

GeneWatch UK response to MHRA consultation on the future regulation of medical devices in the United Kingdom

November 2021

GeneWatch UK is a not-for-profit organisation which aims to ensure that genetic science and technologies are used in the public interest. Over the past twenty years, we have conducted a number of investigations of commercial genetic services provided via the internet, high-street stores, alternative health providers and private medical practitioners.

The focus of our response to this consultation is therefore on the regulation of genetic and genomic tests, including software, as an aspect of the regulation of In Vitro Diagnostics (IVDs).

All the genetic tests we have investigated have made invalid clinical claims; including false claims about disease risk (including risk of cancer) and misleading statements about the role of genetic tests in decision-making about diets, supplements, medication and smoking cessation. Currently no common genetic variants, or combinations of multiple rare genetic variants (now being used in Polygenic Risk Scores, PRS), have been identified that meet medical screening criteria for the general population.^{1,2} Yet, many such tests have been and continue to be marketed to the general population.^{3,4} Although many such genetic and genomic tests are marketed direct to consumer (DTC), some are also sold via private medical practitioners, and in the future there are plans to deliver more genomic tests via the NHS (including, potentially, screening babies' whole genomes at birth and/or returning PRS to large numbers of participants in 'pilot' studies). Since medical professionals will not be able to validate such tests, it is critical that they are covered by the regulatory system.

Our past findings regarding misleading marketing of genetic tests are consistent with investigations conducted by others, including the US Government Accountability Office (GAO)^{5,6}, academic researchers^{7,8} and the House of Commons Science and Technology Committee.⁹ Professional organisations such as the Royal College of Physicians and the British Society for Genetic Medicine have also warned that the analytical validity, sensitivity and clinical utility DTC genomic or genetic testing may be much lower than is popularly perceived, and that for certain types of DTC results, there is a very high chance of false positive or false negative results.¹⁰ Examples of recent concerns include:

- Recent research reports that DNA chips (which measure Single Nucleotide Polymorphisms, SNPs) are extremely unreliable for genotyping very rare pathogenic variants and should not be used to guide health decisions without validation.¹¹ In this study, 20 out of 21 individuals analysed had at least one false positive rare pathogenic variant that had been incorrectly genotyped during commercial testing. This study reinforces earlier reports of serious concerns regarding false positive results from direct-to-consumer genetic tests.^{12,13,14} Such results have real impacts on people's lives: reportedly, at least one patient was scheduled for preventive breast-removal surgery in the NHS after a consumer genetic test suggested she had a BRCA mutation. The surgery was called off at the last moment when an NHS laboratory revealed the result to be a false positive.¹⁵
- A 2019 review of 3,700 Genome Wide Association Studies (GWAS) concluded that most SNP-derived risk predictions are not as good as existing clinically based disease risk predictors (such as blood pressure or cholesterol levels).¹⁶ This study uses a common measure of test performance known as the AUROC, or AUC (Area Under the Receiver Operating Curve). It found that the average GWAS study produces a multi-SNP risk predictor with an AUC of 0.55, which is not much better than random guessing.¹⁷ In a more recent example, the company 23andMe reports a similar low AUC of 0.652 for its type 2 diabetes genetic risk score in people of 'European ancestry' reducing to 0.588 in people categorised as 'African American'.¹⁸

With such poor predictions, there is a danger that people will be misled into believing they do not need to adopt healthy lifestyles (if they are told they are not at 'high genetic risk'), or do need unnecessary medical check-ups or perhaps medication (if they are told they are at 'high genetic risk'). A recent paper (which has not yet been peer reviewed) also highlights how individuals cannot be confident that their Polygenic Risk Score has correctly placed them in a high (or low) genetic risk category, due to the very large error bars (95% confidence intervals) in these calculations.¹⁹

- More recently, a study of DTC tests claiming to identify genetic susceptibility to COVID-19 concluded that they provide inconsistent results and are not based on established scientific information.²⁰ Although this conference presentation has not been peer reviewed, its conclusions are not surprising since studies in this area have calculated low (or, in some cases undetectable) SNP-based heritabilities.²¹ A low heritability inevitably implies a low AUC, and hence very poor predictive value.²²

There is widespread agreement on the standards that genetic and genomic tests should meet: however, there is currently limited monitoring or enforcement of such standards. This lack of regulation has been widely regarded as inadequate to protect consumers purchasing DTC genetic tests and users of genetic tests within health services.^{23,24,25} GeneWatch UK has argued since 2002 that "*Genetic tests need urgent regulation by a statutory body to ensure their validity and usefulness*" and first published a detailed briefing in making the case for regulation in the UK in 2004.^{26,27} Recognition of this problem eventually led to the development of the In Vitro Diagnostics Regulation (IVDR) in the EU and to action by the FDA in the USA.²⁸ These developments involve an important step away from self-regulation to requiring clinical evidence to support claims and protect public health. GeneWatch UK therefore welcomes the MHRA's proposals to align regulation in Great Britain with international standards, and to recognise new developments such as the increasing importance of regulating the software and algorithms used to calculate genetic risks. In the context of the Medicines and Medical Devices Act 2021 Assessment, we note that the issue of public trust is also important and should have been included: the UK will only be seen as a favourable place for R&D if misleading and unsubstantiated tests are not allowed to flood the market.

Fully informed consent and confidentiality are also of critical importance in genomic medicine. Hence, requirements for clinical studies must be consistent with international ethical standards such as the Helsinki Declaration, and relevant legislation designed to protect privacy and human rights, such as the Human Tissue Act, Data Protection Act and Human Rights Act.

GeneWatch UK agrees and supports the majority of proposals in the consultation. However, we note a number of areas where they could be improved. In particular:

- It should be made explicit that the 'health institution' exemption does not apply to screening, due to the potential for large numbers of false positive and false negative test results. Health institutions which provide diagnostic services to others should not be able to use the exemption, due to the scale of testing and the potential for harm to large numbers of people if such tests are not properly regulated.
- All health-related genetic tests should be 'prescription-only', so that requirements for fully-informed consent and ethical requirements (especially in relation to children and vulnerable persons) can be met, and genetic counselling provided as and when required.
- The use of the term 'left-over samples' is potentially misleading and open to abuse (Sections 34 and 35). Under data protection legislation, biological samples are collected from an individual for a specific purpose, and it is important that data protection principles and the provisions of the Human Tissue Act continue to apply.

In particular, undertaking genetic testing, or even whole genome sequencing, of samples in the absence of fully informed consent is likely to lead to a major loss of public trust. Genetic data obtained from DNA chips or sequencing is sufficient to act as a biometric identifier for individuals or their relatives, allowing them to be tracked by commercial interests (e.g. for marketing purposes) or by police or security services (allowing an unacceptable level of surveillance and interference with human rights). It should therefore be clarified that samples collected for other purposes should not be used for genetic or genomic testing without fully informed consent.

- Diet-related disease is a major killer, yet genetic tests combined with dietary advice and/or advice to take supplements are sometimes marketed as 'lifestyle' tests, with the aim of avoiding regulation. Similar concerns apply to tests combined with mental health advice, advice to quit smoking, or advice on sport and exercise. Misleading information or advice in any of these areas could lead to negative impacts on individual health and/or public health, if the wrong recommendations are provided to the wrong people. The definition of an in-vitro diagnostic test should be clarified, so that it is clear that such tests are covered by the regulation.
- Although the requirements to create a register of devices and to require a public summary of clinical investigations do improve transparency, the level of transparency could be rather limited. It is essential that the device registration information provides a sufficient level of transparency for members of the public (and/or their doctors, or independent scientists) to understand how a particular conclusion regarding their diagnosis/prognosis was reached, which is arguably both an ethical and legal requirement in the context of algorithmic decision-making.²⁹ This is of considerable practical importance because different genetic test providers often give contradictory results.
- Software as a medical device (SaMD) used to analyse human genetic data should be in Class C (the same as human genetic testing), otherwise it will lead to the illogical result that stand-alone software may have weaker regulatory requirements and thus, for example, a polygenic risk score (PRS) that could not be returned to someone when they have a genetic test (due to poor performance) could be returned to them online via stand-alone software.
- Consideration of environmental sustainability (Section 71) should also include energy use, as this is a major consideration for algorithms derived from sample storage in biobanks and large-scale data storage (including genomic data).³⁰ Measures to reduce the environmental impacts of medicine are beginning to be considered in the context of the use and disposal of plastic and release of greenhouse gases by asthma inhalers, for example.³¹ However, energy use by 'Big Data', including genomics, should also be considered, if significant negative impacts on emissions targets are to be avoided.
- The 'CE plus UKCA' route should be sufficient to achieve certification for both EU and UK markets. Other 'domestic assurance' and 'pre-market approval' routes to market risk undermining the regulatory system and losing public trust.

Finally, GeneWatch UK notes that the proposed substantial delays to implementation contained in Section 74 are generally consistent with delays in implementing the requirements of the IVDR in the EU, where the European Commission has noted that the COVID-19 pandemic has on the one hand confirmed the need for a robust regulatory framework, but on the other hand posed challenges to implementation (mainly due to lack of capacity of notified bodies).³² However, whilst recognising there are current limitations to regulatory capacity, we remain concerned that such regulations have been a long time in development and that any delay could lead to negative impacts on human health, as poorly performing tests which provide misleading information can continue to be marketed. At minimum, safeguards retained by the EU during the proposed extended transitional period should also be implemented in the UK, namely market and post-market surveillance,

vigilance, and registration of economic operators and devices. In addition, it does not assist companies or the public to delay implementation of requirements for clinical investigations, since this risks the relevant data not being collected (or being collected in an unethical way) and therefore not being adequate to support a subsequent application to place the test on the market when the transitional period is over.

Chapter 1: Scope of the Regulations

Section 1 - Medical device and IVD scope

Q1.1 Do you think the scope of the UK medical devices regulations should be expanded to include the additions suggested above? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes. In the context of genetic/genomic testing, it is particularly important to include prediction, predisposition and prognosis of disease within the scope, and to include the software, which is commonly used to combine the risks of multiple genetic variants.

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

The scope should refer to all products which provide health-related information by means of examination of samples or data derived from the human body. This should ensure the scope includes genetic tests marketed with dietary recommendations, supplements, and advice on mental health or lifestyle, even if the specific medical conditions involved (such as type 2 diabetes, obesity or depression) are not explicitly mentioned.

Whilst we do not suggest that genetic tests claiming solely to identify a person's ancestry are included in the scope, it should be noted that polygenic risk scores (PRS) are increasingly being combined with ancestry testing in order to provide different health predictions to different populations. In this context, it should be noted that the use of genetically-derived ancestry estimates will also require regulatory oversight.

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.

The proposed definition means that genetic/genomic tests and software (including software which combines measurements of multiple genetic variants) which claim to predict disease risk or drug response, or diagnose a medical condition, clearly fall within the scope of the Regulation, whilst stand-alone genetic ancestry or paternity tests do not.

However, the definition should be clarified to ensure that all tests providing health-related information (such as dietary advice, or advice to quit smoking) are covered, since incorrect dietary or other public health advice could have significant adverse public health implications. A number of misleading genetic tests combined with dietary advice or advice to quit smoking have been sold in the past.^{33,34,35} Commercial companies continue to sell genetic tests with dietary advice, making unsubstantiated promises for 'a longer, healthier and happier life'.³⁶ Although not stated explicitly, such tests rely on genetic associations with diet-related conditions such as type 2 diabetes, obesity and cancers, which should be covered by the regulation.

