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Alternative Routes to Market for Medical Devices

CONTENTS

The Birmingham Health Partners Centre for Regulatory Science & Innovation was established in 2020 to support the development and delivery of novel therapeutics and medical devices in the UK, through advanced regulatory standards and tools. A truly multidisciplinary initiative, the CRSI aims to bring together experts in medicinal science, health policy and management, clinical trial design, medical law, and patient-reported outcomes research, from across BHP member organisations. The mission of the CRSI is to drive innovation in regulatory science to promote efficient, safe, and cost-effective implementation of new therapies, for the benefit of patients and society. **www.birminghamhealthpartners.co.uk**

The Regulatory Horizons Council (RHC) is an independent expert committee that identifies the implications of technological innovation, and provides government with impartial, expert advice on the regulatory reform required to support its rapid and safe introduction.

March 2021

Executive Summary

Now that the UK has left the EU and the Medicines and Medical Devices Bill has received Royal Assent and become law, there is unique opportunity for the UK to update the way it regulates medical devices to promote patient outcomes and population health, stimulate innovation, and ensure that the UK remains at the forefront of the global life sciences sector. The Regulatory Horizons Council commissioned the Birmingham Health Partners Centre for Regulatory Science and Innovation to collate multi-stakeholder views on 'potential alternative routes to market for medical devices that are currently being used internationally that could be transposed to the UK market and regulatory system'.

The CRSI team began by performing a literature review using PubMed and Google Scholar to search the published literature and Google Search Engine to search the grey literature. We then used qualitative methods to comprehensively collate the views of stakeholders from across the medical device sector: i) one-on-one, semi-structured interviews with stakeholders were conducted; ii) a multidisciplinary stakeholder workshop was convened to review initial findings and discuss areas of agreement and disagreement; and iii) a post-workshop survey was distributed to attendees to further explore areas of contention discussed during the workshop. All data were subsequently analysed using a framework approach.

The evidence gathering and stakeholder engagement process identified three systems in operation internationally that are particularly relevant to the UK as it considers its approaches to the regulation of medical devices: Medical Device Single Audit Program (MDSAP), U.S. Food and Drug Administration (FDA), and Mutual Recognition Agreements (MRA). These systems are not mutually exclusive and the UK could choose to adopt certain aspects of each approach.

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Medical Device Single Audit Program The MDSAP, developed by the International Medical Device Regulators Forum (IMDRF), provides a single audit program that satisfies the quality management system (QMS) requirements of the participating regulatory authorities to varying degrees as they choose to utilise it. Joining the MDSAP as a Participating Country would effectively reduce the regulatory burden on both UK medical device companies marketing products in five major medical device markets and international companies seeking to sell devices in the UK, enhancing public and patient access to medical devices in the UK. More broadly, as a Participating Country, the UK would be able to influence strategy within this international initiative to promote global harmonisation and convergence in medical device regulatory practices relating to QMS. However, the UK must appreciate that joining the single audit programme would likely involve operational complexities and require a transition period. Additionally, the IMDRF's actions are likely to focus and prioritise items concerning the interest of international regulatory authorities, which may not always align proportionately to the UK's interests, for example, regulating certain state-of-the-art medical devices. The UK must balance the benefits of joining the MDSAP against the potential impact on its regulatory flexibility and independence.

U.S. Food & Drug Administration The most common regulatory pathway for bringing medical devices to the US market and the most commonly referenced regulatory pathway by stakeholders is the premarket notification (510(k)) program. A similar, but more strict route has been introduced in the EU MDR, where an adequate demonstration of medical device equivalency may be used to satisfy one aspect of the regulatory submission - the clinical investigation requirement. Implementation of a more extensive equivalence-based approval process that is similar to 510(k) would speed the path to market for new devices in the UK, increasing the number and diversity of products made available. However, under this model, additional measures should be considered to safeguard public safety, as regulatory authority approvals would largely be determined by how much substantial equivalence is reasonable; in other words, how much divergence is permitted before a device is no longer substantially equivalent to its predicate. More generally, the UK needs to ask itself whether it wants a supervisory (where the Medicines and Healthcare products Regulatory Agency (MHRA) designates third-party bodies to perform the majority of regulatory assessments) or an interventionist (where the MHRA performs the majority of regulatory assessments itself) regulatory system. Adopting an FDA-style interventionist model would require the MHRA to significantly expand its role and responsibilities.

Mutual Recognition Agreements MRAs are trade agreements by which two or more countries agree to accept one another's conformity assessment certificate of medical devices. Establishing MRAs will increase efficiency in both the UK's regulatory system and the regulatory systems of its international counterparts by jointly leveraging regulatory resources. This allows a greater coverage in regulating devices between countries in MRAs, addressing the anticipated capacity gaps in UKCA registration. By extension, this would allow MHRA to reallocate resources towards inspection of medical devices with potentially higher public health risk or those with a higher public interest. However, it is important to appreciate that it takes time to build the trust that is required to negotiate bilateral or multilateral MRAs.

