks failure to regulate a device according to its true risk profile if a manufacturer fails to provide a comprehensive description that states its true intended purpose.

In addition to the manufacturer's technical documentation, risk profiles on the basis of performance evaluations or clinical investigations and other existing requirements in Article 2(12) should remain. Post-market surveillance of how consumers are using the device in practice may also be necessary to determine an objective 'intended purpose'. Assessing this documentation should be part of the remit of approved bodies, who should be sufficiently resourced to undertake this work.

Q2.1 Do you think the scope of the UK medical devices regulations should be broadened to include devices without a medical purpose with similar risk profiles to medical devices?

Yes

Q2.2 Please provide your reasoning for your response to question 2.1.

The traditionally clear delineation between medical and non-medical purposes is increasingly blurred, and the overlap between personal interest and utility from testing, and clinical utility, is no longer clear-cut. Some degree of regulatory oversight is appropriate for all products with health and wellbeing related purposes, to protect consumers.

We support a proportionate approach that regulates medical devices commensurately with the risk of harm that they pose. All the devices listed in paragraph 2.3 seem candidates for inclusion. As a health policy think tank interested in genetic and genomic testing, we would support diagnostic tests for health and wellbeing being included. As a starting point, the requirement should be for manufacturers to demonstrate scientific and clinical validity for these devices, as well as regulating the claims that are made.

We believe that this is a proportionate approach to tackle both the challenge of maintaining UK market attractiveness (by keeping abreast of innovation) whilst making clear provision for broadening the MHRA's regulatory reach, enabling greater oversight of devices that have similar risk profiles to medical devices. Given the trend for rapid technological development this proposal seems like an appropriate 'catch all' response to prevent consumer/ patient harm. Depending on their risk profile, this would encompass non-medical devices that are used for medical purposes, for example, devices used by citizens on a direct-to-consumer basis without medical oversight or guidance. If this approach was not adopted, an overly narrow interpretation of what constituted a medical device could put consumers at risk of exploitation and jeopardise patient safety.

Q2.3 If you have answered 'yes' to question 2.1:

a. please outline which products from the list at paragraph 2.3, and any others, you consider should be brought into scope of the UK medical devices regulations

Diagnostic tests are of particular interest to us as a science for health policy think tank with a focus on genomics and other 'omics

technologies. We welcome such tests being brought within the ambit of the regulations in a proportionate manner, irrespective of how they are marketed, because of the harms that can result from misinformation, misunderstanding and misguided reliance on the results of such tests.

b. please describe how these products should be assessed to ensure that they are safe and perform as intended.

Polygenic risk scores are a good example of a test that could be brought within the ambit of regulation through these reforms. These scores aggregate multiple genetic factors to create a composite 'polygenic' score which provides a measure of individual risk for a specific trait or characteristic. Our recent publication on polygenic risk scores (PRS) [addressed the challenges of their regulation and evaluating their clinical utility](#).

Clarity is needed on whether such tests amount to a single device or whether each stage of testing amounts to a 'device' itself, due to their fundamental design as a system of interoperable elements.

Guidance is needed on the quality and quantity of evidence required for market authorisation. Furthermore, a clear distinction between models, tools and tests and how the relationship between these device 'elements' will be regulated is required.

Surveillance throughout their lifecycle is also imperative for performance monitoring and notification of adverse events. Notified bodies will need to be resourced sufficiently and to have technical expertise.

c. please outline how you think these products should be classified (for example, whether they should be classified in line with medical devices that have similar functions and risks).

The list of devices in 2.3 are wide ranging. Classification may need to be adopted on a case by case basis depending on factors such as intended use, target population, what combination of models, tools and tests form the device, and the training and qualification of users. In the case of polygenic risk scores, once these factors are clarified it should then be easier to match PRS devices to medical devices with similar functions and risks. This may be more labour intensive but would be likely to provide greater safety and effective oversight. It is possible that the MHRA's airlock classification rule could be used, where genetic testing is coupled with software elements and that unique combination presents a sufficiently novel device.

We consider that products in the category 2.3 h (diagnostic tests for health and wellbeing, and specifically forms of genetic or genomic tests for health and wellbeing applications) should fall within the scope of medical device regulations. This is because the results of testing with many such products may have, or may be perceived by users to have, medical implications, and clarity on these issues is important. We suggest that evidence of analytical validity should be assessed alongside the validity and utility of health-related performance claims to ensure clarity over what information the tests do (and do not) provide for users.

Q2.4 Do you think that manufacturers of the products listed at paragraph 2.3 should be required to register them with the MHRA? (see Chapter 4, Section 21 for further information on registration requirements)

Yes

Q2.5 Please provide any other comments you wish to make about the possible regulation of products without a medical purpose as medical devices and your reasoning (including any available relevant evidence) to support your answers to questions 2.1-2.4. Please include any impacts on, and implementation considerations for, you or other stakeholder groups.

The requirement for registration should be contingent on the risk profile of the device. Many of the devices in 2.3 potentially pose significant risks to patient safety, suggesting that they should be registered with the MHRA. In the case of PRS, depending on the purpose, and given the apparent novelty of both the genetic and software testing elements of PRS, it seems appropriate that such devices be registered with the MHRA. Doing so would increase trust through transparency due to the novelty that arises via the unique combination of software and genetic testing within a single device.

Furthermore, our work on medical device regulation has highlighted the potential for manufacturers to market predictive tests as recreation for consumers, rather than as medical devices. Bringing marketing and advertising materials into the ambit of documentation that could be assessed by regulators would go some way to ensuring that the scope of regulation is proportionate.