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' / 'No' / 'Don't Know/No Opinion'Yes/No/Don't Know/No Opinion)

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.

There are important differences between the evidence required for different purposes. For example, if a genetic test is used to aid diagnosis in a person with symptoms there will be less concern about false positive results than if the same test is used as a screening test in the general population, where false positive results might lead to significant harm to health. Genetic tests also often depend on context, including family history, for correct interpretation.³⁷ The risk associated with a particular variant or combination of variants may also depend on age, environment, ancestry, and socio-economic status.^{38,39,40,41,42} Thus, it is important that the manufacturer has defined the purpose and context of the test.

Section 2 - Products without a medical purpose

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' / 'No' / 'Don't Know/No Opinion')

Yes

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

See response to Q1.3. The scope should be clarified to ensure that all tests providing health-related information (such as dietary advice, or advice to quit smoking) are covered
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
- b. please describe how these products should be assessed to ensure that they are safe and perform as intended.
- 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).

See response to Q1.4.

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' / 'No' / 'Don't Know/No Opinion')

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.

Section 3 - Exclusion of products that contain viable biological substances

Q3.1 Do you think that products which contain viable biological substances should be excluded from the scope of the UK medical devices regulations? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q3.2 Please provide your reasoning (including any available relevant evidence) to support your answer to question 3.1, including any impacts on you or other stakeholder groups.

Section 4 - Exclusion of food

Q4.1 Do you think that food should be excluded from the scope of the UK medical devices regulations? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q4.2 Please provide your reasoning (including any available relevant evidence) to support your answer to question 4.1, including any impacts on you or other stakeholder groups.

Chapter 2: Classification

Section 5 - Classification of general medical devices

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' / 'No' / 'Don't Know/No Opinion')

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

Q5.3 Please outline any other amendments which should be made to the classification rules (including implementing rules and related definitions).

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.

Chapter 3: Economic Operators

Section 6 - Essential requirements for medical devices

Q6.1 Do you think the essential requirements of the UK medical devices regulations should be amended as set out in paragraph 6.4? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q6.2 Please outline any other amendments which should be made to the essential requirements of the UK medical devices regulations.

Q6.3 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 6.1-6.2, including any impacts on you or other stakeholder groups.

Section 7 - Manufacturer obligation – measures for recompense

Q7.1 Do you think that the UK medical devices regulations should include a requirement for manufacturers to have measures in place (for example, sufficient financial coverage) for recompensing those impacted by adverse incidents with medical devices on the UK market? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q7.2 Please set out the reasoning for your answer to question 7.1, including any expected impacts of the change on you or other stakeholder groups and key implementation considerations.

Misleading genetic tests can lead to significant adverse impacts on patients: for example, in the case of false positive diagnoses, people could take unnecessary medication or even have prophylactic surgery to remove their breasts.^{43,44,45,46} A requirement for liability insurance could have two important consequences. Firstly, it can provide financial compensation to anyone adversely affected by an erroneous diagnosis/prognosis. Secondly, it provides an important incentive for regulatory compliance, as it is likely manufacturers would have to demonstrate this in order to obtain valid insurance.

Section 8 - Health Institutions

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' / 'No' / 'Don't Know/No Opinion')

Yes.

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

A 'health institution' means an organisation the primary purpose of which is the care or treatment of patients or the promotion of public health. The definition should not allow devices benefitting from any health institution to be transferred to another legal entity, or be used outside the health institution, and should not apply to devices that are manufactured on an industrial scale. The use of the 'health institution' exemption must be justified (in its documentation) by evidence 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. The concept of 'health institution' should not cover establishments primarily claiming to pursue health interests or healthy lifestyles, such as gyms, spas, wellness and fitness centres.

It is important that the use of the 'health institution' exemption does not lead to the roll out of unregulated tests to large numbers of people in the entire NHS, for example, as this would mean the regulatory regime would fail to provide the necessary protections for public health.

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'/'No'/'Don't Know' or /'No Opinion')

Yes

Q8.4 Do you think that 'in house' manufactured devices should be exempt from UKCA marking requirements? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

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' / 'No' / 'Don't Know/No Opinion')

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.

The regulation should not allow devices benefitting from any health institution to be transferred to another legal entity, or be used outside the health institution, and should not apply to devices that are manufactured on an industrial scale. The use of the 'health institution' exemption must be justified (in its documentation) by evidence 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. The concept of 'health institution' should not cover establishments primarily claiming to pursue health interests or healthy lifestyles, such as gyms, spas, wellness and fitness centres.

The 'health institution' exemption should not apply to screening, due to the potential for large numbers of false positive and false negative test results.

Q8.7 Do you think that health institutions should be required to register medical devices manufactured or modified 'in house' with the MHRA? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q8.8 Do you think that health institutions should be required to register clinical investigations / performance studies with the MHRA? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes. It is important that the ethical and scientific standards required for clinical investigations/performance studies also apply to patients with rare diseases, for example, who may be tested via this exemption.

Q8.9 Do you think that the provisions in paragraph 8.9 should be introduced for health institutions? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes.

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? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes.

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.

The exemption should be allowed to ensure patient access to tests for rare diseases, for example, which may not be available on the market due to rarity of some relevant conditions. However, it should not render the regulation effectively useless by allowing the roll out of tests to the whole UK population via the NHS (e.g. via whole genome sequencing at birth, or polygenic risk scores, PRS, to large numbers of the adult population), because this would likely lead to harm to public health due to the poor predictive value of such test and the potential for large numbers of false negatives and false positives.

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?

No.

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)?

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.

The Supra-Regional assay service already supplies some genetic tests, including the APOE polymorphism test, associated with variations in cholesterol levels and with risk of Alzheimers' Disease.⁴⁷ This is a test which could be supplied to large numbers of patients, both within the NHS and privately, and it should be properly regulated. Similarly, tests provided by the Genetics Enzymes Service should be regulated to ensure that patients are not provided with misleading test results.⁴⁸ Given the long transition period provided, and the well-established nature of many of these conditions in the literature, it should be possible for the necessary clinical evidence to be provided to obtain the UKCA mark.

As noted in response to Q8.6, any exemption (if granted) should not be applied to screening, due to the potential for large numbers of false negatives and false positives.

Section 9 - Distance sales

Q9.1 Do you think that we should introduce the requirements set out in paragraph 9.5 for medical devices or services sold or provided at a distance through electronic means? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q9.2 Do you think that we should introduce the requirement set out in paragraph 9.6? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q9.3 Please outline any other requirements that should be introduced for medical devices that are subject to distance sales.

A major issue in relation to distance sales of genetic/genomic tests is how consent is obtained, particularly in relation to children or other vulnerable persons. There is considerable potential for abuse, for example, ordering tests for children which undermine their rights to make their own decisions as they grow up, in breach of numerous ethical guidelines.⁴⁹ Other vulnerable persons, for example people suffering from mental illness, may also be put at risk. Since genetic tests can also reveal non-paternity, this means that non-consensual paternity testing may also be facilitated, with the potential to destroy families and undermine the best interests of the child. It is also widely regarded as essential to provide genetic counselling services (before and after testing) for at least some genetic tests.

The easiest way to address these concerns is to make all health-related genetic tests 'prescription-only'. This goes beyond the provisions in the EU IVD Regulation, for example, because this issue is regarded as one for national governments, but a ban on DTC tests has already been implemented in several countries, including France, Germany, Portugal and Switzerland.⁵⁰ This would not necessarily prevent medical practitioners from ordering genetic or genomic tests online, but those practitioners (rather than a tick box on a website) would

be responsible for ensuring that patients have consented and that ethical guidelines for testing children and other vulnerable persons have been followed.

Q9.4 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 9.1-9.3, including any impacts on you or other stakeholder groups.

The majority of DTC genetic/genomic tests are provided via the internet and there is significant concern about poor consent requirements, misinformation, and impacts on vulnerable people, including children.^{51, 52, 53}

Section 10 – Claims

Q10.1 Do you think that we should introduce the provisions set out in paragraph 10.4? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q10.2 Please provide your reasoning (including any available relevant evidence) to support your answer to question 10.1, including any impacts on you or other stakeholder groups.

Studies have repeatedly identified misleading claims in relation to genetic tests, including the US Government Accountability Office (GAO)^{54,55}, academic researchers^{56,57} and the House of Commons Science and Technology Committee.⁵⁸ Professional organisations such as the Royal College of Physicians and the British Society for Genetic Medicine have also warned that the analytical validity, sensitivity and clinical utility DTC genomic or genetic testing may be much lower than is popularly perceived, and that for certain types of DTC results, there is a very high chance of false positive or false negative results.⁵⁹ Recent research reports that DNA chips (which measure Single Nucleotide Polymorphisms, SNPs) are extremely unreliable for genotyping very rare pathogenic variants and should not be used to guide health decisions without validation.⁶⁰ In this study, 20 out of 21 individuals analysed had at least one false positive rare pathogenic variant that had been incorrectly genotyped during commercial testing. This study reinforces earlier reports of serious concerns regarding false positive results from direct-to-consumer genetic tests.^{61,62,63} Such results have real impacts on people's lives: reportedly, at least one patient was scheduled for preventive breast-removal surgery in the NHS after a consumer genetic test suggested she had a BRCA mutation. The surgery was called off at the last moment when an NHS laboratory revealed the result to be a false positive.⁶⁴ More recently, a study of DTC tests claiming to identify genetic susceptibility to COVID-19 concluded that they provide inconsistent results and are not based on established scientific information.⁶⁵ Although this conference presentation has not been peer reviewed, its conclusions are not surprising since studies in this area have calculated low (or, in some cases undetectable) SNP-based heritabilities.⁶⁶ A low heritability inevitably implies a low AUC, and hence very poor predictive value.⁶⁷

Similar concerns are likely to apply to Polygenic Risk Scores (PRS), which are expected to be much more widely marketed in future (both DTC and within the NHS). For example, A 2019 review of 3,700 Genome Wide Association Studies (GWAS) concluded that most SNP-derived risk predictions are not as good as existing clinically based disease risk predictors (such as blood pressure or cholesterol levels).⁶⁸ This study uses a common measure of test performance known as the AUROC, or AUC (Area Under the Receiver Operating Curve). It found that the average GWAS study produces a multi-SNP risk predictor with an AUC of 0.55, which is not much better than random guessing.⁶⁹ In a more recent example, the company 23andMe reports a similar low AUC of 0.652 for its type 2 diabetes genetic risk score in people of 'European ancestry' reducing to 0.588 in people categorised as 'African American'.⁷⁰ With such poor predictions, there is a danger that people will be misled into

believing they do not need to adopt healthy lifestyles (if they are told they are not at 'high genetic risk'), or do need unnecessary medical check-ups or perhaps medication (if they are told they are at 'high genetic risk'). A recent paper (which has not yet been peer reviewed) also highlights how individuals cannot be confident that their Polygenic Risk Score has correctly placed them in a high (or low) genetic risk category, due to the very large error bars (95% confidence intervals) in these calculations.⁷¹

Section 11 - Quality Management Systems

Q11.1 Do you think that we should introduce the detailed requirements for Quality Management Systems outlined in paragraph 11.3 ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q11.2 Please outline any other requirements which should be included in the manufacturer's Quality Management System.