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Key Findings

Potential alternative routes to market for medical devices that are currently being used internationally that could be transposed to the UK market and regulatory system

	IMDRF Medical Device Single Audit Program (MDSAP)	U.S. Food and Drug Administration (FDA)	Mutual Recognition Agreement (MRA)
Strengths	Recognition of a single audit across the five participating countries (Australia, Brazil, Canada, Japan, USA) facilitates access to overseas markets and could accelerate time-to-market for medical devices. The procedures and practices across participating regulatory authorities and third-party Auditing Organisations have been praised for consistency, predictability, and transparency.	There are a range of routes to market within a single regulatory system which provides medical device companies with the flexibility to choose the most appropriate route for a specific product. Having a single, centralised agency, which acts as both legislator and regulator, makes it easier for regulators to enforce regulation and allows for greater coordination across the system. The 510(k) pathway is the most common regulatory pathway for bringing medical devices to the US market, the most novel regulatory pathway to the UK, and the most commonly referenced regulatory pathway by stakeholders. It offers a more efficient route to market for low to moderate-risk devices that are substantially equivalent to a legally marketed 'predicate' device.	An MRA is an efficient regulatory solution that avoids duplication of regulatory inspections, thereby saving time, money, and facilitating market access. This form of trade agreement can encourage greater international harmonisation of regulatory standards. As demonstrated by the MRA in place between Australia and the EU, regulators can choose to conduct targeted product assessments for medical devices that are not regulated by their trading partners as well as high-risk or novel medical devices that they would prefer to regulate themselves.
Weaknesses	Participating Countries use the outcomes of the MDSAP audit differently which means that medical device manufacturers may have to undertake additional activities to gain access to a market. Additional technical documentation, separate to the MDSAP certificate, may be required to demonstrate compliance with the requirements of specific regulatory jurisdictions, because the MDSAP is only an audit of a medical device manufacturer's quality management system. Establishing and harmonising new standards for innovative medical devices is challenging because the proposed methods need to be accepted and integrated across five separate countries.	The Third Party Review Program (3P510k), which the FDA recently introduced to allow third-party organisations to review 510(k) submissions, has introduced issues associated with decentralised regulatory systems, such as inconsistency in approach. The lack of consensus regarding how much divergence is permitted before a device is no longer substantially equivalent to its predicate has raised concerns that some devices, which should warrant a more robust regulatory review, are inappropriately and unsafely made available on the market via the 510(k) pathway. Some stakeholders commented that the two most commonly used regulatory routes within the FDA (Premarket Approval and 510(k)) are rigid, lengthy, and costly.	Mutual recognition requires significant levels of trust between trading partners which takes time to build. Coordination of post-market surveillance processes and activities across multiple trading partners can be challenging. Over-reliance on an external regulatory authority with no legal responsibility for the public health of your population may raise questions regarding liability, although recognising the manufacturer or their representative in the UK would be the ones ultimately liable for the device once it is placed on the UK market.
Appropriateness to the UK	Joining the MDSAP as a Participating Country would provide UK medical device companies with a more efficient route to five large international markets. By extension, joining would also support companies seeking to sell devices with MDSAP certificates in the UK, promising patients and the public in the UK greater choice of and access to medical devices. More widely, by becoming a member of the MDSAP, the UK would be involved in an international initiative to accelerate medical device regulatory harmonisation and convergence. The process of joining the single audit programme will not, however, be so simple and may require a transition period. Additionally, the UK must appreciate that the IMDRF's focus will be on international regulatory affairs, which may not always align with the UK's interests to, for example, regulate certain state-of-the-art medical devices. The UK must balance the benefits of joining the MDSAP against the potential impact on its regulatory flexibility and independence.	Adopting an equivalence-based approval process similar to the FDA's 510(k) pathway in the UK could potentially accelerate market access for new devices that are substantially equivalent to predicates, adding device diversity and creating market competition. However, extra measures, including ensuring that there is clearer consensus on how much divergence is permitted before a device is longer substantially equivalent to its predicate, need to be in place to protect patient safety. More broadly, the UK needs to ask itself whether it wants a supervisory (where the MHRA designates third-party bodies to perform the majority of regulatory assessments) or an interventionist(where the MHRA performs the majority of regulatory assessments itself) regulatory system. Switching to an FDA-style interventionist model would require the MHRA, as the UK's regulatory authority, to significantly expand its role and responsibilities.	Establishing MRAs will increase efficiency in both the UK's regulatory system and the regulatory systems of its international counterparts by strengthening the use of each other's regulatory expertise and resources. This provides a practical way to address anticipated capacity gaps in UKCA registration and would allow MHRA to reallocate resources towards inspection of medical devices with potentially higher public health risk or those with a higher public interest. However, it is important to appreciate that it takes time to build the trust that is required to negotiate bilateral or multilateral MRAs.

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Abbreviations

BHP	Birmingham Health Partners
CRSI	Centre for Regulatory Science and Innovation
EU	European Union
FDA	Food and Drug Administration
IMDRF	International Medical Device Regulators Forum
MDSAP	Medical Device Single Audit Program
MHRA	Medicines and Healthcare products Regulatory Agency
MRA	Mutual Recognition Agreements
QMS	Quality Management System
RHC	Regulatory Horizons Council
UK	United Kingdom of Great Britain and Northern Ireland
UKCA	United Kingdom Conformity Assessed
US	United States

Acknowledgements

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Disclaimers

While this report was commissioned by the Regulatory Horizons Council, Birmingham Health Partners Centre for Regulatory Science and Innovation retained full editorial control of the report's content.

This report reflects the views of a range of stakeholders and should not be attributed to specific individuals or organisations unless explicitly stated.

Drs Han and Ibrahim contributed equally to this report and are recognised as joint first authors.