5.8 The MHRA considers that the classification rules for general medical devices (excluding IVDs) in the UK medical devices regulations could be amended to change the classification of certain devices, and bring into scope of the classification rules, products that did not previously fall within the definition of a medical device or within the scope of the classification rules.

5.9 The classification rules could be amended to provide as follows:

- active implantable medical devices and their accessories could be classified as Class III
- in vitro fertilisation (IVF) and assisted reproduction technologies (ART) could be classified as Class III
- surgical meshes could be classified as Class III
- total or partial joint replacements (except ancillary components such as screws, wedges, plates and instruments) could be classified as Class III
- spinal disc replacement implants and implantable medical devices that contact the spinal column (except ancillary components such as screws, wedges, plates and instruments) could be classified as Class III
- medical devices incorporating nanomaterial could be classified between Class IIa – III depending on potential internal exposure levels
- non-invasive medical devices which come into contact with mucous membrane (not only injured skin) could be classified between Class I – IIa depending on intended use. Injured skin or mucous membrane could mean an area of skin or a mucous membrane presenting a pathological change or change following disease or a wound
- invasive medical devices with respect to body orifices, other than surgically invasive medical devices, which are intended to administer medicinal products by inhalation could be classified as

Class IIa, unless their mode of action has an essential impact on the efficacy and safety of the administered medicinal product or they are intended to treat life-threatening conditions, in which case they could be classified as Class IIb

- medical devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by or locally dispersed in the human body could be classified as:
 - class III if they, or their products of metabolism, are systemically absorbed by the human body in order to achieve the intended purpose;
 - class III if they achieve their intended purpose in the stomach

or lower gastrointestinal tract and they, or their products of metabolism, are systemically absorbed by the human body

- class IIa if they are applied to the skin or if they are applied in the nasal or oral cavity as far as the pharynx, and achieve their intended purpose on those cavities; and
- class IIb in all other cases.
- active therapeutic medical devices with an integrated or incorporated diagnostic function which significantly determines the patient management by the medical device, such as closed loop systems or automated external defibrillators, could be classified as class III.

Q5.1 Do you think the classification rules for general medical devices in the UK medical devices regulations should be amended in any or all of the ways set out in paragraphs 5.8-5.10?

Yes

Q5.2 If you have answered yes to question 5.1 please specify which of the amendments should be made.

The proposals in paragraph 5.9 seem proportionate and appropriate. One other regulatory consideration not mentioned in this consultation is considering introducing specific rules about who should use these devices and the circumstances of their use. This might be appropriate for some classes of product (e.g. IVF and ART regulated by the HFEA).

Q5.4 Please provide your reasoning (including any relevant evidence) to support your answer to questions 5.1-5.2, including any impacts on you or other stakeholder groups.

In general we support a proportionate regulatory regime with oversight relating to the risks that are posed, since obvious exceptions lead to a lack of trust in the system. There needs to be a mechanism to bring in oversight of new products without having to resort to regulatory change.

More specifically we suggest that more attention should be given to closed loop systems which patients and consumers may use without oversight from healthcare professionals. Depending on the application and context, these could pose significant risks to patient safety and potentially need close scrutiny.

8.3 The MHRA considers that, in addition, the UK medical devices regulations could be amended to specifically exempt health institutions from meeting certain regulatory requirements and to clarify which requirements must be met. Further information is provided in the paragraphs below.

8.4 The MHRA considers that the UK medical devices regulations could be amended to include a definition of a 'health institution' to provide clarification as to which entities the health institution exemption, described in paragraph 8.3, would apply to.

Q8.1 Do you think that the UK medical devices regulations should include a definition of the term 'health institution' to provide clarification as to which entities the health institution exemption would apply to?

Yes

Q8.2 If you answered 'yes' to question 8.1, please outline what you think should be included in this definition.

Yes, a definition is welcome and would provide clarity to the healthcare sector. However, the nature of modern health and diagnostic services may be challenging to define in Regulations so it may be beneficial to set a definition which is subject to authoritative interpretation by the MHRA in associated guidance that can be updated over time. Any development of regulation in this area should take account of the fact that the genetic/genomic testing for the NHS is highly centralised. The Genomic Laboratory Hubs in England provide tests to many health institutions and would potentially be excluded by this provision unless an exemption applied.

Defining a health institution according to primary purpose is sensible as in the EU MDR/IVDR definitions. However, this may not always be straightforward to apply in practice, such as where private services are subcontracted by a health institution to provide services on their behalf. Another potential complication is where health institutions are defined in terms of being in a single geographical location. This may pose definitional challenges where a health institution is geographically dispersed.

8.5 The MHRA considers that the UK medical devices regulations could be amended to clarify that medical devices manufactured and modified 'in house' must meet the relevant essential requirements (see Section 6) of the UK medical devices regulations, but would not

need to bear the UKCA marking.

Q8.3 Do you think that the UK medical devices regulations should require 'in house' manufactured devices to meet the relevant essential requirements of the UK medical devices regulations?

Yes

Q8.4 Do you think that 'in house' manufactured devices should be exempt from UKCA marking requirements?

Yes

8.6 The MHRA considers that the UK medical devices regulations could be amended to require health institutions to meet certain requirements for 'in house' manufacturing. This could include obligations for the health institution to:

- a. apply a suitable Quality Management System (see Section 11 for more detail)
- b. justify why the target patient group's needs cannot be met with an equivalent medical device available on the market
- c. draw up a publicly available declaration that their medical devices meet the relevant essential requirements of the UK medical devices regulations
- d. keep technical information available for the MHRA, review clinical use of the medical devices and take necessary corrective actions
- e. report certain types of incidents relating to medical devices manufactured 'in house' to the MHRA.