Q11.3 Do you think that all manufacturers, including Class I and general IVD manufacturers, should be required to apply an appropriate Quality Management System? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q11.4 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 11.1-11.3, including any impacts on you or other stakeholder groups.

QMS is essential to implement the regulatory requirements and hence to protect public health.

Section 12 - UK Responsible Persons

Q12.1 Do you think the UK Responsible Person should be explicitly required in the UK medical devices regulations to have an address in the UK at which they are "physically located"? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q12.2 Do you think the UK Responsible Person should be legally liable for defective medical devices on the same basis as the manufacturer as outlined in paragraph 12.5? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q12.3 Do you think the UK medical devices regulations should include a requirement for manufacturers and UK Responsible Persons to draw up a legal contract as outlined in paragraph 12.6? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q12.4 Do you think that the UK medical devices regulations should include the requirement for manufacturers to draw up a changeover agreement when changing their UK Responsible Person as set out in paragraph 12.7? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q12.5 What time-period should be specified for the retention of technical documentation relating to implantable devices by the UK Responsible Person?

- a. 11-15 years after the last product has been manufactured
- b. 16-20 years after the last product has been manufactured
- c. for the expected lifetime of the device, after the last product has been manufactured
- d. Other (please specify)

Q12.6 What time-period should be specified for the retention of technical documentation relating to non-implantable devices by the UK Responsible Person?

(d)

- a. 1-5 years after the last product has been manufactured
- b. 10 years after the last product has been manufactured
- c. 11-15 years after the last product has been manufactured
- d. for the expected lifetime of the device, after the last product has been manufactured
- e. Other (please specify)

Q12.7 Do you think the UK medical devices regulations should introduce an obligation on UK Responsible Persons to retain documentation in cases where the manufacturer has ceased activity? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q12.8 Do you think UK Responsible Persons should be required to have at least one Qualified Person that is permanently and continuously at their disposal as set out in paragraph 12.10? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q12.9 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 12.1-12.8, including any impacts on you or other stakeholder groups.

It is essential that it is clear who is legally responsible if regulation is to be implemented effectively.

Section 13 – Obligations of importers and distributors

Q13.1 Do you think that importers and distributors should be required to meet the requirements outlined in paragraph 13.4? ('Yes' / 'No' / 'Don't Know/No Opinion' / 'Partial' – please specify which options)

Yes

Q13.2 Please outline any other requirements which should be introduced for importers and distributors.

Q13.3 Do you think that fulfilment service providers should be regarded as importers under the UK medical devices regulations? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q13.4 Do you think that economic operators should be required to inform the MHRA if they are aware of any issues that will interrupt supply / cause a shortage of medical devices on the UK market, as set out in paragraph 13.6? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q13.5 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 13.1-13.4, including any impacts on you or other stakeholder groups.

Section 14 - Qualified Persons

Q14.1 Do you think manufacturers should be required to have at least one Qualified Person available within their organisation as set out in paragraph 14.3? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q14.2 What qualifications and / or experience should the Qualified Person have in order to be eligible for this role?

Q14.3 Do you think that small and medium enterprises (SMEs) should be excluded from this requirement and instead be required to have a Qualified Person permanently and continuously at their disposal? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q14.4 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 14.1-14.3, including any impacts on you or other stakeholder groups.

Section 15 - Cases in which obligations of manufacturers apply to other economic operators

Q15.1 Do you think that the circumstances in which an economic operator other than the device manufacturer would be required to assume the responsibilities of the manufacturer should be clarified, as set out in paragraph 15.5? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q15.2 Do you think that the UK medical devices regulations should be amended to clarify the circumstances in which an economic operator would not be required to take on the responsibilities of a manufacturer, as set out in paragraph 15.6? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q15.3 Do you think that the UK medical devices regulations should outline the requirements that economic operators would need to meet in circumstances where they have made a modification, without taking on the obligations of the manufacturer, as set out in paragraph 15.7? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q15.4 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 15.1-15.3, including any impacts on you or other stakeholder groups.

Genetic test manufacturers commonly provide tests to other providers, for example private health practitioners, and in some cases these practitioners develop their own software to interpret the results. In such cases it is critical that economic operators are responsible for any changes they have made, as changes can lead to misleading results which could have negative impacts on a person's health.

Chapter 4: Registration and UDI

Section 17 - Identification within the supply chain

Q17.1 Do you think the UK medical devices regulations should include the requirements set out in paragraph 17.1 for economic operators to ensure traceability of medical devices? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q17.2 Please outline any other traceability requirements which should be introduced for economic operators.

Q17.3 If we were to introduce a requirement for economic operators to be able to track the supply of medical devices, and to keep the records pertaining to that for a specific time period (as set out under paragraphs 17.3 and 17.4 above), what time period should be specified?

Misleading genetic test results, if not corrected, could have an impact over the lifetime of a patient, hence traceability should apply over sufficiently long timescales to ensure any erroneous results can be corrected.

Q17.4 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 17.1-17.3, including any impacts on you or other stakeholder groups.

Section 18 - Nomenclature

Q18.1 Please select which nomenclature, for purposes of medical device identification, should be required under the UK medical devices regulations: (GMDN / EMDN / Other (please specify))

Q18.2 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 18.1-18.2, including any impacts on you or other stakeholder groups.

Section 19 - Unique Device Identification

Q19.1 Do you think that the UK medical devices regulations should include a definition of the term 'Unique Device Identifier'? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q19.2 If you answered 'yes' to question 19.1, please outline what you think should be included in this definition.

'Unique Device Identifier' ('UDI') means a series of numeric or alphanumeric characters that is created through internationally accepted device identification and coding standards and that allows unambiguous identification of specific devices on the market.

Q19.3 Do you think the UK medical devices regulations should require manufacturers to assign UDIs to medical devices before they are placed on the market? (Yes/No/Don't Know/No Opinion)

Yes

Q19.4 If you have answered 'yes' to question 19.3, please outline any particular requirements which should be introduced in regards to how UDIs should be applied to medical devices and any aspects which require clarification.

A new UDI should be required whenever there is a change that could lead to misidentification of the device and/or ambiguity in its traceability. In particular, this should include any change in the version of the device, including its software. This is important because the same genetic variants can be interpreted (or misinterpreted) in multiple ways depending on the software, leading to changes in whether a person is categorised as at high or low risk of a particular disease. This is particularly the case for Polygenic Risk Scores (PRS) where the uncertainty is particularly high.⁷²

Q19.5 Should devices that are reusable bear a UDI carrier (e.g. barcode) that is permanent and readable after each process on the device itself? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q19.6 Please outline whether you think there should be any exceptions to this rule and please provide examples and reasoning.

Q19.7 Should the UK medical devices regulations include requirements for Basic UDI-DI to identify medical device models? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q19.8 Do you think manufacturers should be required to assign and apply UDIs to their medical devices before applying to Approved Bodies for conformity assessment? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q19.9 Do you think the UK medical devices regulations should stipulate that the UDI or Basic UDI-DI of a medical device should be provided in the circumstances set out in paragraph 19.12? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q19.10 Please outline any other circumstances in which the UDI or Basic UDI-DI should be provided for a medical device.

Q19.11 Do you think that certain medical devices should be exempt from the UDI requirements? ('Yes' / 'No' / 'Don't Know/No Opinion')

No

Q19.12 If you have answered 'yes' to question 19.11, please outline what medical devices should be exempt.

Q19.13 Should manufacturers of custom-made devices be required to assign a unique serial number to the device? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q19.14 Please outline which issuing entities should be designated by the MHRA. In your response please provide the following information: a. should the MHRA designate one or multiple UDI issuing entities? b. if there should be one issuing agency, which one (and why)? c. if there should be multiple issuing agencies, which ones (and why)?

A single agency is less likely to lead to confusion.

Q19.15 Do you think manufacturers should be required to keep an up-to-date list of all UDIs they have assigned to medical devices as part of the technical documentation? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q19.16 If you answered 'yes' to question 19.15, how long should manufacturers be required to hold this information? When responding to this question, please indicate whether you think there should be different minimum periods of retention depending upon type of device / risk classification.

Q19.17 Do you think economic operators should be required to store the UDI numbers of certain medical devices? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q19.18 If you have answered 'yes' to question 19.17, please select which groups of medical devices which should fall under this requirement:

- a. all implantable medical devices
- b. Class III implantable medical devices
- c. Class IIb implantable medical devices
- d. Other – please specify
- e. Don't Know/No Opinion

Q19.19 Do you think healthcare professionals and/or health institutions should be required to store the UDIs of certain medical devices? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q19.20 If you have answered 'yes' to question 19.19, please outline what types / risk classification of medical devices should fall under this requirement.

- a. all implantable medical devices
- b. Class III implantable medical devices

c. Class IIb implantable medical devices

d. Other – please specify

e. Don't Know/No Opinion

Q19.21 Do you think that the UK medical devices regulations should introduce new rules for the UDI system, to provide clarity? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q19.22 If you have answered 'yes' to question 19.21 please outline what rules the UK medical devices regulations should include in regard to the UDI system.

Q19.23 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 19.1-19.22, including any impacts on you or other stakeholder groups.

Section 20 - Great Britain database on medical devices

Q20.1 Do you think that we should introduce the proposal outlined in paragraph 20.1? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q20.2 Please provide your reasoning (including any available relevant evidence) to support your answer to question 20.1, including any impacts on or implementation considerations for you or other stakeholder groups.

This proposal should ensure that known problems are acted upon. For example, evidence that DNA chips are not a reliable means of genotyping very rare pathogenic variants, and that false positive results can have serious adverse effects.^{73,74,75,76,77}

Section 21 - Registration of medical devices

Q21.1 Do you think manufacturers should be required to provide the information in List One (at end of this Section) to the MHRA upon medical device registration? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q21.2 Please specify any changes proposed and your rationale in relation to question 21.1.

Q21.3 Which of the following entities should be permitted to submit device registration information to MHRA (select all that apply):

a. UKRPs and UK-based manufacturers (current requirement)

b. non-UK based manufacturers

c. authorised third party submitters

d. other – please specify

Q21.4 What mechanisms should be in place to submit data?

a. web form

b. machine-to-machine (e.g. HL7 etc)

c. other – please specify

Q21.5 Please outline the timeframes that you think should apply to this additional registration information.

Q21.6 Should the information that the MHRA gathers at the point of medical device registration be made publicly available via a website or similar platform? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes.

Q21.7 If you have answered 'yes' to question 21.6, please outline what information should be shared and provide your rationale and key considerations or limitations (please note sharing of information would be subject to UK GDPR requirements).

It is essential that the device registration information provides a sufficient level of transparency for members of the public (and/or their doctors, or independent scientists) to understand how a particular conclusion regarding their diagnosis/prognosis was reached, which is arguably both an ethical and legal requirement in the context of algorithmic decision-making.⁷⁸ This is of considerable practical importance because different genetic test providers often give contradictory results.

Q21.8 Do you think the UK medical devices regulations should include a requirement for manufacturers to register with the MHRA before applying to an Approved Body for conformity assessment and for the Approved Body to verify this registration? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q21.9 Should economic operators be given up to 30 days to update an MHRA registration record after a change has been made to a device's registration details? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q21.10 Please provide reasoning to support your answer to question 21.9.

Genetic/genomic test providers make occasional changes to the technology used (for example, upgrading the DNA chip) and frequent changes to software (which can give a significantly different result - for example, changing a person's risk assessment for a particular condition from low genetic risk to high genetic risk, or vice versa). If regulation is to be meaningful, changes must be submitted to the registration system as soon as possible.