Professor Melanie Calvert (MC) receives funding from the NIHR Birmingham Biomedical Research Centre, the NIHR Surgical Reconstruction and Microbiology Research Centre, NIHR ARC West Midlands at the University of Birmingham and University Hospitals Birmingham NHS Foundation Trust, Health Data Research UK, Innovate UK, Macmillan Cancer Support, and UCB Pharma. MC has received personal fees from Astellas, Takeda, Merck, Daiichi Sankyo, Glaukos, GSK, and the Patient-Centered Outcomes Research Institute.

Funding

This report was supported by a Quality-related Research grant from Research England.

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Stakeholders

We extend our thanks to the following people who kindly agreed to participate in the preparation of this report:

Adrian Jonas	National Institute for Health and Care Excellence
Alan Fraser	University Hospital of Wales
Anne Vanhoestenberghe	University College London
Antoine Valterio	ResMed
Carolyn Ruston	National Physical Laboratory
Charles de Rohan	The Binding Site
Charlie Winkworth-Smith	Knowledge Transfer Network Neurotechnology Special Interest Group
Chris Pomfrett	National Institute for Health and Care Excellence
Christina Silcox	Duke-Margolis Center for Health Policy
David Grant	Enesi Pharma Ltd
Doris-Ann Williams*	British In Vitro Diagnostics Association
Eamonn Hoxey	E V Hoxey Ltd
Gary Price	Centre for Patient Reported Outcomes Research Patient Partner
Hugh Harvey	Hardian Health
Ian Newington	National Institute for Health Research
Ivan Perez Chamorro	MedBoard
Ivor Gillbe	Bioinduction Ltd
James Carpenter	SurePulse Medical Ltd
James Pink	NSF International
Jane Wilson	Intuitive Surgical
Johannes Starlinger	Starlinger+ Digital Health Architects
John Wilkinson	Global Medical Device Nomenclature
Kathy Oliver	International Brain Tumour Alliance
Kevin Butcher	North American Science Associates
Martin Levermore	Medical Devices Technology International Ltd
Michael Kipping*	Innovate UK
Omar Moreea	National Institute for Health and Care Excellence
Phil Brown*	Association of British HealthTech Industries
Rob Turpin	British Standards Institution
Tim Constandinou	Imperial College London
Tim Denison	University of Oxford
Tom Beale	Centre for Process Innovation
Tom Campbell	The Magstim Company Ltd
Tom Clutton-Brock	University of Birmingham
Warren Jameson	North American Science Associates

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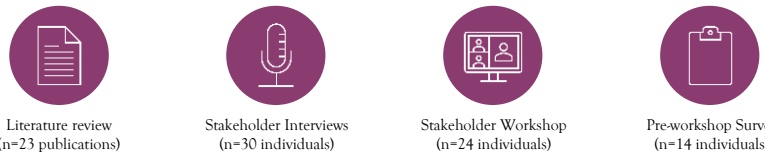
APPENDIX 1: Methods

Qualitative methods were used to collate the views of stakeholders from across the medical device sector.

1. Data Collection

Data were collected from four sources:

Figure 1. Data Sources.



1.1. Literature Review

A literature review was conducted on 08 January 2021. PubMed and Google Scholar were used to search published literature and Google Search Engine was used to search grey literature. Only the first 100 citations from Google Scholar and Google Search Engine were screened due to time constraints. Citations were independently screened by two co-investigators (DH and HI) according to predefined inclusion and exclusion criteria. Disagreements were resolved via consensus. A total of 23 citations were included in the literature review.

Table 1. Search Terms

PubMed		Google Scholar	Google Search Engine
Search Terms	Record no.	routes to UK market for medical devices OR medical device	routes to UK market for medical devices OR medical device
1 Medical device			
2 Medical devices			
3 OR (1-2)	1,561,169		
4 United Kingdom			
5 Brexit			
6 OR (4-5)	907,740		
7 Healthcare market			
8 Healthcare markets			
9 Health care market			
10 Health care markets			
11 Healthcare sector			
12 Health care sector			
13 Healthcare industry			
14 Health care industry			
15 Healthcare industries			
16 Health care industries			
17 OR (7-16)	72,186		
18 Pre market requirement			
19 Premarket requirement			
20 Device approval			
21 Devices approval			
22 Medical device approval			
23 Medical devices approval			
24 Device approval process			
25 Devices approval process			
26 Medical device approval process			
27 Medical devices approval process			
28 Regulatory framework			
29 Regulatory science			
30 Medical device legislation			
31 Medical devices legislation			
32 OR (18-31)	171,996		
33 3 AND 6 AND 17 AND 32	74		