Q8.5 Do you think that health institutions should be required to meet the requirements set out in paragraph 8.6 when manufacturing or modifying medical devices 'in house'?

Yes

Q8.6 Please outline any other requirements which should be introduced for health institutions carrying out 'in house' manufacturing or modification of medical devices.

While greater oversight of health institution developed devices may be proportionate it is important that compliance does not present a disproportionate burden that risks the development of, for example, tests for rare disorders where there may be no or limited alternatives available on the market, or, appropriate 'in house' tests where market alternatives are too expensive for adoption/commissioning by publicly funded health services.

It is also important that meeting essential UK requirements does not add to the regulatory burden associated with demonstrating compliance in other jurisdictions. Aligning MHRA requirements with other legislative requirements or international standards such as ISO standards or the EU MDR and IVDR would reduce the potential burden on developers, manufacturers and other stakeholders.

8.7 The MHRA considers that the UK medical devices regulations could be amended to require health institutions to register medical devices manufactured or modified 'in house' with the MHRA. The public declaration (see paragraph 8.6, point c) could be requested by the MHRA during the registration process. If these provisions were to be introduced, the registrations made by health institutions would appear on the MHRA's Public Access Database for Medical Device Registration, with the aim of improving transparency.

Q8.7 Do you think that health institutions should be required to register medical devices manufactured or modified 'in house' with the MHRA?

Yes

8.8 The MHRA considers that the UK medical devices regulations could be amended to require health institutions to register clinical investigations / performance studies involving medical devices manufactured or modified 'in house' with the MHRA. For further questions on clinical investigations / performance studies conducted by health institutions please see Chapter 7, Section 46.

Q8.8 Do you think that health institutions should be required to register clinical investigations / performance studies with the MHRA?

Yes

8.9 The MHRA considers that the UK medical devices regulations could be amended to enable the MHRA to request that the relevant health institution provides further information about the devices it has manufactured or modified 'in house', including details about the manufacturing processes.

Provisions could also be introduced to require the MHRA to restrict the use of such medical devices and to inspect the activities of relevant health institutions.

Q8.9 Do you think that the provisions in paragraph 8.9 should be introduced for health institutions?

Yes

8.10 The MHRA considers that the UK medical devices regulations could provide that the health institution exemption shall not apply to medical devices manufactured on an industrial scale and that such medical devices must meet all the relevant provisions of the UK medical devices regulations.

Q8.10 Do you think that medical devices manufactured on an 'industrial scale' should be excluded from the health institution exemption and required to meet all relevant provisions of the UK medical devices regulations?

Don't know

Q8.11 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 8.1-8.10, including any impacts on you or other stakeholder groups.

It may be proportionate to exclude medical devices manufactured on an industrial scale from the health institution exemption, since this would give these organisations a competitive advantage over other commercial companies. However applying this in practice is problematic since almost all genetic and genomic services used by the NHS might be caught by this provision (e.g. centralised genomic sequencing and most testing for rare diseases; i.e. all the tests in the National Genomic Test Directory).

Many NHS pipelines include commercial stakeholders (e.g. Illumina and Genomics England)

Defining 'industrial scale' proportionately is key: it is not clear whether the determining factor is the geographical spread of providers or patients over multiple locations, or the volume of tests/devices produced.

The EU IVDR Article 5(5) contains the following criteria all of which must be met in order for the health institution exemption to apply:

- a) devices must not be transferred to another legal entity
- b) manufacture and use occur under appropriate QMS
- c) compliance with EN ISO 15189
- d) the HI provides information that the target patient groups specific needs 'cannot be met or cannot be met at an appropriate level of performance by an equivalent device available on the market

More work is needed to determine what constitutes an 'equivalent' device - and specifically whether this includes cost as well as performance criteria

Aligning UK regulation with European standards but not EU regulations may ensure de facto EU alignment without necessitating regulatory concordance.

8.11 The MHRA considers that the UK medical devices regulations could provide that the health institution exemption shall apply to a health institution which provides routine or a specialist diagnostic service to other health institutions.

Q8.12 Should the 'in-house exemption' be applicable to health institutions which provide routine or specialist diagnostic services to other health institutions (e.g. the Supra regional assay service) or another body?

Yes

Q8.13 If you have answered 'yes' to question 8.12, please outline any circumstances in which the exemption should not apply (e.g. if the services are provided for commercial / profitable purposes or to private patients or providers outside its intrinsic health function)?

'Intrinsic health function' may be difficult to interpret. Private providers of healthcare services may also be providing an intrinsic health function albeit funded through a private route. Public services are increasingly contracting out some of their services to private providers to meet demand. Workforce shortages are likely to increase these pressures in future.

Q8.14 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 8.12-8.13, including any impacts on you or other stakeholder groups.

All the genetic / genomic tests provided via the NHS National Genomic Test Directory are centrally managed and would be potentially caught by this provision. This requirement also conflicts with existing strategic policy, namely to centralise test provision (e.g. the centralised service already implemented to provide whole genome sequencing for England and Wales) and other key policies in this area, for example, [Genome UK: the future of healthcare](#).

For countries such as the UK that have a publicly funded health service, rationalising services to increase efficiency, optimise performance and reduce costs is in the public interest. Restricting the use of the in-house exemption purely to allow competition from a range of providers seems disproportionate, provided that there are other drivers to ensure accountability (i.e. that the service works efficiently whilst maintaining high quality standards).

We would therefore support the use of the in-house exemption to support routine or specialist diagnostic services to other health institutions

The inclusion of direct to consumer genetic tests should be within the regulatory scope of the MHRA, but exclusion of these tests from the health institution exemption might help the NHS manage the interface between self-funded tests and health service authorised tests more effectively.