Q21.11 Do you think the UK medical devices regulations should include a requirement for economic operators to confirm all data submitted in their registration one year after submission and then every second year thereafter? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q21.12 How should economic operators be identified within the MHRA registration system?:

- a. MHRA generated reference number (not internationally recognised)
- b. DUNs (internationally recognised external reference)
- c. GLN (internationally recognised external reference)
- d. other (please specify)

Q21.13 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 21.1-21.12, including any impacts on you or other stakeholder groups.

Chapter 5: Approved Bodies

Section 23 - Requirements of Approved Bodies

Q23.1. Do you think the UK medical devices regulations should place more stringent requirements on Approved Bodies as set out in paragraph 23.3? ('Yes' / 'No' / 'Don't Know/No Opinion')

yes

Q23.2. Please outline any other requirements which should be introduced for Approved Bodies.

Q23.3. Do you think that Approved Bodies should be able to conduct fully remote or hybrid audits of their clients in specific circumstances, as outlined in paragraph 23.4? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q23.4. If you answered 'yes' to question 23.3 please outline any criteria you consider should apply to the use of remote and hybrid audits, and the expected impact of this change including any key implementation considerations that need to be considered.

Q23.5. Please select the option you agree with:

To become designated as an Approved Body the company/organisation:

- a. should be a distinct legal entity based in the UK (the company as a whole)
- b. should be a distinct legal entity based in the UK or have a branch in the UK
- c. other (please specify)
- d. don't know/no opinion

Q23.6. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 23.1-23.5, including any impacts on you or other stakeholder groups.

Section 24 – Subsidiaries

Q24.1. Do you think that Approved Bodies using subsidiaries should meet the requirements set out above? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q24.2. Please outline any other requirements which should be placed on Approved Bodies using subsidiaries.

Q24.4. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 24.1-24.2, including any impacts on you or other stakeholder groups.

Section 25 - Approved Body designation and monitoring

Q25.1. Do you agree that the UK medical devices regulations should require Approved Bodies applying for designation to hold appropriate UKAS accreditation? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q25.2. Do you think the UK medical devices regulations should include the requirements set out in paragraph 25.4 for MHRA assessment of Approved Bodies? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q25.3. Please outline any other requirements which should be introduced for MHRA assessment of Approved Bodies.

Q25.4. Do you think that the MHRA should be able to perform remote audits of Approved Bodies or their subsidiaries in specific circumstances? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q25.5 If you answered 'yes' to question 25.4, please outline any criteria you consider should apply to the use of remote audits, and the expected impact of this change including any key implementation considerations that need to be taken into account.

Q25.6. Do you think the transitional arrangement above for 'roll over' of Medical Device & Active Implantable Medical Device Approved Body designation is suitable? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q25.7. Please explain your reasoning to question 25.6 and expand on what you consider would be suitable criteria for this 'roll over' if any.

Q25.8. Do you think that the MHRA should be required to perform the tasks set out in paragraph 25.7 in the event of Approved Body designation withdrawal, restriction, or suspension? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q25.9. Do you think that the UK medical devices regulations should set out the circumstances in which certificates shall remain valid on an ongoing basis or for a defined time period in the event of designation withdrawal? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q25.10. If you have answered 'yes' to question 25.9 please outline any circumstances in which certificates should remain valid on an ongoing basis or for a defined time period.

Q25.11. Do you think the UK medical devices regulations should introduce requirements set out in paragraph 25.9 for Approved Bodies in relation to how they conduct their activities? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q25.12. Please outline any other requirements which should be introduced in relation to how Approved Bodies conduct their activities.

Q25.13. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 25.1-25.12, including any impacts on you or other stakeholder groups.

Chapter 6: Conformity Assessment

Q26.1 Do you think the conformity assessment requirements for medical devices should be clarified and strengthened for medical devices as set out in paragraph 26.6 above? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q26.2. Please outline any other clarifications or additions to requirements that you think should be introduced to strengthen the conformity assessment of medical devices under the UK medical device regulations. Please include your rationale and any expected impacts on you/other stakeholder groups (including any implementation considerations such as guidance that may be required).

Q26.3. The current timeframe for which manufacturers must retain technical documentation is 15 years for implantable devices, and 5 years for all other medical devices. We are considering whether this is sufficient. An option is for this to be 15 years for implantable devices and 10 years for other medical devices. For how long should the manufacturer be required to keep technical documentation for a medical device they have manufactured?

- a. 1-5 years after the last product has been manufactured
- b. 6-10 years after the last product has been manufactured
- c. 11-15 years after the last product has been manufactured
- d. For the expected lifetime of the device, after the last product has been manufactured
- e. Other (please specify)

Q26.4. Do you think that certain conformity assessment routes, including those in paragraph 26.8 or others, should be removed from the UK medical devices regulations?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q26.5. If you have answered 'yes' to question 26.4, please outline which conformity assessment routes could be removed from the UK medical devices regulations.

Q26.6. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 26.1-26.5, including any impacts on you or other stakeholder groups.

Section 27 - Mechanism for transparency and scrutiny of conformity assessments of certain medical devices

Q27.1. Do you think Approved Bodies should be required to notify the MHRA of certificates they have granted for general medical devices with the accompanying documentation set out in paragraph 27.2? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q27.2. Do you think the MHRA should apply additional scrutiny to the conformity assessment report for certain classes/types of medical devices? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q27.3. If you have answered 'yes' to question 27.2 please outline which types/classes of medical devices this additional scrutiny should apply to.

Our answer relates to genetic/genomic tests only. Categories include d) (highest risk IVDs, including genetic tests used as companion diagnostics) and e) (machine learning based medical devices, including genetic/genomic tests which utilise machine learning software).

Q27.4. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 27.1-27.3, including any impacts on you or other stakeholder groups.

Companion diagnostics include pharmacogenetic tests which can change a prescribing decision in ways that can harm a patient if the results are wrong. Machine learning software can lead to risks of genetic variants being combined in ways that are not easily verified or understood, potentially providing misleading information that could harm health.

Section 28 - Certificates of Conformity

Q28.1. Do you think the UK medical devices regulations should detail the minimum content of Certificates of Conformity? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q28.2. If you have answered 'yes' to question 28.1, please outline what should be included as part of the content of a Certificate of Conformity (you may reference bullet points a-l above).

Q28.3. Do you think Approved Bodies should be allowed to impose restrictions/requirements on the use/follow-up of certain medical devices? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q28.4 If you have answered 'yes' to question 28.3, please outline what restrictions / requirements Approved Bodies could impose.

False positives and false negatives from genetic/genomic tests can lead to harms to health. The extent of such harm depends on how the test is used, for example as a diagnostic or screening test, in a specified population, or more widely and with or without additional information (such as family history). In addition, there are ethical issues, such as the requirement to allow children to decide whether or not to take a genetic test relating to adult-onset conditions when they grow up, and providing genetic counselling where necessary. It is therefore critical that tests can be restricted to specific groups of people to ensure they are valid and used ethically and only when they are of benefit to patients.

Q28.5. Do you think the UK medical devices regulations should require Approved Bodies to enter information about certificates into the MHRA registration system? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q28.6. If you have answered 'yes' to question 28.5, please outline what certificate information Approved Bodies should be required to enter into the MHRA registration system.

Information regarding suspended, withdrawn and reinstated certificates and any restrictions imposed on certificates.

Q28.7. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 28.1-28.6, including any impacts on you or other stakeholder groups.

As noted in the response to Q28.4, it is critical that genetic/genomic tests can be restricted to specific groups of people to ensure they are valid and used ethically and only when they are of benefit to patients. It is important that patients and their doctors can see this information.

Section 29 - Voluntary change of Approved Body

Q29.1. Do you think the UK medical devices regulations should set out the minimum content that should be included in the agreement for a change of Approved Bodies? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q29.2. If you have answered 'yes' to question 29.1, please outline what this agreement should include.

Q29.3. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 29.1-29.2, including any impacts on you or other stakeholder groups.

It is important that manufacturers cannot 'cherry pick' a notified body that they believe will give a more favourable assessment.

Section 30 - Declaration of Conformity

Q30.1. Do you think that the UK medical devices regulations should set out the minimum content requirements for the Declaration of Conformity? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q30.2. If you have answered 'yes' to question 30.1, please outline what the requirements for the Declaration of Conformity should be (you may refer to bullet points *a-i in paragraph 30.3).

Points a) to i).

Q30.3. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 30.1-30.2, including any impacts on you or other stakeholder groups.

It must be possible for test users, health providers and independent experts to check what is on the market and whether it has been conformity assessed.

Chapter 7: Clinical Investigation / Performance Studies

Section 31 - Clinical evaluation (general medical devices)

Q31.1 Do you think that the specific requirements, outlined in paragraph 31.11, that relate to claiming equivalence should be introduced?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q31.2. Please provide any additional information (for example outline what requirements you think should be introduced around claiming equivalence or explain why you do not agree that additional requirements should be introduced).

Q31.3. Do you think that manufacturers of products without an intended medical purpose should be required to perform clinical investigations or other pre-market studies involving human subjects / participants as set out in paragraph 31.12?

('Yes' / 'No' / 'Don't Know/No Opinion')

Section 32 - Performance evaluation (IVDs)

Q32.1. Do you think that confirmation of conformity of an IVD with the UK medical devices regulations should be based on scientific validity, analytical and clinical performance data?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q32.2 Do you think that manufacturers should be required to produce a performance evaluation report as part of the technical documentation for the device?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q32.3. Do you think manufacturers should be required to specify and justify the level of clinical evidence necessary to demonstrate conformity with the UK medical devices regulations?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q32.4. Do you think the UK medical devices regulations should require manufacturers to rely on data from their own clinical performance studies unless they can justify reliance on other sources of clinical performance data?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q32.5. If you have answered 'yes' to question 32.4, please outline what factors you think this justification could include.

Q32.6. Do you think the UK medical devices regulations should require that the performance evaluation is updated throughout the lifetime of the IVD and used to update the technical documentation listed in paragraph 32.11?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q32.7 If you have answered 'yes' to question 32.6, please outline how you think the performance evaluation should be updated by the manufacturer and if there is any other technical documentation which should be updated.

It is critical that any updates take into account (i) any developments in the scientific literature (which frequently shows the level of risk associated with a newly discovered genetic variant declining over time as more evidence is collected) and; (ii) any changes in technologies (e.g. DNA chips or whole genome sequencing) or the software used to interpret the results (which can result in significant changes to the information given to the person being tested).

Q32.8. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 32.1-32.7, including any impacts on you or other stakeholder groups.

Misleading genetic test result can have significant negative impacts on individuals. This can include, for example, the impacts of false positive results leading to unnecessary treatment (including surgery), reproductive decisions based on false positive results⁷⁹, or false reassurance regarding the risk of late-onset diseases, such as type 2 diabetes or cancers.

Section 33 - General requirements regarding clinical investigations (general medical devices)

Q33.1. Do you think that clinical investigations regulated under the UK medical devices regulations should be limited to those carried out for one of the purposes outlined in paragraph 33.5?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q33.2. Do you think that, if the sponsor is based outside the UK, they should be required to appoint a legal representative in the UK as outlined in paragraph 33.6?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q33.3. Do you think that the legal representative should be responsible for ensuring compliance with the sponsor's obligations and be the addressee for all communications with the sponsor?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q33.4. Do you think that any communication with that legal representative should be deemed to be communication with the sponsor?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q33.5. Do you think the UK medical devices regulations should set out the obligations of the sponsor, including those outlined in paragraph 33.7?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q33.6. Please outline any other requirements which should be introduced for the sponsor.