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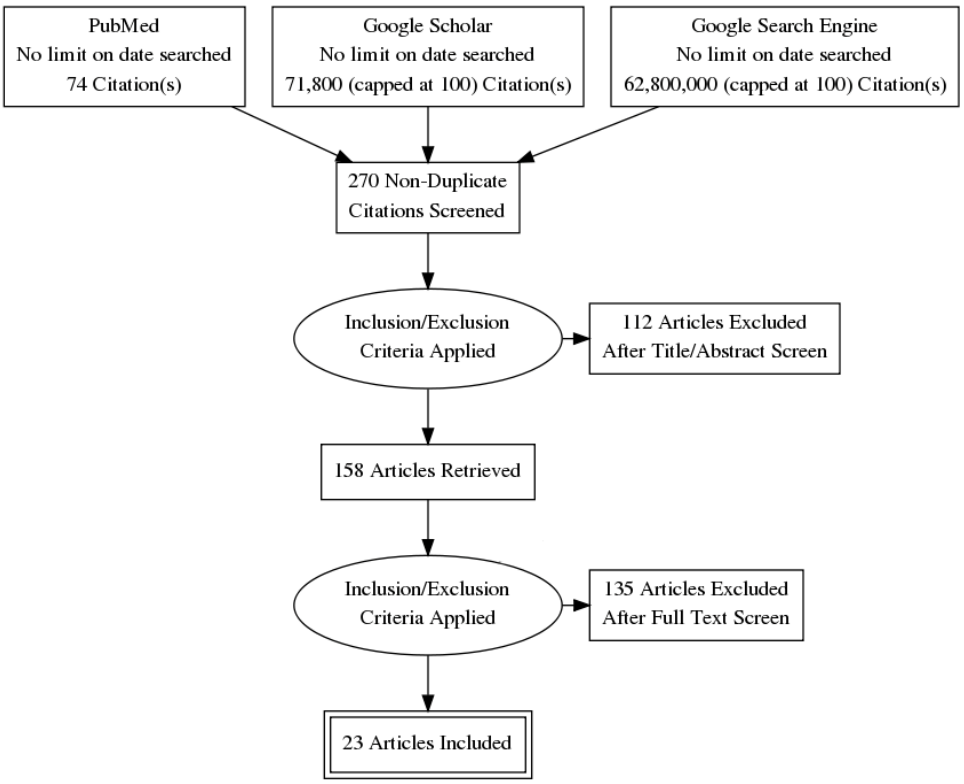
Table 2. Inclusion and Exclusion Criteria for Literature Review.

Inclusion criteria	Exclusion criteria
English language	Non-English language
Any format of document	
Any date	
Medical devices and/or in vitro medical devices	
New/alternative/international routes/ways to access/ways to enter the UK market	Current/existing/EU routes/ways to access/ways to enter the UK market
National and international regulations	

Figure 2. Flow Diagram for Literature Review.



1.2. Stakeholder Interviews

Stakeholder interviews were conducted online via MS Teams between 04 January 2021 and 02 February 2021. A total of 30 one-on-one, semi-structured interviews were conducted with stakeholders from across the medical device sector: medical device companies (n=7), regulatory consultancies (n=6), UK Government agencies (n=5), product testing or certifying bodies (n=4), academics and clinicians (n=4), trade associations (n=2), and patient and public partners (n=2).

1.3. Stakeholder Workshop

A workshop was conducted online via MS Teams on 09 February 2021. The aim of the workshop was to discuss areas of agreement and disagreement identified after analysis of data from the literature review and stakeholder interviews. A total of 24 stakeholders attended the workshop.

1.4. Post-Workshop Survey

A post-workshop survey was conducted online via Qualtrics Survey Software between 19 February 2021 and 05 March 2021. The survey was designed to further explore areas of contention discussed during the workshop. A total of 14 stakeholders completed the survey.

2. Data Analysis

Data were managed and analysed thematically using the framework approach. This method allows a comprehensive review of collected narratives, that is driven by stakeholders' original accounts and literature review. Raw data from the four sources were analysed by two co-investigators (DH and HI). The interviews were reviewed and coded independently using the stakeholder interview questions as an initial thematic framework. Textual codes were grouped into clusters around similar and interrelated concepts and a matrix of themes were created and analysed within Google Sheets.

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IMDRF Medical Device Single Audit Program (MDSAP)

**[I]=Stakeholder interview; [LR]=Literature Review; [W]=Stakeholder Workshop*

Pros		Cons		Appropriateness	
Single audit used in lieu of multiple separate audits or inspections, that is recognised in five participating regulatory authorities	[I] • Simple • Recognition from 5 participating regulatory authorities - Australia, Brazil, Canada, Japan, USA • Alignment with the rest of the world. • Less tied by the restraints of resources, infrastructure • Opens up wider global markets - more than just EU • Harmonization	Establishing and harmonising standards, especially for innovative medical devices, is challenging	[I] •Harmonisation of technical requirement for digital processors will be very hard •Difficulty making it happen •Slow progress is being made but will not be doable within the next few years	Joining as Participating Country will be challenging for the UK, MD-SAP auditors, and the MD-SAP Participating Countries and may, for example, require another transition period	[I] • The blockers associated with using the MD-SAP would be the time period required to transition. We would need one ('transition period') like we have now for UKCA.
	[LR]		[LR]		[LR]
	[W]		[W] • There is a challenge of integrating new methods of evaluating and assessing newer technologies, where existing standards are not fit-for-purpose. • MDSAP audit organisations do not sufficiently understand the regulations of the 5 participating countries. They tend to know Australia and Canada. US ok but Brazil and Japan does not get an adequate crack of the whip.		[W] • There is a limit to the number of countries who can join MDSAP, as James has indicated auditors presently have to learn 5 x different country regulations, there is a limit to the number of regulations they can learn. • EC reminded the UK there is usually 2-3 yrs of observer status before you can join as a member of the IMDRF.
Transparent assessment program overseeing the compliance of Auditing Organisations	[I] • Transparent, free access to online resources	Only quality management system (QMS) therefore no review of technical documentation	[I] • Only QMS therefore no review of technical documentation	QMS, which involves reviewing technical documents, would need to be done by MHRA, which currently lacks resources – the UK could try to introduce a review of technical documents into the QMS, but this would require "buy-in" from existing countries	[I] • QMS needs to be done by local health authorities therefore the MHRA would be required to do this job which would require taking on a whole new role of looking at technical documentation which they are currently not prepared to do • Enabling a 3rd party (e.g. NBs/ABs) to review technical documentation would require UK changing MDSAP policy which is unlikely to be possible • Joining the MD-SAP and trying to introduce a review of technical documentation into it would be the best option • It is unlikely that the UK would get sufficient buy-in from existing Participating Countries to make such changes. As it stands, Australia is the only country in MD-SAP that wants to include technical documentation alongside the QMS remit
	[LR]		[LR]		[LR]
	[W]		[W] • MDSAP is a method of securing standard control in a single process between regulators, not for approving devices. The standards for clinical evidence and tech files (TF) assessment - there is an issue of engagement with academic/clinical standards which are generated internationally for high risk medical devices. • MDSAP is a method of assessing quality control in a standard way via a single process between different regulators rather than a way of approving a device		[W] • IMDRF has had a programme looking at single technical document review for a number of years but, some argue that this has not gathered much traction. • NBs/ABs could focus on technical documentation (TD) assessment, rather than QMS assessment.