53.2. The UK medical devices regulations provide for four categories of IVDs, in order of increasing perceived risk to patient safety:

- General IVDs, i.e. all IVDs other than those covered below
- IVDs for self-testing (a medical device intended by the manufacturer to be able to be used by lay persons in a home environment) - excluding self-test medical devices covered below
- IVDs in the classifications stated in Part IV of the UK medical devices regulations, Annex II List B [¹]: which, amongst others, includes reagents products for rubella, toxoplasmosis and phenylketonuria as well as medical devices for self-testing for blood sugar.
- IVDs in the classifications stated in Part IV of the UK medical devices regulations, Annex II List A [²]: which includes reagents and products for HIV I and II, Hepatitis B, C and D, and reagent products for determining ABO systems and anti-kell including those used to test donated blood plus tests for screening.

53.3 We propose to amend the IVD classification rules to increase the level of scrutiny applied to IVD devices. These rules could, for example, be amended to take into account the intended purpose of the medical device and to reflect relevant international systems of regulation including the EU IVDR and the IMDRF approach. The aim of this approach would be to drive greater patient safety through increased medical device scrutiny of IVD products placed on the UK market.

Q53.1. Should the classification rules for IVD products under the UK medical devices regulations be amended to align to the EU approach to IVD classification, as set out in the IVDR?

Yes

Q53.2. Should the classification rules for IVD products under the UK medical devices regulations be amended to align to the International Medical Devices Regulatory Forum (IMDRF) approach to IVD classification?

Yes

Q53.3. Are the current IVD regulatory requirements for each class of IVD proportionate to their risk?

No

Q53.4. Does the current approach to classification sufficiently cover the digital/software aspect of IVDs?

No

Q53.5. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 53.1-53.4, including any impacts on you or other stakeholder groups.

We support the classification rules for IVD products being aligned to the EU approach to IVD classification as set out in the IVDR, or with the IMDRF approach. The current classification is inadequate in that many digital and software devices are not regulated by the current directive at all. The current IVD regulatory requirements are not proportionate to their risk and require urgent reform especially for regulating those devices which use artificial intelligence or machine learning which may be highly dynamic, opaque or which are capable of 'learning' and development without any or much human intervention.

54.2. The UK medical devices regulations do not currently include specific requirements relating to genetic testing. Under the current regulations it is possible for a genetic test to receive a CE or UKCA marking on the basis of an analytical study which demonstrates the medical device's performance. This is due to these devices being classified as low-risk devices under the current UK medical device regulations. There has been a long-standing concern amongst stakeholders that the current regulatory requirements are not sufficiently robust within this area. This includes requirements around the information provided to users of genetic tests. The UK medical device regulations could be amended to reflect some of the concerns raised such as those relating to the risk classification of genetic tests and ensuring users of genetic tests are provided with the appropriate information on the nature, significance and implications of their test

Q54.1. Should the UK introduce requirements around the information and data provided to individuals on the nature, significance, and implications of genetic tests?

Yes

Q54.2. Should the UK medical device regulations be amended to align with the EU approach to the classification of genetic tests as set out in the IVDR?

Yes

Q54.3. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 54.1-54.2, including any impacts on you or other stakeholder groups.

The application and potential personal and clinical significance and implications of different forms of genetic tests vary widely. They may form part of a standard range of clinical investigations in a manner akin to many non-genetic tests; or may in other cases have profound medical implications for the patient and potentially family members; or in still other cases contribute only limited predictive information, such as a small component of overall disease risk.

Clear distinction between different types of applications would enable proportionate information to be provided to individuals. This could ensure that all information is made available in the case of more significant applications, whilst avoiding potentially confusing and unhelpful information for more routine applications.

Introducing a high-level requirement to provide individuals with information on the nature, significance and implications of genetic tests would protect all individuals undertaking tests, including those not accessed via a medical professional. We suggest that this requirement could be disapplied if health professionals deliver these tests as part of health or social care. Although some genetic tests are robust diagnostic or predictive tests, others may be more uncertain and the standards that should be applied should build on professional best practice.

Of note, a patient's need for information before and after a genetic test may be highly individualised and heavily dependent on context. Ensuring that any information provided is congruent with an individual patients' needs, values and beliefs is a core component of medical practice [GMC Duties of a Doctor] and has been ratified in case law [the Montgomery case].

Best practice guidance developed by professional organisations such as the British Society for Genetic Medicine and the Joint Committee on Medical Genetics can supplement professional standards.

Section 55. Companion Diagnostics

55.2. The UK Medical Devices Regulations do not include specific provisions for a CDx device. These medical devices would typically fall under the lowest risk category. However, there have been concerns relating to how CDx devices are classified and the level of clinical evidence required to place these products onto the market.

55.3. Therefore, the UK medical devices regulations could be amended to -

- introduce classification rules specifically for CDx devices which are proportionate to their risk
- introduce specific clinical evidence requirements for CDx (please refer to Section 34 on requirements relating to performance studies for IVD devices, including CDx)

Q55.1. Should Companion Diagnostics be treated differently to other IVDs? (i.e. with respect to classification).

Yes.

Q55.2. How do we ensure the clinical evidence requirements for Companion Diagnostics are clear, appropriate, and proportionate to the risk? For example, should they differ for CDx that predict benefit / efficacy vs those that predict toxicity / harm?

We think differentiating CDx on this basis could be too simplistic. In both cases, the scale of the predicted risk or benefit could be more important. For example, a CDx which potentially causes severe toxicity resulting in death should be subject to a higher degree of scrutiny than a CDx that resulted in minor harm.