Q33.7. Do you think the UK medical devices regulations should set out the minimum requirements for the clinical investigation report, including those outlined in paragraph 33.8?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q33.8. Please outline any other requirements which should be introduced for the clinical investigation report.

Q33.9. Do you think the UK medical devices regulations should require the sponsor to publish the clinical investigation report?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q33.10. Do you think the UK medical devices regulations should include the additional detailed requirements relating to the methods for a clinical investigation as outlined in paragraph 33.10?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q33.11. Please outline any other requirements which should be introduced relating to the methods for a clinical investigation.

Q33.12. Do you think the UK medical devices regulations should set out the detailed requirements for the clinical investigation plan, including those outlined in paragraph 33.12?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q33.13. Please outline any other requirements should be introduced for the clinical investigation plan.

Q33.14. Do you think the UK medical devices regulations should set out the requirements that must be met for performing a clinical investigation, including those outlined in paragraph 33.13?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q33.15. Please outline any other requirements that should be met when performing a clinical evaluation.

Q33.16. Do you think the UK medical devices regulations should set out the rights of subjects/participants to withdraw from clinical investigations, as outlined in paragraph 33.14?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q33.17 Do you think the qualification requirements for investigators of clinical investigations and personnel involved in clinical investigations, including those outlined in paragraph 33.15, should be introduced?

(‘Yes’ / ‘No’ / ‘Don’t Know/No Opinion’)

Q33.18 Please outline any other requirements which should be introduced for investigators of clinical investigations and the personnel involved in clinical investigations.

Section 34 - General requirements regarding performance studies (IVDs)

Q34.1. *Do you think we should require that, where appropriate, performance studies be performed in circumstances similar to the normal conditions of use of the medical device?

(‘Yes’ / ‘No’ / ‘Don’t Know/No Opinion’)

Yes

Q34.2. Do you think the UK medical devices regulations should set out in detail the specific requirements for the performance studies in paragraph 34.5 above?

(‘Yes’ / ‘No’ / ‘Don’t Know/No Opinion’)

Yes

Q34.3. If you have answered ‘yes’ to question 34.2, please outline what you think the specific requirements of the performance study should be.

The rules on performance studies should be in line with well-established international guidance in this field, such as the international standard ISO 14155:2011 on good clinical practice for clinical investigations of medical devices for human subjects.

Performance studies should meet all ethical and legal requirements such as compliance with the Helsinki Declaration, Data Protection Regulation, Human Tissue Act, Human Rights Act, etc. There should be a requirement for ethical review and approval by an independent ethics body. The special nature of genetic information, including the importance of privacy should be taken into account. Genetic information should not be collected or shared without fully informed consent and minors must have the right to reconsent when they have capacity. There must be a right to withdrawal from studies.

A ‘performance study’ means a study undertaken to establish or confirm the analytical or clinical performance of a device. The ‘performance of a device’ means the ability of a device to achieve its intended purpose as claimed by the manufacturer. A ‘performance study plan’ should be provided which describes the rationale, objectives, design methodology, monitoring, statistical considerations, organisation and conduct of a performance study. Annex XIII of the EU’s IVDR provides a suitable list of requirements.

Sponsors should report certain adverse events and device deficiencies that occur during interventional clinical performance studies. ‘Device deficiency’ means any inadequacy in the identity, quality, durability, reliability, safety or performance of a device for performance study, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

Q34.4. Do you think the UK medical devices regulations should set out the obligations for the sponsor of a performance study, including those outlined in paragraph 34.7?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q34.5. Please outline any other obligations for the sponsor of a performance study which should be.

It is not sufficient to report only a summary of the study. It is essential that the device registration information provides a sufficient level of transparency for members of the public (and/or their doctors, or independent scientists) to understand how a particular conclusion regarding their diagnosis/prognosis was reached, which is arguably both an ethical and legal requirement in the context of algorithmic decision-making.⁸⁰ This is of considerable practical importance because different genetic test providers often give contradictory results.

Q34.6. Do you think sponsors should be required to implement a clinical performance study plan?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q34.7. Do you think detailed requirements for the clinical performance study plan should be set out in the UK medical devices regulations?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q34.8. If you have answered 'yes' to question 34.7, please outline what you think the requirements for the clinical performance study plan should be.

Annex XIII of the EU's IVDR provides a suitable list of requirements.

Q34.9. Do you think this obligation should also extend to other types of performance studies (other than clinical performance studies)?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q34.10. Do you think the UK medical devices regulations should set detailed requirements for the purpose, methods, objectives and ethical considerations for a performance study including those outlined in paragraph 34.9?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes. However, we disagree with the reference to 'left over samples' in 34.9 (h). The use of the term 'left-over samples' is potentially misleading and open to abuse (Sections 34 and 35). Under data protection legislation, biological samples are collected from an individual for a specific purpose, and it is important that data protection principles and the provisions of the Human Tissue Act continue to apply. In particular, undertaking genetic testing, or even whole genome sequencing, of samples in the absence of fully informed consent is likely to lead to a major loss of public trust. Genetic data obtained from DNA chips or sequencing is sufficient to act as a biometric identifier for individuals or their relatives, allowing them to be tracked by commercial interests (e.g. for marketing purposes) or by police or security services (allowing an unacceptable level of surveillance and interference with human rights).

It should therefore be clarified that samples collected for other purposes should not be used for genetic or genomic testing without fully informed consent.

Q34.11. Please outline any other requirements for performance studies which should be introduced.

Q34.12. Do you think sponsors should be required to provide a clinical performance study report?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q34.13. Do you think the UK medical devices regulations should set out the minimum requirements for the clinical performance study report?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q34.14. If you have answered 'yes' to question 4.13, please outline what the requirements for the clinical performance study report should be.

The clinical performance study report should contain documented information on the clinical performance study protocol plan, results and conclusions of the clinical performance study, including negative findings. The results and conclusions should be transparent, free of bias and clinically relevant. The report should also include any protocol amendments or deviations.

Q34.15. Do you think this obligation should also extend to analytical performance studies?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q34.16. If you have answered 'yes' to question 34.15, what types of performance study (other than clinical performance studies) do you think should be subject to a clinical performance study report?

Q34.17. Do you think the UK medical devices regulations should require the clinical performance study report be published?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q34.18. Do you think the UK medical devices regulations should require ALL performance studies involving human samples to be subject to ethical review by an ethics committee?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q34.19. Do you think that performance studies involving companion diagnostics should be subject to the same requirements as all other performance studies?

(‘Yes’ / ‘No’ / ‘Don’t Know/No Opinion’)

Q34.20. Do you think that performance studies involving companion diagnostics using only left-over samples should NOT be subject to the same requirements as all other performance studies?

(‘Yes’ / ‘No’ / ‘Don’t Know/No Opinion’)

No. The use of the term ‘left-over samples’ is potentially misleading and open to abuse. Under data protection legislation, biological samples are collected from an individual for a specific purpose, and it is important that data protection principles and the provisions of the Human Tissue Act continue to apply. In particular, undertaking genetic testing, or even whole genome sequencing, of samples in the absence of fully informed consent is likely to lead to a major loss of public trust. Genetic data obtained from DNA chips or sequencing is sufficient to act as a biometric identifier for individuals or their relatives, allowing them to be tracked by commercial interests (e.g. for marketing purposes) or by police or security services (allowing an unacceptable level of surveillance and interference with human rights). It should therefore be clarified that samples collected for other purposes should not be used for genetic or genomic testing without fully informed consent.

Q34.21. Do you think that performance studies involving companion diagnostics using only left-over samples should be notified to the MHRA?

(‘Yes’ / ‘No’ / ‘Don’t Know/No Opinion’)

Yes

Q34.22. Do you think the conditions for conducting a performance study should be set out in the UK medical devices regulations, including those outlined in paragraph 34.15?

(‘Yes’ / ‘No’ / ‘Don’t Know/No Opinion’)

Yes

Q34.23. Please outline any other conditions which should be met when conducting a performance study.

The information provided should be consistent with the requirements of the Helsinki Declaration, especially article 26, which requires participants to be informed of “*sources of funding, any possible conflicts of interest, institutional affiliations of the researcher*”.⁸¹

Q34.24 Do you think the rights of subjects to withdraw from a performance study should be included in the UK medical devices regulations, as set out in paragraph 34.16?

(‘Yes’ / ‘No’ / ‘Don’t Know/No Opinion’)

Yes

Q34.25. Do you think the UK medical devices regulations should set out requirements for the investigator and other personnel involved in the performance study, including those outlined in paragraph 34.17?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q34.26. If you have answered 'yes' to question 34.25, please outline what you think the requirements should be.

Q34.27. Do you think that the UK medical devices regulations should require that, where appropriate, the facilities where the performance study is to be conducted should be suitable for the conduct of the study?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q34.28. Do you think that, where appropriate, the setting and users of the medical device in the clinical performance study should be similar to the intended setting and intended users of the medical device?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q34.29. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 34.1-34.28, including any impacts on you or other stakeholder groups.

Section 35 - Informed consent

Q35.1. Do you think the UK medical devices regulations should include requirements for obtaining informed consent from individuals participating in a clinical investigation or performance study?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q35.2. If you have answered 'yes' to question 35.1, please outline what the requirements for obtaining informed consent should be.

The consent requirements should be consistent with the requirements of the Helsinki Declaration.⁸²

Q35.3. Please outline any circumstances in which you think the requirements for obtaining informed consent might be waived? (e.g. observational studies where only fully de-identified data and/or left-over samples are used, or cluster randomised trials).

Q35.4. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 35.1-35.3, including any impacts on you or other stakeholder groups.

Section 36 - Specific requirements for clinical investigations / performance studies

Q36.1. Do you think additional requirements, including those outlined in paragraph 36.3, should be required for clinical investigations or performance studies on minors?

(‘Yes’ / ‘No’ / ‘Don’t Know/No Opinion’)

Yes

Q36.2. Please outline any other requirements which should be introduced for clinical investigations or performance studies on minors.

Studies should not use tests for children which undermine their rights to make their own decisions as they grow up, i.e. the tests should be directly relevant to the direct care of the child. Relevant ethical guidelines should be followed. If there are no urgent medical reasons, all guidelines recommend postponing genetic/genomic testing until the child can consent to testing as a competent adolescent or as an adult.⁸³

Q36.3. Do you think additional requirements, including those outlined in paragraph 36.4, should be required for clinical investigations or performance studies on pregnant or breastfeeding women?

(‘Yes’ / ‘No’ / ‘Don’t Know/No Opinion’)

Yes, in the context of prenatal testing.

Q36.4. Please outline any other requirements which should be introduced for clinical investigations or performance studies on pregnant or breastfeeding women. Genetic counselling must be provided.⁸⁴

Q36.5. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 36.1-36.4, including any impacts on you or other stakeholder groups.

Section 37 - Clinical investigations / Performance studies in emergency situations

Q37.1. Do you think the conditions should be set out in which informed consent to participate in a clinical investigation or performance study may be obtained or given after the decision to include the subject in a clinical investigation or performance study due to an emergency situation?