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*[I]=Stakeholder interview; [LR]=Literature Review; [W]=Stakeholder Workshop

Pros	Cons		Appropriateness	
	No access to EU and China	[I] • EU does not recognise MDSAP (since the EU participate as an "official observer") • No access to EU and China	The IMDRF is unlikely to produce regulation for innovative medical devices if those devices are not used on sufficient scale internationally; the UK cannot rely on the IMDRF to regulate all types of medical devices and may need to, at times, produce its own regulation for state-of-the-art technologies	[I]
		[LR]		[LR]
		[W]		[W] • Common devices/materials do not need to be re-tested. Standards work should be focussed on innovative devices/materials rather than re-assessing "me-too" devices/materials. Ie. skin contact devices with well established materials do not need to be audited by the regulatory authority - devices such as this can be regulated by declarations rather than updated reassessment) • Naturally in more novel devices the default to an international standard will only be driven by a consensus to adopt international standards. As a result we need to understand if our innovation portfolio and health needs are in-line with the international standards development. • Where they are not we need to ensure that there is consensus within the UK and any other scientific and medical input so state-of-the-art (technology) is understood and applied.
			Joining as Participating Country provides opportunity to be involved in international regulations	[I] • This would give the UK an opportunity to be involved in the development of future international regulations (e.g. data compatibility and alignment) and ensure that these regulations work for the UK as well as other countries
				[LR] • There is a limit to the number of countries who can join MDSAP, as James has indicated auditors presently have to learn 5 x different country regulations, there is a limit to the number of regulations they can learn, would the UK be allowed to join MDSAP?
				[W] • The UK would have to be a very active partner in the single audit model for this to give the UK the necessary confidence • FDA are pushing harmonisation and sharing of burden because they don't have the capacity. Hence MDSAP, move to ISO 13485, and further developments. It is a direction of travel... don't underestimate the power of quality management systems. • The IMDRF/ ISO/IEC standards need to be complied with regardless of what route to market is used. The UK should consider changing the way it inputs into international standards. We have an excellent group of core experts and knowledge in the UK and should seek to identify areas where we could increase our leadership roles in IMDRF/SO/IEC. • Last year the IMDRF closed (i.e. finished the work) its standards working group. This could mean that there are limited opportunities for the UK to get involved in work around technical standards. There is, however, a gap remaining around clinical standards, which are important for clinical safety, that the UK could get involved in. • MDSAP is not a joint approval process. The EU has not been able to join MDSAP as the EU does not approve medical devices, this is done by NBs. If the UK is going to continue to use NBs (ABs) for UKCA mark, the UK may also been barred from MDSAP. • One of impediments of the IMDRF has been lack of engagement by the EU over the last 10 years. The UK could provide badly needed support and impetus.
			Politically palatable	[I] •The most politically palatable option would be MD-SAP as this meets the political will to diverge from the EU, but it still does not open up the EU market. •The best option for the UK is to build on MDD using principles of IMDRF and to beef it up to respond to the safety issues that led to the drive to the MDR.
				[LR]
				[W]

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U.S. Food and Drug Administration (FDA)