Q55.3. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 55.1-55.2, including any impacts on you or other stakeholder groups.

We support the introduction of classification rules specifically for CDx devices which are proportionate to their potential benefits and risks.

Other factors which might be relevant includes the amount of evidence available to support the performance, safety and effective of the CDx for the specific application. The knowledge and expertise of the users of the CDx, and the characteristics of any drug or intervention which is used in combination with a CDx are also important.

The PHG Foundation project on Black Box Medicine and Transparency proposed a novel 'Interpretability by Design' framework for [regulating black box algorithms](#). This framework proposed assessment of the following factors in determining the potential risks posed by novel software forming a device. These included:

Opacity; automation; adaptivity; incompleteness; ground truth (or lack thereof); and risk associated with the use of the device.

Many of these principles are also relevant to the use of a CDx in combination with a medicinal product or proposed intervention.

56.2. The UK Medical Device Regulations do not include specific regulatory requirements around IVD products placed onto the UK market through distance sales. We propose that distance selling of IVD products should be required to comply with the UK Medical Device Regulations in order to be placed on the UK market.

Q56.1. Should it be made clearer that providers of testing services who supply IVDs to the UK market (through electronic or other distance sale methods), are subject to the same requirements of the UK Medical Device Regulations as apply to economic operators in the traditional supply chain?

Yes

Q56.2. Should it be made clearer that those selling testing services, which include the provision of IVDs into the UK, be required to register their medical devices with the MHRA?

Yes

Q56.3. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 56.1-56.2, including any impacts on you or other stakeholder groups.

We support these proposals but it may be difficult for the MHRA to enforce these requirements in respect of any medical device available on the internet to UK citizens. Having laws that cannot or will not be enforced undermines public trust and the role of the regulator. It is partly for this reason that alignment between UK regulation and EU or between the UK and IMDRF might lessen this enforcement challenge, if requirements across jurisdictions are aligned in future.

57.2. Our proposals aim to ensure the regulation of SaMD is clear, effective, and proportionate to the risks these medical devices present. MHRA is considering what changes to The UK Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations) and related guidance could help achieve this. The majority of change required is likely to be in the form of guidance rather than legislation.

58.1 To clarify the meaning and scope of term 'software' we propose adding a new definition to the UK medical device regulations. In that context we propose adding the following definition of 'software' to the UK medical devices regulations: 'a set of instructions that processes

input data and creates output data . This definition is consistent with the definition in this Guidance document Medical Devices - Scope, field of application, definition - Qualification and Classification of standalone software- MEDDEV 2.1/6.

Q58.1 Do you think that we should introduce the definition of software set out above?

Yes

Q58.2 Do you think there are any other definitions that need to be added to, or changed in, the UK medical devices regulations to further clarify what requirements apply to placing SaMD on the UKmarket? ()

Yes

Q58.3 If you have answered yes to question 58.2, please outline what additions / modifications are required.

We suggest further clarifications to the requirements of SaMDs on the basis of the FDA's recently [published report](#) and our own cumulative findings on [algorithms as MDs](#), such as the need for:

1. Real world data performance to be included in any performance evaluations
2. A 'modification plan' for machine learning software and AI that outlines the manufacturer's intend changes through any machine learning methods that the device uses, and clarity on how such devices will remain safe throughout any modifications over time
3. A tailored approach to machine learning devices as certain machine learning-based modifications may need to be flagged as 'higher risk' to enable proportionate monitoring of machine learning devices; not all should necessarily fall under a stricter classification categories
4. Stakeholder-targeted transparency will be relevant as we have found that patients/ users are less concerned with how the devices work and are more focused on how to interpret the results/ result accuracy; whereas, medical professionals are more interested in clinical accuracy, including, risks, faults and interpretative guidance they may need to be aware of when advising patients. Consequently, devices with the need for medical professional interpretation and oversight should be held in higher risk categories and be less available for commercial use. Those targeted directly at lay consumers should provide such consumers towards interpretative guidance, risk disclosure information, and towards care professionals where necessary.

The main headings would be best mentioned in legislation but explained through [further relevant guidance for manufacturers](#).

Q58.4 Please provide your reasoning to support your answers to

questions 58.1-58.3, including any impacts on you or other stakeholder groups and any available relevant evidence.

There are a variety of different definitions of software in use. We support the adoption of the proposed definition, it is potentially inclusive and consistent with relevant guidance. In combination with other criteria (e.g. for determining the purposes to which medical devices and IVDs are put) it creates a proportionate and responsible remit for regulation by the MHRA. We have explored different types of software and their differences in our report Algorithms as Medical Devices.

We have included the links to relevant supporting materials in the previous answer. We have also conducted roundtable discussions with key stakeholders on ethical and legal issues specific to AI and have found that there was broad agreement that the existing framework was too complex and did not fit the needs for communicating the attributes of machine learning systems to patients and consumers, which further supports our final suggestion of a requirement of 'stakeholder-targeted transparency'. We suggest that any definitional clarity is best advanced through engagement between the MHRA and stakeholders to develop guidance on the topic rather than attempting to embed definitions in legislation.

59.1 SaMD can be deployed to UK by websites, app stores and via other electronic means including deployment from websites hosted in other jurisdictions. We are considering whether regulatory change is needed to clarify or add to the requirements for placing SaMD on the market in these circumstances. In particular we are proposing that the definition of 'placing on the market' could be modified to clarify when SaMD deployed on websites, app stores (for example Google Play and Apple stores) and via other electronic means accessible in the UK amounts to 'placing on the market'.

59.2 Please note that under the UK medical devices regulations, devices placed on the market must be registered with the MHRA. For further information please see Chapter 4.