(‘Yes’ / ‘No’ / ‘Don’t Know/No Opinion’)

Q37.2. Please provide your reasoning (including any available relevant evidence) to support your answer to question 37.1, including any impacts on you or other stakeholder groups.

Q37.3 Do you think that systems should be put in place for compensation as set out in paragraph 37.4?

(‘Yes’ / ‘No’ / ‘Don’t Know/No Opinion’)

Yes.

Q37.4. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 37.1-37.3, including any impacts on you or other stakeholder groups.

Misleading genetic tests can lead to significant adverse impacts on patients: for example, in the case of false positive diagnoses, people could take unnecessary medication or even have prophylactic surgery to remove their breasts.^{85,86,87,88}

Section 38 - Application for clinical investigations / performance studies

Q38.1. Do you think detailed requirements for the clinical investigation or performance study application form and the accompanying documentation required, including those outlined in paragraph 38.2 should be outlined?

(‘Yes’ / ‘No’ / ‘Don’t Know/No Opinion’)

Yes

Q38.2. Please outline any other requirements which should be introduced for the application form and accompanying documentation.

Q38.3. Do you think the UK medical devices regulations should outline the relevant timescales that the applicant and the MHRA should conform to when an application for a clinical investigation or performance study is submitted to the MHRA?

(‘Yes’ / ‘No’ / ‘Don’t Know/No Opinion’)

Yes

Q38.4. If you have answered ‘yes’ to question 38.3, please outline what appropriate timescale should be.

Q38.5. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 38.1-38.4, including any impacts on you or other stakeholder groups.

Section 39 - Assessment of applications for clinical investigation / performance study by the MHRA

Q39.1. Do you think the MHRA should be required to assess applications for performance studies?

(‘Yes’ / ‘No’ / ‘Don’t Know/No Opinion’)

Yes

Q39.2. Do you think the detailed requirements for assessment of the application for clinical investigations or performance study should be outlined by the MHRA?

(‘Yes’ / ‘No’ / ‘Don’t Know/No Opinion’)

Yes

Q39.3. If you have answered ‘yes’ to question 39.2, please outline what you think the requirements for assessment of the application for clinical investigation or performance study should be.

Risks to subjects that are assessed should include privacy risks.

Q39.4. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 39.1-39.3, including any impacts on you or other stakeholder groups.

Genetic information can act as a 'genetic fingerprint' to identify individuals and members of their family. Collection, storage and use of such information can facilitate the tracking and exploitation of individuals and their relatives by commercial companies, the state, or anyone who can infiltrate the system.

Section 40 - Conduct of a clinical investigation / performance study

Q40.1. Do you think the UK medical devices regulations should set out the requirements for the conduct of a clinical investigation or performance study, as outlined in paragraph 40.2?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q40.2. Please outline any other requirements which should be introduced for the conduct of a clinical investigation or performance study.

Q40.3. Do you think that the MHRA should be required to inspect, at an appropriate level, clinical investigation, or performance study site(s)?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q40.4. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 40.1-40.3, including any impacts on you or other stakeholder groups.

Section 41 - Clinical investigations / Performance studies regarding devices bearing the UKCA marking

Q41.1. Do you think the sponsor should be required to notify the MHRA of a clinical investigation or performance study within a specified time period prior to the start of that clinical investigation or performance study as outlined in paragraph 41.3?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q41.2. If you have answered 'yes' to question 41.1, please outline what you think the specified time period should be.

Q41.3. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 41.1-41.2, including any impacts on you or other stakeholder groups.

Section 42 - Modifications to clinical investigations / performance studies

Q42.1. Do you think the UK medical devices regulations should set out the procedures for sponsors intending to introduce modifications to a clinical investigation or performance study, including the procedures outlined in paragraph 42.2?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q42.2. Please outline any other procedures which should be introduced and/or what the timeframes for the procedures in paragraph 42.2/suggested procedures should be.

Q42.3. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 42.1-42.2, including any impacts on you or other stakeholder groups.

Section 43 - Corrective measures to be taken by the MHRA in relation to a clinical investigation / performance study

Q43.1. Do you think that the MHRA should be able to take the measures outlined in paragraph 43.2 in cases where it is considered that the requirements of the UK medical devices regulations in regards to a performance study have not been met?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q43.2. Please outline any other measures which should be introduced for either a clinical investigation or performance study.

Q43.3. Do you think, except where immediate action is required, that the sponsor or the investigator or both should be asked for their opinion regarding the corrective measures outlined in paragraph 43.2 (suggested measures)?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q43.4. If you have answered 'yes' to question 43.3, please outline what you think should be the specified time period for the sponsor or investigator to give their opinion.

Q43.5. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 43.1-43.4, including any impacts on you or other stakeholder groups.

Section 44 - Information from the sponsor at the end of a clinical investigation / performance study or in the event of a temporary halt or early termination

Q44.1. Do you think the procedures, including those outlined in paragraph 44.2 which must be undertaken and the timeframes which would apply at the end of a clinical investigation or performance study, or in the event of a temporary halt or early termination should be specified?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q44.2. Please outline any other procedures which should be included and/or what the timeframe for notification should be for the procedures in paragraph 44.2/suggested procedures.

Q44.3. Please provide your views on what these timescales should be and your reasoning (including any available relevant evidence) to support your answers to questions in 44.1-44.2, including any impacts on you or other stakeholder groups.

Section 45 - Recording and reporting of adverse events that occur during clinical investigations / performance studies

Q45.1. Do you think sponsors of clinical investigations and performance studies should be required in legislation to fully record and provide information on adverse events, serious adverse events and medical device deficiencies including those set out in points (a) to (d) in paragraph 45.3?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q45.2. Do you think sponsors should be required to report, without delay, to the MHRA, the events set out in points (a) to (c) of paragraph 45.4?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q45.3. Do you think, where necessary, sponsors should be able to submit an initial report that is incomplete, followed up by a complete report?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q45.4. Do you think the UK medical devices regulations should require sponsors to report to the MHRA any event referred to in paragraph 45.4 that has occurred in a non-UK country in which a clinical investigation or performance study is performed under the same clinical investigation or performance study plan?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q45.5. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 45.1-45.4, including any impacts on you or other stakeholder groups.

Section 46 - Types of clinical investigations / performance studies and exemptions / authorisations

Q46.1. Do you think the UK medical devices regulations should allow for exemptions from some of the requirements of the Regulations for certain types of clinical investigations and performance studies as outlined in paragraph 46.4?

('Yes' / 'No' / 'Don't Know/No Opinion')

No

Q46.2. If you have answered 'yes' to question 46.1 please outline what types of clinical investigations and performance studies you think should be exempted.

Q46.3. Do you think that healthcare institutions should be required to notify certain types of clinical investigation / performance studies to the MHRA for authorisation before proceeding?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q46.4. If you have answered 'yes' to question 46.3 please outline what types of clinical investigations / performance studies should meet the requirements of the UK medical devices regulations.

Any large-scale study which moves beyond the rationale for the healthcare institution exemption i.e. is for a test which is to be applied at scale or is for all but very small patient groups for whom tests would not otherwise be available.

Q46.5 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 46.1-46.4, including any impacts on you or other stakeholder groups.

Section 47 - Summary of safety and clinical performance

Q47.1. Do you think the UK medical devices regulations should introduce the requirement for an SSCP for medical devices?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q47.2. If you have answered 'yes' to question 47.1, please outline what classes/types of medical devices should require an SSCP.

Yes

Q47.3. Do you think the UK medical devices regulations should set out the minimum content of the SSCP included in paragraph 47.5?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q47.4. Please outline any other content which should be included in the SSCP for a medical device.

All the information in points a) to k).

Q47.5. Please select one of the following:

a.

a. the manufacturer should upload the full SSCP to the MHRA registration system

b. the manufacturer should upload a link to the SSCP to the registration system

c. the manufacturer should not be required to upload the SSCP to the registration system

d. other – please specify

e. don't know/no opinion

Q47.6. Do you think an Approved Body should validate the SSCP for a medical device?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q47.7. If you have answered 'yes' to question 47.6, please outline how this procedure should be carried out.

Q47.8. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 47.1-47.7, including any impacts on you or other stakeholder groups.

These are all important aspects to maintaining transparency and trust in the regulation.

Chapter 8: Post-market Surveillance and Vigilance

Q48.1. Do you think manufacturers should be required to implement a post-market surveillance system based on a post-market surveillance plan, which collates and utilises information from the range of sources listed in paragraph 48.4?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q48.2. Do you think the UK medical devices regulations should provide a detailed outline of what the post-market surveillance plan should address, including the examples given in paragraph 48.5?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q48.3. Please outline any other elements that a post-market surveillance plan should address.

Q48.4. Do you think the UK medical devices regulations should require IVD manufacturers to carry out post-market performance follow-up (PMPF) and to use PMPF findings to update the IVD's performance evaluation?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q48.5. Do you think the UK medical devices regulations should outline what should be included in the PMCF or PMPF plan, including the examples given in paragraph 48.8?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q48.6. Please outline any other elements that a PMCF/PMPF plan should be required to address.

Q48.7. Do you think that manufacturers should be exempt from the requirement to perform PMCF/PMPF for a medical device or IVD pursuant to a PMCF/PMPF plan if such manufacturers provide sufficient justification?

('Yes' / 'No' / 'Don't Know/No Opinion')

No

Q48.8. Do you think the UK medical devices regulations should include requirements for manufacturers to summarise and present the information from their post-market surveillance activities in a post-market surveillance report or a periodic safety update report as they are described in paragraph 48.9?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q48.9. If you have answered 'yes' to question 48.7, please outline which types or classes of medical devices should be subject to a post-market surveillance report and if there are any other elements which should be required for the post-market surveillance report.

Q48.10. If you answered have answered 'yes' to question 48.7, please outline which types or classes of medical devices should be subject to a periodic safety update report and if there are any other elements that should be required for a periodic safety update report.

Q48.11. If you answered have answered 'no' to question 48.7, please outline any alternative requirements for how the manufacturer should summarise and present post-market surveillance data.

Q48.12. Do you think manufacturers should upload post-market surveillance data to the MHRA devices register upon registration renewal?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q48.13. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 48.1-48.12, including any impacts on you or other stakeholder groups.

Section 49 - Reporting of serious incidents and field safety corrective actions

Q49.1. Do you think the UK medical devices regulations should include requirements for manufacturers to report incidents and FSCAs to the MHRA including points (a) and (b) as above?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q49.2. Do you agree with the proposed definitions for 'serious incident', 'serious deterioration' and 'serious public health threat'?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q49.3. If you have answered 'no' to question 49.2, please outline what you would change about the proposed definitions?

Q49.4. Do you think the manufacturer should be required to report any serious incident in line with the time periods above?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q49.5. If you have answered 'no' to question 49.4, please outline what the timeframe for reporting serious incidents should be, or any other changes you would make to the criteria set out in paragraph 49.9.

Q49.6. Do you think the UK medical devices regulations should specify further procedures for manufacturers regarding the reporting of serious incidents and field safety corrective actions (FSCAs) including (but not limited to) the points made in paragraph 49.10 above?

('Yes' / 'No' / 'Don't Know/No Opinion')

Q49.7. Please outline any other requirements which should be introduced regarding reporting of serious incidents and field safety corrective actions should be.

Q49.8. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 49.1-49.7, including any impacts on you or other stakeholder groups.