**[I]=Stakeholder interview; [LR]=Literature Review; [W]=Stakeholder Workshop*

Pros		Cons		Appropriateness	
Range of routes to market within one system (de novo, 510(k), emergency use authorization, breakthrough device designation) provides flexibility	[I] •Different routes (e.g. PMA, 510(k), EUA, etc.) available enables flexibility •The FDA has trained its staff to understand the basics of different medical devices	Centralisation results in a rigid, lengthy, and costly regulatory process	[I] •The process is slow. •The FDA approval process still ultimately requires significant amounts of paperwork •Rapidly-evolving draft guidance, where sometimes FDA interpretation differs from the general industry consensus - can be "caught out" (e.g. combination devices) •Takes safety and efficacy into account during approval process but does not consider clinical utility which means that it does not guarantee sales on the market as health insurance systems will not necessarily pay for it just because it has FDA approval - there is no single definition of clinical utility and different health insurance systems will ask for different data to perform their internal clinical utility assessment	A centralised government agency with less reliance on third party conformity assessment bodies may create less competition in the medical device regulation market	[I]
	[LR] •Better coordination and ease of enforcing regulatory requirements		[LR] •(Procurement process (to multiple insurance companies in the US) is separate to the market approval process.) "The aim of German legislation is to guarantee a quick transfer of innovative technologies into hospital practice. In German hospitals, clinicians can use new devices bearing a CE mark for the indications specified unless the German Federal Joint Committee, which is responsible for assessing medical treatments, has expressly ruled out their use. Hospitals are therefore able to use new treatments before and during any assessment." •Uncertainty: There is no certainty at the start of the approval process that a device will be approved for market. Nor is there any certainty about how much testing will be necessary or how much time it will take before there is a “go” or “no go” decision from the FDA. As a result, there is also no certainty about how much it will cost to supply the FDA with the required information. One inventor who has had recent experience with the FDA described the problem with uncertainty this way: “Due to ‘regulatory uncertainty,’ a euphemism for the complete and utter capriciousness and unpredictability in the FDA review process of new medical products, venture capitalists are becoming less inclined to fund very early stage companies •Both premarket approval and premarket notification (510(k)) can mean long waiting times that can be costly in terms of repaying loans and losing firstmover advantage. For PMA the average review time in 2010 was 419 days, which dropped to 266 days in 2012.49 These times do not, of course, include the four to five years needed to conduct clinical trials in situations for which the FDA requires them. •The FDA review process is almost twice as long as that of its European counterpart, the European Medicines Agency, for devices not requiring clinical data, and almost three times as long for devices that do. On average the United States takes six months, whereas European countries take three months. Citizens of countries with efficient and less uncertain and complex regulatory approval processes gain earlier access to innovative medical technology, and providers in those countries benefit from more experience in using new devices.		[LR]
	[W]		•[W]		[W] •What are the fundamental features of the regulatory system? Is it supervisory or is it interventionist? Supervisory is cheaper and less complex; interventionist (more like US) is costly and more complex.

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*[I]=Stakeholder interview; [LR]=Literature Review; [W]=Stakeholder Workshop

Pros		Cons		Appropriateness	
Single centralised agency acting as both legislator and regulator enables better coordination, control, and ease of enforcing regulations	[I] •The regulators (FDA) are civil servants employed by the US government rather than commercial companies (like in the EU and UK). The problem with commercial companies in the EU and UK is that there are "too many people telling you what the rules of the game are". This is not the case in the US system. •The FDA acts as both regulator and expert. Simpler than the EU model in that you simply submit your application and wait to hear back from them with a list of what information they wanted. •Long-standing large single system that regulates all medical devices •More direct control •Same body that effectively makes and judges rules	Despite the effort to centralise the system, involvement of third parties and field offices, secondary to lack of capacity, suffer from problems associated with the de-centralised system	[I]	Equivalence process where minor modifications to devices can be evaluated against predicates rather than having to start from scratch (510(k)) adds competition and can reduce duplication of efforts	
	[LR] •The clear benefit from having a government regulated agency is that all information regarding any medical device is within one harmonized and centralized agency, rather than seventy different agencies.		[LR]		
	[W]		[W] •The FDA does still use 3rd parties for MDSAP audits to correct their lack of regulatory capacity. The FDA also has field offices around the US conducting the quality audit side of things. These field offices suffer from the problems associated with a decentralised system i.e. lack of consistency. There are consistent battles between the field office and the central office. This would also likely apply to the China CFDA model. •FDA recently started a programme (i.e. 510(k) Third Party Review Program - 3P510k) to subcontract class II devices using 3rd parties		
Proactive, responsive and manufacturer-friendly process	[I] •More user friendly in that you provide the same amount of information overall but in a stepwise manner. This means manufacturers are not faced with the mammoth task of having to produce all the documentation on day one. This is particularly helpful for small and medium-sized enterprises who do not have regulatory experts in house. •The FDA was previously considered to be unresponsive and opaque but nowadays the FDA is more responsive and approachable and easier to communicate with •Has a 'can-do attitude' •More pragmatic medical device risk classification (e.g. risk score calculator software would be classified as 2A under EU MDR, while it is exempt from regulatory process - saves time & cost) •"More proactive" •Specific contact point for guidance (easy, highly accessible compared to the MHRA, NBs) •More clarity on different requirements (became less reviewer-dependent and reduced inter-reviewer variation)	Regulatory requirements felt to be inhibitory with regards to innovation – one study from Journal of Medical Devices reports almost nine out of 10 companies surveyed felt that FDA is unnecessarily hindering innovation	[I]		
	[LR] •The FDA Product Classification Database is an excellent resource. You can search by device name, review panels, product codes, and much more. The output from that search will provide you with a wealth of information that will help you develop a regulatory strategy that makes sense for your product. •Another thing often overlooked is the ability to solicit feedback early on from the FDA on your regulatory pathway through the FDA pre-submission program. This can be a very effective way to proactively work with the FDA to alleviate any concerns and be confident in your plan for getting to market.		[LR] •The U.S. medical device industry is a highly regulated sector of the economy plagued with bureaucracy and complex regulations. Regulatory requirements have strongly swayed manufacturers' decisions around investments in, and development of, new products. According to a study done for the Journal of Medical Devices, almost nine out of 10 companies surveyed felt that FDA is unnecessarily hindering innovation and decreasing American competitiveness in the global marketplace		
	[W]		[W]		