Q59.1 SaMD can be deployed in the UK by websites hosted in other jurisdictions. Is there any need for greater / clearer requirements in such deployment?

Yes

Q59.2 Do you think that the definition of placing on the market should be revised as set out above?

Don't know

Q59.3 Please provide your reasoning to support your answers to questions 59.1-59.2, including any impacts on you or other stakeholder groups and any available relevant evidence.

Explicit clarification on whether the MHRA is intending to treat app stores and such websites as economic operators is needed. Such an approach could significantly reduce the number of medical software devices available on the internet. If the MHRA is to increase its remit significantly to include app stores and other such websites, it needs to be sufficiently resourced to deal with the greater volumes of applications that could result, and ideally provide for meaningful sanctions if software is unregistered. However, greater requirements for registration could also impede consumer access to potentially beneficial innovative MedTech. Apps that monitor diabetes (blood sugar levels) is just one specific area where apps have revolutionised some UK patients' lives and their healthcare experiences.

60.1 We propose to change the classification of SaMD to ensure the scrutiny applied to these medical devices is more commensurate with their level of risk and more closely harmonised with international practice. We propose to follow (with minimal adaptations to suit the UK context) the risk categorisation (and associated definitions) in the IMDRF Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations.

60.2 We anticipate this will require updating the IMDRF SaMD category numbering (I, II, III, IV) to reflect the classification numbering for medical devices under the UK medical devices regulations (I, IIA, IIB, III), adding classification implementation rules, and definitions of the following terms:

- a. critical
- b. serious
- c. non-serious
- d. treat or diagnose
- e. drive clinical management, and
- f. inform clinical management.

Q60.1 Do you think we should amend the classification rules in UK medical devices regulations to include the IMDRF SaMD classification rule (with supporting definitions and implementing rules) as set out in paragraph 60.2?

Yes

Q60.2 Please set out your rationale and any impacts you expect this change would have.

Generally, we welcome updates to the classifications of certain devices to reflect international best practice and the new risks that such devices pose. This could help tighten safety requirements and the 'whole life-cycle' surveillance processes of such devices, which are growing in complexity and numbers, and in turn, could better

ensure patient safety. However, we would caution against treating all software devices as the same. It is imperative that a case by case approach is adopted, and clear rubrics provided to manufacturers to clarify when certain devices deserve higher classification. An example provided in the proposal is that 'active therapeutic devices with diagnostic functions' could be classified as class III. Without further definition, both input-output software and machine learning models could ostensibly fall under this categorisation without further rationale. Further still, some machine learning models will present higher risk than others, even if they both 'actively diagnose'. Context is crucial to proportionate regulation.

We encourage the MHRA to provide further definitional clarity in both its classifications and subsequent guidance to acknowledge that not all 'similarly defined' devices are equal. Doing this should avoid disproportionate regulation that impedes UK consumers' access to life-changing software devices. The 'who', 'where', 'when', 'how' and outcome impact for using such devices needs to be considered on an individual basis.

61.1 We are also considering introducing an 'airlock classification rule'. This is a provision that would allow for a temporary classification to be applied to some SaMD (which is likely to involve monitoring and restricting the SaMD as if it were a high-risk device) where the risk profile is unclear. This could allow early access to market for novel and innovative SaMD whilst ensuring the safety of users and patients until the risks of the device are properly understood.

Q61.1 Do you think we should introduce an 'airlock classification rule' for SaMD with a risk profile that is not well understood?

Yes

Q61.2 Please provide your reasoning to support your answer to question 61.1 including any expected impacts on you or other stakeholder groups and any available relevant evidence.

We have found the airlock classification rule to be one of the most innovative and interesting aspects of the proposals. We think this is an exciting development that strikes a proportionate balance between patient safety and maintaining UK market attractiveness.

Nevertheless, we would still urge that all enhanced monitoring and market surveillance procedures do all that they can to prioritise patient safety. We would also welcome further clarity on who would make the eventual determination on classification i.e., the MHRA or the manufacturer. Additionally, we encourage the MHRA to do more to ease the impending bottleneck which may threaten to either entirely undermine such innovative features or, risk technically 'unclassified' devices remaining on the market for too long as 'yet to be officially classified devices', whilst they wait to be addressed in the approved body backlog.

62.1 SaMD is subject to essential requirements that apply to medical devices more broadly. We want to ensure software as a medical device (SaMD) receives adequate pre-market scrutiny to assure its safety, quality and performance and ensure the essential requirements in place meet this need.

Q62.1 Do you consider additional essential requirements should be in place to assure the safety and performance of SaMD specifically?

Yes

Q62.2 Please set out, and explain your rationale for, any additions and outline any expected impacts.

Software is typically more dynamic and adaptive than other types of medical devices. Providing for that degree of adaptivity may require additional essential requirements. One particular challenge that might need to be addressed is how incremental changes are made, and the extent to which small changes arising from verification and validation can be incorporated within existing pipelines, and whether/when modified software needs to be treated as an entirely novel device (i.e., the ship of Theseus problem).

Q62.3 Do you consider regulations should set out SaMD essential requirements separate from those for other general medical device types?

Yes

Q62.4 Please provide your reasoning (including any available relevant evidence) to support your answers to question 62.1-62.2, including any impacts on you or other stakeholder groups.

We would expect that software will become increasingly complex and consequently, may deservedly be treated differently to non-software based/using medical devices. If doing so would increase patient safety, we would welcome that change. It also seems that other countries are also adopting a similar approach to regulating software, through software specific provisions (e.g., the USA).