Section 50 - Trend reporting

Q50.1. Do you think the manufacturer should be required to report any statistically significant increase in the frequency or severity of incidents/erroneous results as set out in paragraph 50.3 above?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q50.2. Please provide your reasoning (including any available relevant evidence) to support your answers to question 50.1 , including any impacts on you or other stakeholder groups.

Section 51 - Analysis of serious incidents and field safety corrective actions

Q51.1. Do you think manufacturers should be required to issue field safety notices (FSNs) as part of their field safety corrective actions and to submit the content of the FSN to the MHRA for comment, except in cases of emergency?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q51.2. Do you think the UK medical devices regulations should set out the minimum requirements for the content of field safety notices issued by manufacturers?

('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q51.3. Do you think the MHRA should be required to notify the manufacturer or their UK Responsible Person of new risks it has identified through active monitoring of data in cases where these risks have already been subject to public disclosure?

(‘Yes’ / ‘No’ / ‘Don’t Know/No Opinion’)

Yes

Q51.4. If we were to mandate patient and public involvement and engagement in the medical device regulations, as part of manufacturers’ vigilance obligations, what form should this take?

Patients and the public and civil society organisations should be able to report concerns including misdiagnoses or any evidence regarding poor performance or adverse events. In addition, a broader level of engagement could cover ethical and social issues, including privacy.

Q51.5. At what stages would you expect manufacturers to engage patients and the public?
Multiple Choice:

a.

a. periodically once their medical device is on the market

b. only when they or the MHRA becomes aware of a safety issue with the device

c. other – please specify?

Q51.6. Please provide your reasoning (including any available relevant evidence) to support your answers to questions 51.1-51.5, including any impacts on you or other stakeholder groups.

Members of the public and civil society organisations or others (independent scientists, journalists) may become aware of performance issues and/or ethical and social issues through their own experience and/or investigations. These could include, for example, obtaining different interpretations of their genetic information from different manufacturers, being given a misdiagnosis, privacy breaches, experience with lack of access to genetic counselling, or implications for family members.

Chapter 9: In vitro Diagnostic Medical Devices

Section 53. IVD Classification Rules

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’ / ‘No’ / ‘Don’t Know/No Opinion’)

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’ / ‘No’ / ‘Don’t Know/No Opinion’)

Q53.3. Are the current IVD regulatory requirements for each class of IVD proportionate to their risk? ('Yes' / 'No' / 'Don't Know/No Opinion')

No.

Q53.4. Does the current approach to classification sufficiently cover the digital/software aspect of IVDs? ('Yes' / 'No' / 'Don't Know/No Opinion')

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.

Genetic tests are currently classified as 'low risk' and effectively self-regulated. This lack of regulation has been widely regarded as inadequate to protect consumers purchasing DTC genetic tests and users of genetic tests within health services.^{89,90,91} The EU IVDR classification system would address these concerns.

Section 54. Genetic Testing

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' / 'No' / 'Don't Know/No Opinion')

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' / 'No' / 'Don't Know/No Opinion')

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.

Genetic tests are currently classified as 'low risk' and effectively self-regulated. This lack of regulation has been widely regarded as inadequate to protect consumers purchasing DTC genetic tests and users of genetic tests within health services.^{92,93,94} Making the proposed changes would help to address these concerns by requiring the necessary clinical evidence to support manufacturers claims.

In addition, all health-related genetic tests should be 'prescription-only', so that requirements for fully-informed consent and ethical requirements (especially in relation to children and vulnerable persons) can be met, and genetic counselling provided as and when required.

Section 55. Companion Diagnostics

Q55.1. Should Companion Diagnostics be treated differently to other IVDs? (i.e. with respect to classification). ('Yes' / 'No' / 'Don't Know/No Opinion')

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?

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.

Companion diagnostics include pharmacogenetic tests which can change a prescribing decision in ways that can harm a patient if the results are wrong.

Section 56. Distance Selling

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' / 'No' / 'Don't Know/No Opinion')

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' / 'No' / 'Don't Know/No Opinion')

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.

A major issue in relation to distance sales of genetic/genomic tests is how consent is obtained, particularly in relation to children or other vulnerable persons. There is considerable potential for abuse, for example, ordering tests for children which undermine their rights to make their own decisions as they grow up, in breach of numerous ethical guidelines.⁹⁵ Other vulnerable persons, for example people suffering from mental illness, may also be put at risk. Since genetic tests can also reveal non-paternity, this means that non-consensual paternity testing may also be facilitated, with the potential to destroy families and undermine the best interests of the child. It is also widely regarded as essential to provide genetic counselling services (before and after testing) for at least some genetic tests.

The easiest way to address these concerns is to make all health-related genetic tests 'prescription-only'. This goes beyond the provisions in the EU IVD Regulation, for example, because this issue is regarded as one for national governments, but a ban on DTC tests has already been implemented in several countries, including France, Germany, Portugal and Switzerland.⁹⁶ This would not necessarily prevent medical practitioners from ordering genetic or genomic tests online, but those practitioners (rather than a tick box on a website) would be responsible for ensuring that patients have consented and that ethical guidelines for testing children and other vulnerable persons have been followed.

Chapter 10: Software as a Medical Device

Section 58. Scope and definitions

Q58.1. Do you think that we should introduce the definition of software set out above? ('Yes' / 'No' / 'Don't Know/No Opinion')

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 UK market? ('Yes' / 'No' / 'Don't Know/No Opinion')

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

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.

Section 59. Distance sales

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' / 'No' / 'Don't Know/No Opinion')

Yes

Q59.2. Do you think that the definition of placing on the market should be revised as set out above? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

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.

Currently, customers may get their genome tested by one manufacturer and share the data (sequence or SNPs) with other providers online, so that the data is analysed using different software. Other aspects (such as privacy protections and consent requirements) may also differ. It is important that all manufacturers supplying SaMD are regulated, not just the manufacturer who undertook the initial analysis of the individual's genome.

Section 60. Classification: Risk categorisation

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' / 'No' / 'Don't Know/No Opinion')

No

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

Consistent with the EU IVDR, software which drives a device or influences the use of a device should be classified in the same class as the device. If the software is independent of the device, it should be classified in its own right. However, this should be consistent with the application, to avoid inconsistencies. So, software as a medical device (SaMD) used to analyse human genetic data should be in Class C (the same as human genetic testing), otherwise it will lead to the illogical result that stand-alone software may have weaker

regulatory requirements and thus, for example, a polygenic risk score (PRS) that could not be returned to someone when they have a genetic test (due to poor performance) could be returned to them online via stand-alone software.

It should be noted that the IMDRF SaMD classification rule is old and does not include prediction and prognosis, and thus its use would invalidate and undermine the updated classification rules used for IVDs elsewhere in the proposed regulation.

Section 61. Classification: Airlock classification rule

Q61.1. Do you think we should introduce an 'airlock classification rule' for SaMD with a risk profile that is not well understood? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

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

Section 62. Pre-market requirements

Q62.1. Do you consider additional essential requirements should be in place to assure the safety and performance of SaMD specifically? ('Yes' / 'No' / 'Don't Know/No Opinion')

If SaMD is correctly classified (see Q60.2) it should not be necessary to develop new requirements as these will already have been considered in the context of the requirements for human genetic testing. If, on the other hand, a new classification system is used for software a whole new raft of requirements will need to be developed.

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

Q62.3. Do you consider regulations should set out SaMD essential requirements separate from those for other general medical device types? ('Yes' / 'No' / 'Don't Know/No Opinion')

See answer to Q62.1.

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

Section 63 - Post-market requirements

Q63.1 Do you think the UK medical devices regulations should mandate a 'report adverse incident' link as set out above? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes. Reporting requirements should mirror those for the relevant device type (e.g. software that analyses human genetic data should have the same reporting requirements as human genetic tests).

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

Q63.3 Do you think that regulations should enable predetermined change control plans? ('Yes' / 'No' / 'Don't Know/No Opinion')

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.

Obviously, if the software changes, the results can change (giving a different diagnosis, prognosis or risk assessment), so this needs to be regulated.

Section 64 - SaMD Cyber Security

Q64.1 Do you consider existing UK medical devices regulations need to include cyber security and/or information security requirements? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

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

Security of genetic/genomic information is absolutely critical to maintaining public trust.

Q64.3 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 64.1-64.2, including any impacts on you or other stakeholder groups.

Genetic data obtained from DNA chips or sequencing is sufficient to act as a biometric identifier for individuals or their relatives, allowing them to be tracked by commercial interests (e.g. for marketing purposes) or by police or security services (allowing an unacceptable level of surveillance and interference with human rights). Individuals and their relatives can also be tracked and identified using their DNA by anyone who infiltrates the system. This could, for example, put adults or children fleeing domestic abuse at risk.

Section 65 - Artificial intelligence as a/in a medical device (AIaMD)

Q65.1 Are there other statutory changes required to effectively regulate AIaMD over and above the changes detailed for SaMD above? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q65.2 If you have answered 'yes' to question 65.1, please outline what additional changes you consider are required.

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' / 'No' / 'Don't Know/No Opinion')

Yes

Q65.4 If yes, do you think the UK medical devices regulations should be amended to require this? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q65.5 Should the UK medical devices regulations mandate logging of outputs of further auditability requirements for all SaMD or just AIaMD for traceability purposes? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

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?

Obviously, if the software changes, the results can change (giving a different diagnosis, prognosis or risk assessment), so this needs to be regulated.

Chapter 11: Implantable Devices

Section 66 - Implantable Devices

Q66.1 Do you think there should be any changes to the scope of medical devices regulated as implantable devices? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q66.2 If you have answered 'yes' to question 66.1, please set out any implantable devices you consider should be brought into or removed from the scope of implantable devices regulated.

Q66.3 Please set out your reasoning in relation to questions 66.1 and 66.2, and any expected impacts (including implementation considerations). Please consider whether any further clarity is needed on what is out of scope of regulated implantable medical devices.

Q66.4 In relation to implantable devices, do pre-market evidence requirements need to change, particularly in respect to:

a. clinical investigations: should requirements for clinical investigations be more robust than those conducted for non-implantable devices? ('Yes' / 'No' / 'Don't Know/No Opinion')

b. technical documentation reviews: should requirements be more robust than those for non-implanted devices of the same risk category? ('Yes' / 'No' / 'Don't Know/No Opinion')

c. any exemptions required for certain implantable devices (e.g. screws, wedges)? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q66.5 Please explain your rationale for your responses to question 66.4, including how and why you think any changes are needed, including any expected impacts.

Q66.6 What are your views on adding additional conditions to the introduction of new implantable medical devices to the UK market? Please consider: what controls should be in place? For how long? To what types of devices should controls apply?

Q66.7 Should there be more stringent controls over the use of implantable devices? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q66.8 Please select any/all of the options listed in paragraph 66.4 (d) you consider should be introduced:

being supplied only to medical device users in centres specialising in their use

being supplied to medical device users by practitioners with specialist expertise and experience in the treatment of the condition requiring the device

administered with proactive follow up with patients (for example, monitoring longer term patient outcomes or feedback post-implant)

Q66.9 Are there any other controls over implantable devices you think should be introduced?