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*[I]=Stakeholder interview; [LR]=Literature Review; [W]=Stakeholder Workshop

Pros		Cons		Appropriateness
Pros of 510(k) equivalence process	[I] •Undercut the price •Equivalence testing process is good for quicker regulation of low-risk medical devices •Reduces duplication: notion of referencing materials that are already filed •Straight-forward •Fair process •More focus on safety in terms of patient outcomes i.e. performance standards are higher •Time for assessment/approval is legally protected which means there is more certainty going into the process how long it will take •Less paperwork/bureaucracy •510k, more pragmatic than EU Substantial Equivalence (With 510k, once predicate is found, you can focus on comparing and contrasting the risk, rather than ""diluting"") •Efficient for "me-too" devices that are very similar to devices that have already sought and been granted regulatory approval •Easier to implement •Adds competition to the sector	Cons of 510(k) equivalence process e.g. lack of requirement for rigorous new clinical evidence to approve iterative medical devices can potentially have a negative impact on safety	[I] •Difficulty in assessing substantial equivalence between predicates and "new" devices •Lack of consensus regarding how much variation is allowed before something is no longer equivalent •Cannot be applied to innovative devices •Based on equivalence to medical devices that were put on the market many years ago and that may no longer the best reference standard •-Time for assessment is legally protected so there is more time pressure and therefore there is less time for FDA and manufacturers to negotiate and communicate which means that if you are not approved then you need to go back to square one and start over again •Less focus on safety in the process i.e. production processes •difficult to know when an iteration to an established medical device (predicate device) represents a significant divergence	
	[LR] •When clinical trials are required for devices, they frequently do not meet the same strict standards for clinical evidence that are required for drugs; they are often nonrandomized, nonblinded, do not have active control groups and lack hard endpoints(30). In fact, such rigorous clinical trials may not always be feasible—randomization and blinding of patients or physicians for implantable devices is nearly impos-sible.		[LR] •Too many high-risk devices are evaluated through less rigorous review mechanisms. Over the last 10 years, only about 2% of medical devices have undergone PMA. A GAO study found that between 2003 and 2007, only 79% of Class III devices actually underwent PMA, with the remainder proceeding through the 510(k) pathway. •The FDA mandates only that PMA applications provide a reasonable assurance of safety and effectiveness. The evidence available suggests that this typically means applications were approved based on a single clinical study. In addition, only a minority of trials are randomized or blinded, use an active control group and hard endpoints, and are consistent in the way they account for patients and report data. •There has been growing concern that the 510(k) route involves a far lower degree of scrutiny than PMA and is being used inappropriately for some devices, and that both processes involve far less regulatory oversight than approval of new drugs. Even PMA scrutiny is not very high—typically only one or two studies are submitted, of which the majority are non-randomised, single arm studies with fewer than 100 participants. • It is worrisome that predicates can include devices that were on the market before regulatory requirements to prove safety and efficacy existed, and even voluntarily recalled devices. Thus, it is not uncommon for a medical device to reach the market in the UnitedStates without ever having been tested in humans. •A recent study investigating 113 recalled devices that had caused serious health problems found that most had been approved through the 510(k) route or had been deemed such low risk that they were exempted from regulatory review. •The lack of requirement for rigorous new clinical evidence to approve the majority of medical devices and the use of predicate data can furthermore have a palling effect on the motivation of industry to conduct expensive trials to demonstrate clinical efficacy or superiority, as well as on the pursuit of truly new innovation •Unlike PMA, direct evidence of safety and effectiveness is usually not required for 510(k) submissions, and only 10% to 15% of submissions contain any clinical data. Furthermore, devices deemed substantially equivalent to devices previously cleared by the FDA do not need to go through the premarket approval process, even if that previous model was never assessed for safety and effectiveness or recalled for a major safety defect. •The FDA, however, still has not classified some of the "grandfathered" devices. As of early 2013, 19 different types of Class III devices are allowed to reach patients through 510(k) clearance. Consequently, potentially high-risk devices continue to reach the market without ever being tested in humans. One such example is metal-on-metal hip implants. •When the substantial equivalence process is carried through multiple generations, it may lead to the marketing of devices that bear little resemblance to any predicate devices, leading to the phenomenon known as "piggybacking." Piggybacking allows "a chain of devices to link a new postamendment device to earlier postamendment devices that ultimately could be traced back to a preamendment device." The products may be dissimilar "in purported intended use or in technological features. Piggybacking issues are apparent in many cases, such as the DePuy hip replacement •Ninety-nine percent of all medical devices fall under the 510(k) classification (about 1 out of 140 are classified PMA). A 2010 study found that "the average total cost for participants to bring a low- to moderate-risk 510(k) product from concept to clearance was approximately $31 million, with $24 million spent on FDA-dependent and/or related activities." In other words, more than 75 percent of the cost of getting a low- to medium-risk product to market is interacting with the FDA" •Both premarket approval and premarket notification (510(k)) can mean long waiting times that can be costly in terms of repaying loans and losing firstmover advantage. One study found that it takes an average of five months for the FDA to review and clear a 510(k) medical device. That's an average, meaning many take longer—and, of course, that's only if the FDA doesn't reject a submission for being incomplete or improperly formatted. Other studies show that decisions about 510(k)s took an average of 143 days as of September 30, 2012	
	[W]		[W] •Assessment of devices in the USA going through the 510(k) Premarket notification (PMN) identified that over 80% of the clinical data was of very low quality (case-series and below). This is contrary to the drivers of Cumberlege •Caution against reviewing some devices in the UK and accepting others on the basis of equivalence as accepting previous standards is how previous problems with medical devices have arisen •There is a potential risk with 510(k) if the predicate is a moving feast so the 'minor' modification ends up a long way from the original fully assessed device	