63.1 We are proposing:

a. that, in order to allow accurate and swift reporting via the Digital Yellow Card Scheme, SaMD should have a hyperlink to MHRA endorsed websites where a person can 'report an adverse incident with a medical device' where appropriate, and

b. that certain SaMD change management processes such as 'predetermined change control plans' should be provided for.

Q63.1 Do you think the UK medical devices regulations should mandate a report adverse incident link as set out above?

Yes

Q63.2 Please set out your rationale and any expected impact and any available relevant evidence to support your answer to question 63.1.

We consider that this is a really encouraging development. The FDA appears to be adopting a similar approach in their focus on enabling developers to have greater post-market surveillance under their 'real world performance' action plan, which is particularly necessary for machine learning software. As they state, 'gathering performance data on the real-world use of the SaMD may allow manufacturers to understand how their products are being used, identify opportunities for improvements, and respond proactively to safety or usability concerns.' Reporting adverse incidents is just one way of doing this but a welcome one.

Q63.3 Do you think that regulations should enable predetermined change control plans?

Yes

Q63.4 If you answered yes to question 63.3, what should these entail? Please set out your rationale, any expected impact and any available relevant evidence.

The FDA has begun to explore the use of predetermined change control plans and plans to issue guidance on this topic. Making provision for these plans seems sensible and is [in alignment with other jurisdictions](#). Any plans should entail a description of the envisioned modifications, the methodology being used to implement those changes and demonstrate how risks will be mitigated.

64.1 We want to ensure SaMD has sufficient cyber security and information security both for the purposes of the direct safety of the device (from the perspective of, for example, whether its functioning could be tampered with) and also the security of personal data held on or in relation to the device. We are therefore proposing that manufacturers of SaMD be required to meet certain minimum requirements relating to security measures and protection against unauthorised access.

Q64.1 Do you consider existing UK medical devices regulations need to include cyber security and/or information security requirements?

Yes

Q64.2 If you have answered 'yes' to Q 64.1, what should this entail and why? What would be the expected impacts?

Cyberattacks on healthcare institutions rose significantly during the pandemic. The Wall Street Journal estimated that cyberattacks rose 42% in the US and that hacking incidents compromised more than

half of all last year's data breaches (62% rise from 2019 in the US). In the UK, COVID-19 has also shifted greater emphasis towards telehealth. The UK also saw a spate of hacks: the Conti ransomware attack on HSE in 2021, the WannaCry attack impacted a third of NHS Trusts in 2017. Cybersecurity experts have argued that too much focus is being placed on data protection and too little on the security and integrity of software medical devices, where any breach could lead to serious harm or even death.

This would be best addressed in guidance that is supplementary to provisions that ensure security. That guidance should provide information to users on spotting abnormal behaviours and guidance on good IT hygiene from developers would help prevent attacks. For example, the National Audit Office identified that WannaCry was an unsophisticated attack and could have been prevented following basic security practices. Although this was an attack on healthcare institutions, it reinforces the point that human intervention and oversight is still a key frontline defence from cyberattacks. Such attacks should also be recorded via the yellow card scheme to help manufacturers keep informed of any security weaknesses or risks that their devices pose.

65.1 AIaMD is a subset of software as a medical device. Given this, MHRA views the changes noted above as also having benefits for the regulation of AIaMD. In addition, we are considering other changes to the Regulations specific to AIaMD. For example, we propose amending the Regulations to require performance evaluation methods for diagnostic AI which would take a comparable approach to performance evaluation methods used for in vitro diagnostic medical devices in terms of requiring demonstration similar to that of scientific validity along with analytical and clinical performance. This approach would build upon IMDRF's Software as a Medical Device (SaMD): Clinical Evaluation.

Q65.1 Are there other statutory changes required to effectively regulate AIaMD over and above the changes detailed for SaMD above?

Don't know

Q65.3 Do you consider the use of IVDR-type performance evaluation methods (akin to scientific validity, analytical performance, and clinical performance) for diagnostic software but especially AI (even where no IVD data is used) to be appropriate?

Yes

Q65.4 If yes, do you think the UK medical devices regulations should be amended to require this?

Yes

Q65.5 Should the UK medical devices regulations mandate logging of outputs of further auditability requirements for all SaMD or just AlaMD for traceability purposes?

Don't know

Q65.6 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 65.1-65.5, including any impacts on you or other stakeholder groups, including how burdensome would further requirements along these lines be?

Whether changes are made in regulation or in other ways, there should be as clear as possible Clearer definitional distinctions between different types of software/ AI in order are needed in order to more proportionately regulate 'software'.

In general, we support regulatory requirements that are commensurate with the potential risks associated with a device. In many contexts, simple algorithms may pose minimal risks to users and may not justify the burden of auditability requirements described above. However AlaMD may more complex, but also more opaque, as the internal logic of the decision process may not be transparent. For these devices, mandating logging of outputs of further auditability requirements for AlaMD is a much better evaluation method and should be more familiar to software developers who will be used to routinely running software testing (i.e., black and white box testing) akin to a performance evaluation, rather than clinical investigations.

72.1 The MHRA is considering introducing routes to the UK market which can be utilised by manufacturers with a Medical Device Single Audit Programme (MDSAP) certificate, or with an approval from certain other international regulators. Manufacturers entering through these alternative routes could apply for an abridged assessment with an Approved Body. Introducing alternative routes to market could have a number of benefits for example in enhancing the supply of devices to the UK for medical devices regulation to become globally harmonised. Patient safety will remain a priority, and the MHRA has carefully considered how these routes can be introduced with appropriate levels of scrutiny applied to medical devices to ensure they are safe and that they perform as intended.