Q66.10 Do you think that post-market requirements for implantable devices could be strengthened by:

a. clarifying or strengthening the requirements around use of obsolete models of implantable medical devices? ('Yes' / 'No' / 'Don't Know/No Opinion')

b. introducing a requirement for implant information to be provided to recipients of implantable devices? (Yes/No/Don't Know/No Opinion)

Q66.11 Do you think that the UK medical devices regulations should require manufacturers of implantable devices to provide implant information for recipient patients with the device when placing it on the market as set out in paragraph 66.6? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q66.12 If you have answered 'yes' to question 66.11:

a. should manufacturers be required to provide implant cards/leaflets to healthcare settings/professionals? ('Yes' / 'No' / 'Don't Know/No Opinion')

b. what should be included on the implant card and patient information leaflet?

c. should manufacturers be required to make available implant information in both physical and digital formats, (for example, in the form of a card, leaflet or other appropriate format)? ('Yes' / 'No' / 'Don't Know/No Opinion')

d. Should the manufacturer be required to update the digital implant information where appropriate? ('Yes' / 'No' / 'Don't Know/No Opinion')

e. should health institutions be required to make this information available to patients who have been implanted with the device? ('Yes' / 'No' / 'Don't Know/No Opinion')

f. should health institutions be required to log the implant information onto the records of the patient implanted with the device? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q66.13 Are there any implants that should be excluded from the requirement to have accompanying implant information? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q66.14 If you have answered 'yes' to question 66.13, please outline what types of implant should be excluded and why. In your response, please set out any expected impact(s), with consideration of how these could be defined best for clarity of what is in scope of the exemption.

Q66.15 Is there further information we should collect and share about implantable medical devices in particular? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q66.16 Please set out your rationale for your answer to question 66.15. If yes, please include any detail of information you consider should be collected and shared.

Q66.17. What are the key implementation considerations for any changes you have outlined in response to previous questions in this chapter. Please consider: what types of implantable medical devices should these apply to (including any exemptions to them); impacts on inequalities such as access to devices and timeframes; where there should be a phased implementation; and how much guidance/support you think will need to be provided to facilitate transition.

Q66.18 Are there any other key considerations you would like to raise regarding changes to the regulatory framework for implantable medical devices?

Q66.19 Please provide any relevant evidence to support your answers to questions 66.1-66.18 in this section, including any impacts on you or other stakeholder groups, and key implementation considerations for any changes that could be made.

Chapter 12: Other Product-Specific Changes

Section 67 - Re-manufacturing single-use devices

Q67.1 Do you think that the UK medical devices regulations should include the requirements for re-manufacturers of single-use medical devices set out in paragraph 67.5? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q67.2 Please outline any other requirements which should be introduced for the re-manufacturing of single-use devices.

Q67.3 Do you think the UK medical devices regulations should introduce the requirements set out in paragraph 67.6 for re-manufacturers of single-use devices on behalf of healthcare institutions? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q67.4 Please outline any other requirements which should be introduced for the re-manufacturing of single-use devices within healthcare institutions.

Q67.5 Do you think that the MHRA should allow the re-manufacturing of Class I single-use medical devices? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q67.6 If you have answered 'yes' to question 67.5 please outline what the requirements should be in place for the re-manufacturing of Class I single-use medical devices.

Q67.7 Do you think that the MHRA should continue to allow the re-processing of single-use devices? ('Yes' / 'No' / 'Don't Know/No Opinion').

Q67.8 If you have answered 'yes' to question 67.7 please outline what requirements should be put in place for re-processing of single-use devices.

Q67.9 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 67.1-67.8, including any impacts on you or other stakeholder groups.

Section 68 - Systems, kits and procedure packs

Q68.1 Do you think that the UK medical devices regulations should include the term 'kit' when referring to medical devices and products which are assembled together? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q68.2 Should the definitions of systems, procedure packs and kits allow external software (e.g. a specific app identified in the labelling) to be considered as a component of the system, procedure pack or kit? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q68.3 Do you think that assemblers of systems, kits and procedure packs should be required to implement procedures for the factors listed in paragraph 68.6? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q68.4 Please outline any other requirements that you think we should introduce for system and procedure packs and the sterilisation of system and procedure packs.

Q68.5 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 68.1-68.4, including any impacts on you or other stakeholder groups.

Section 69 - Parts and components

Q69.1 Do you think that the UK medical devices regulations should require that any individual or company who supplies an item specifically intended to replace an identical or similar integral part or component of a medical device that is defective or worn should ensure that the item does not negatively affect the safety and performance of the medical device? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q69.2 Do you think an item that is intended specifically to replace a part or component of a medical device and that significantly changes the performance or safety characteristics or the intended purpose of the medical device could be considered to be a medical device in its own right and therefore be required to meet the requirements of the UK medical devices regulations? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q69.3 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 69.1-69.2, including any impacts on you or other stakeholder groups.

Section 70 - Custom-made devices

Q70.1 Do you think that the UK medical devices regulations should include more detailed requirements for the technical documentation that must be drawn up and kept by the manufacturer of a custom-made device, such as those outlined in paragraph 70.5? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q70.2 Do you think that the UK medical devices regulations should introduce more stringent requirements for the post-market surveillance of custom-made devices, such as those outlined in paragraph 70.6? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q70.3 Do you think that the UK medical devices regulations should require manufacturers of certain custom-made devices to implement a QMS which must be certified by an Approved Body? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q70.4 If you have answered 'yes' to question 70.3, please outline what types/classes of custom-made devices should fall under this requirement.

Q70.5 Please outline any further requirements which should be introduced for manufacturers of custom-made devices.

Q70.6 Do you agree that custom-made devices could be manufactured on the basis of an electronic prescription, as outlined in paragraph 70.8? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q70.7 Please provide your reasoning (including any available relevant evidence) to support your answers to questions 70.1-70.6, including any impacts on you or other stakeholder groups.

Chapter 13: Environmental sustainability and public health impacts

Q71.1 To what extent are you or your organisation already implementing, or planning, activities to reduce the impact of medical devices on the environment? Please outline any key activities you have underway or planned.

Q71.2 Do you see a need for additional requirements to be placed on economic operators in order to encourage them to consider and/or mitigate the environmental impact of medical devices they place on the UK market? ('Yes' / 'No' / 'Don't Know/No Opinion')

Yes

Q71.3 Please explain the rationale for your response to question 71.2 and any expected impacts.

Measures to reduce the environmental impacts of medicine are beginning to be considered in the context of the use and disposal of plastic and release of greenhouse gases by asthma inhalers, for example.⁹⁷ This should be extended to reduce the negative impacts on the environment associated with all diagnostics.

Q71.4 What are your views on the options for change outlined in paragraph 71.5? Please state your rationale, key implementation considerations and the expected impact of these options.

Energy use should be added to this, due to climate change.

Q71.5 What other changes or key considerations do you think are needed to ensure more sustainable medical devices?

Consideration of environmental sustainability should also include energy use, as this is a major consideration for algorithms derived from sample storage in biobanks and large-scale data storage (including genomic data).⁹⁸ However, energy use by 'Big Data', including genomics, should also be considered, if significant negative impacts on emissions targets are to be avoided.

Q71.6 What are the key implementation considerations for the options outlined in paragraph 71.5 and any further potential changes you consider are required?

Q71.7 Please set out which options could be introduced quickly (within 1-2 years) and which could be introduced within a longer timeframe?

Consideration of environmental impacts, including energy use, should begin as soon as possible to facilitate the energy transition and avoid locking in poor environmental practices.

Chapter 14: Routes to market

Section 72 - MDSAP and Domestic Assurance

Q72.1 Do you think the MHRA should introduce an alternative route to market which utilises Medical Device Single Audit Programme (MDSAP) certificates? ('Yes' / 'No' / 'Don't Know/No Opinion')

No

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.

There is a big risk of undermining public trust in the regulatory system unless regulatory standards are maintained and the quality of the assessment can be guaranteed.

Q72.3 Do you think the MHRA should introduce an alternative route to market which utilises approvals from other countries (domestic assurance route)? ('Yes' / 'No' / 'Don't Know/No Opinion')

No

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 'CE plus UKCA' route should be sufficient to achieve certification for both EU and UK markets. Other 'domestic assurance' routes to approval via international regulators risk undermining the regulatory system and losing public trust.

Section 73 - Pathway for Innovative MedTech

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' / 'No' / 'Don't Know/No Opinion')

No

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' / 'No' / 'Don't Know/No Opinion')

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.

Fast track routes to market risk undermining the regulatory system, losing public trust and diverting resources to investment in high-risk products that ultimately fail.

Chapter 15: Transitional Arrangements

Q74.1 Do you think that we should introduce the transitional arrangements proposed above in Option 1? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q74.2 Do you think that we should introduce the transitional arrangements suggested above in Option 2? ('Yes' / 'No' / 'Don't Know/No Opinion')

Q74.3 Please give your reasoning for your answer to questions 74.1-74.2. If you have answered 'yes' to either question, please include what you consider the required arrangement(s) and any expected impacts of these on you or other stakeholder groups.

Q74.4 Do you agree with the transitional arrangements suggested in Option 5 above? ('Yes' / 'No' / 'Don't Know/No Opinion')

No.

Q74.5 Please give your reasoning for your answer to question 74.4.

Whilst recognising there are current limitations to regulatory capacity, we remain concerned that such regulations have been a long time in development and that any delay could lead to negative impacts on human health, as poorly performing tests which provide misleading information can continue to be marketed. At minimum, safeguards retained by the EU during the proposed extended transitional period should also be implemented in the UK, namely market and post-market surveillance, vigilance, and registration of economic operators and devices. In addition, it does not assist companies or the public to delay implementation of requirements for clinical investigations, since this risks the relevant data not being collected (or being collected in an unethical way) and therefore not being adequate to support a subsequent application to place the test on the market when the transitional period is over. Therefore, the implementation of regulatory requirements for clinical investigations should not be delayed.

Q74.6 Please set out any other transitional arrangements or considerations you believe are required for putting in place a future regime for medical devices in the UK, why, and the expected impacts on you and other stakeholder groups.

Q74.7 How many years after 1 July 2023 should the MHRA accept UKCA certificates / declarations of conformity issued before 1 July 2023? That is, what would be a suitable 'specified date' for Option 1 above? (30 June 2025, 30 June 2026 or Other – please specify).

Q74.8 How many years after 1 July 2023 the date of implementation of the Regulations should the MHRA accept CE certificates issued before 1 July 2023? That is, what would be a suitable 'specified date' for Option 2 above? (30 June 2027, 30 June 2028 or Other – please specify).

Q74.9 For how long after expiry of the certificate/declaration of conformity or after the 'specified date' should devices covered by the transitional options 1 and 2 be permitted to be supplied to the UK market? (They should not be permitted to be supplied after expiry or cut-off date; 6 months; 12 months)

Q74.10 What additional checks, if any, would you consider to be necessary to allow CE marked products to remain on the Great Britain market after 1 July 2023?

Q74.11 Please provide your reasoning for your proposed dates above.

Chapter 16: Feedback

Section 75 – Feedback

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

Very Poor

Poor

Good

Very good

Excellent

Q75.2 Do you consider the possible changes to UK medical devices regulations set out in this consultation document to be proportionate? ('Yes' / 'No' / 'Don't Know/No Opinion')

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

Q75.4 Please provide any additional feedback comments.

It was not always easy to determine which questions applied to IVDs, as some questions relating to 'medical devices' did apply, but some did not.

It would be helpful if there was a further round of consultation on the draft regulation, as it would then be possible to consider the specifics of what is being proposed.

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