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*[I]=Stakeholder interview; [LR]=Literature Review; [W]=Stakeholder Workshop

Pros		Cons	Appropriateness
Modernizing measures to improve the safety of medical devices	[I]		
	[LR] •Transparency in medical device recalls. When devices fail or have faults they may be recalled. The FDA publishes a list of recalled devices and the regulatory processes they had passed through. •As the public has discovered from defective PIP implants, TVT, and ASR implants, the safety standards and approval process carried out by the Notified Bodies are insufficient to adequately demonstrate patient safety and efficacy. Although the primary goals of the EU are directed toward improving public health, the importance of protection is effectively sub-contracted to the Member State CA who then appoints the Notified Bodies. This delegation enables a private company exclusive control over the inspection, approval and post market surveillance of medical devices. This causes three serious problems: (1) it creates a propensity for Notified Bodies to compete for business; (2) it gives manufacturers the ability to forum shop and potentially resubmit already rejected applications to other Notified Bodies; and (3) it invites corrupt practices resulting in an adverse impact on the overall quality of the healthcare system. The creation of a centralized governmental agency to eradicate the current Notified Bodies' exclusive authority is a practical solution to addressing these public safety concerns.		
	[W]		
Advanced approach to regulation of machine learning (ML)-based software as a medical device (SaMD) e.g. fast-track route for market approval of iterations of algorithms Accelerated routes to regulate the state-of-the-art devices foster a timely, innovation-friendly environment for novel technology, such as AI/ML-based software.	[I] •accelerated approach to addressing novel tech (e.g. ML-based models), making it more favourable to find a fast track route for market approval of iterations of AI model that bypass standard regulatory approval (e.g. in EU, when software engineers need to validate the AI model, package and ship to the customer, whenever you get a new data (and improve the model), that qualifies as a "feature update" which requires a complete renew conformity check and approval on software. This means when AI model is installed in a clinical institution and local data used to optimise the model to the local population, but this is not currently possible in the EU. FDA released draft guidance/action plan on allowing a continued community input for the development of updates.) •More innovation-friendly •While in the USA, the FDA ensures that medical devices are 'reasonably' safe and effective, in Europe, manufacturers must only demonstrate that the device is safe and performs according to its intended use. This subtle dissimilarity is responsible for significant differences in the speed of introduction of the devices into the market and the amount of tests the devices must pass. It is also responsible for innovation being considered faster in Europe.		
	[LR]		
	[W]		
Misc	[I] •Stamp of approval from major countries (e.g. FDA endorsement of 510k -> free registration to Saudi Arabia)		

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Mutual Recognition Agreement (MRA)

*[I]=Stakeholder interview; [LR]=Literature Review; [W]=Stakeholder Workshop

Pros		Cons		Appropriateness	
Reduces cost for regulators and medical device manufacturers by avoiding duplication of regulatory efforts	[I] •Less cost •Increases speed to market •No need for duplication •Consistency in approaches, methodology, documentation	Trust between countries and regulatory authorities takes time to build	[I] •Trust between countries and organisations is required which takes time to build	The UK will need to time to build trust with other countries and regulatory authorities and cannot guarantee that other countries will recognise the UK regulations	[I] •The UK will need to time to build trust with other countries and organisations
	[LR]		[LR]		[LR]
	[W]		[W]		[W] •We have to have our own system that others can trust and recognise for mutual recognition to work •"We can't mandate mutual recognition - no-one else has to accept UKCA" •In case of unilateral recognition, very few countries/regulatory authorities will follow the UK's system
Encourages greater international harmonisation of compliance standards	[I] •Risk management processes are easily understood by the other bodies •Consistency in approaches, methodology, documentation	Coordination issues e.g. post-market surveillance can be fragmented	[I] • Coordination problems e.g. post-market surveillance can be fragmented	Overcomes issues related to lack of regulatory capacity	[I] •Globally, there is no country that can execute all of its regulatory responsibilities on its own. If the UK wants to maintain its current levels of access to medical devices, it needs either (a) mutual recognition (formal) or (b) acceptance of medical devices that approval from other systems (informal
	[LR]		[LR]		[LR]
	[W]		[W]		[W]
Pros associated with TGA-style targeted assessments	[I] •Option to perform additional targeted assessments* (additional benefit of MRA route raised during informal discussion with RHC team)	Cons associated with TGA-style targeted assessments	[I]	Appropriateness of TGA-style targeted assessment	[I]
	[LR]		[LR]		[LR]
	[W] • Only concerned in regulating certain high risk or novel products; the rest is MRA		[W] • Caution against suggestion of only regulating some devices. There have been many patient safety issues following use of equivalence in the past. There needs to be single standards of clinical evidence.		[W] •The TGA model is a good one: they regulate high risk devices (e.g. AIMD) and otherwise have MRAs for lower risk devices. •Caution against suggestion of only regulating some devices. •There needs to be single standards of clinical evidence.

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APPENDIX 3: References

3.1. Literature Review

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