Q72.1 Do you think the MHRA should introduce an alternative route to market which utilises Medical Device Single Audit Programme (MDSAP) certificates?

Yes

Q72.2 Please explain your answer to question 72.1 and, if applicable, please outline any further considerations/requirements that should be in place for accepting MDSAP certificates.

Such an approach could mean that the UK keeps pace with increasingly globalised 'gold' standards, as well as streamlining the process of certification for large manufacturers who float their device on several markets. In principle, the abridged assessment should also help maintain UK attractiveness, but this should not be done at the expense of patient safety. In order for consumers and manufacturers to reap the rewards of such a scheme, it is necessary to mitigate the impending approved bodies' bottleneck. How streamlined this scheme will be is dependent on not just more entities obtaining approved body status but also Auditing Organisation status. Consequently, if nothing is done to aid and encourage entities to obtain these certifications, such a scheme risks pushing more applications towards the gates of the few approved bodies that there are, without anyone to process them. Further delays, due to further bureaucracy could mean that UK patients fail to obtain access to the latest advancements in medical technology and drive manufacturers away from entering their devices onto the UK market.

Q72.3 Do you think the MHRA should introduce an alternative route to market which utilises approvals from other countries (domestic assurance route)?

Yes

73.1 The MHRA is considering an alternative pathway to market for devices that meet certain criteria. These criteria are likely to include factors such as:

- a. size of patient population-- rare conditions / small patient groups
- b. scale of innovation-- devices that will be 'game changers' for end users
- c. size of manufacturer-- targeting small and medium sized enterprises (SMEs).

Q73.1 Do you think the MHRA should introduce a pre-market approvals route to place innovative

medical devices into service for a specified time period and for specific use cases?

Yes

Q73.2 Do you think the MHRA should have powers to conduct conformity assessments and issue approvals in certain scenarios, such as the one outlined in paragraph 73.3?

Yes

Q73.3 Please provide your reasoning (including any available relevant

evidence) to support your answers to questions 72.1-73.2, including any impacts on you or other stakeholder groups and/or any other general comments on how this could be implemented, including potential timeframes and specified uses.

The PHG Foundation is strongly in favour of proportionate measures that facilitate alternative routes to market, particularly for patients with rare conditions or small patient groups, where the development of medical devices might be otherwise poorly resourced or even uneconomic. This proposal should also help smaller organisations involved in the research and development of innovative MedTech, and potentially prevent UK patients from losing out on accessing life-changing support or diagnostic devices. However, it is important that these measures do not compromise patient/user safety - we would not support any measures where patient/ user safety is ultimately compromised in practice.

Q72.4 Please explain your answer to question 72.3 and, if applicable, please outline any further considerations/requirements that should be in place for the domestic assurance route.

The underlying principle of mutual assurance in this scheme could help smaller scale manufacturers, cross-border access to devices on the EU market/ NI (as a similar standards regime) and help maintain UK market attractiveness.

However, the UK would need to encourage auditing organisations to regularly review regulatory changes in participating States. In order for domestic assurance to be effective, participating states will need to have reciprocal trust that other members regulatory oversight is robust, and aligned with UK requirements. This will be vital if the scheme is able to work effectively. Provided that these safeguards are in place, this should help ensure there are sufficient routes to market to offset short-term challenges (such as changing policy environments).

Determining which devices have access to these routes through being 'game changers' for end users could be contentious. We suggest that such support is determined by a representative group of stakeholders, and that these processes are transparent.

As a general comment, clarification is needed on whether such criteria are cumulative or not. If they are, it would limit the number of manufacturers who would potentially benefit from such a scheme.

75.1 We would like to provide you with the opportunity to comment on the level of ambition of the new regulatory system for medical devices, as set out in this consultation, and provide any feedback to help inform the final policy decisions made as a result of this consultation.

Q75.1 How would you rate the level of ambition set out in this consultation?

Excellent

Q75.2 Do you consider the possible changes to UK medical devices regulations set out in this consultation document to be proportionate?

Yes

Q75.3 Please set out your reasoning for your response to question 75.2.

To a significant degree these possible changes reflect the conclusions of our own research and analysis, in particular in relation to Health Institutions, IVDs, Software and AI as a medical device. We welcome them as a proportionate and much needed updating of the regulatory framework that balances the need to protect patients, individuals and consumers, with a regulatory approach that is as flexible and manageable for developers as possible.

Q75.4 Please provide any additional feedback comments.

The PHG Foundation warmly commends the MHRA for their ambitions to update their regulatory oversight to maintain and improve public and patient safety, information provision and decision-making transparency in line with international best practice, whilst simultaneously seeking to deliver flexible, responsive and proportionate regulation of medical devices.

As a policy think-tank working at the interface between new and emerging science and technologies and clinical and public health practice, the PHG Foundation appreciates the increasing challenge this poses, not only due to the sheer pace of innovation, but also because of the appearance of medical devices that are being used in novel ways – such as the application of mathematical algorithms and AI, new digital tools, and the integration of multiple testing modalities and information in diagnostic and predictive testing. The increasingly porous boundaries between formal health service and personal applications to predict, preserve and improve health further complicate the issue. Thus regulatory approaches that maintain appropriate agility and a suitably proportionate approach to potential risks and benefits are critical to balance the speed at which beneficial innovations reach the public, and the rigorous safety and transparency expectations we all share.

In our own areas of expertise including AI, genomics and other 'omic technologies for personalised and precision medicine, we are always happy to provide independent insight or support for the excellent work of the MHRA.

Contact: intelligence@phgfoundation.org

PHG Foundation is a health policy think tank with a special focus on how genomics and other emerging health technologies can provide more effective, personalised healthcare