ASUM
Promoting ultrasound excellence

Regulation of software, including Software as a Medical Device

ASUM TGA Submission

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ASUM Response

We welcome the opportunity for this consultation process to provide our submission with regards to regulatory reform for medical devices. We intend to share some of our knowledge and insights regarding the latest legal reforms in comparative contexts and technological developments relevant to medical imaging processes, specifically ultrasound as a diagnostic tool. These latest developments will highlight the challenges the proposed provisions within this paper.

1. Background

The Australasian Society for Ultrasound in Medicine (ASUM) is the premier multidisciplinary society advancing the clinical practice of diagnostic medical ultrasound for the highest standards of patient care.

Diagnostic ultrasound is one of the most rapidly expanding branches of medicine. Technological developments permit higher resolution images to be obtained with smaller and smaller transducers and equipment. Software upgrades and the introduction of artificial intelligence to assist in a diagnosis is evolving as a fast pace. As a result, ultrasound is now used to examine virtually every part of the body.

The primary role of ASUM is to assist in the dissemination of scientific information, to provide education and to set standards of practice in this continually developing specialty. ASUM do not manufacture or sell ultrasound equipment, but instead work to ensure standards are set and met for the highest standards of patient care.

2. Requirements for SaMD to be included in the ARTG

The proposed changes as documented in this paper for SaMD product regulation are understood and the essential principles have been captured to clarify this, along with international standards and are supported. The classification of ultrasound equipment is already based on diagnostic equipment, along with the need for operator training and dependence required to safely use this for diagnostic purposes. There are many benefits of software-based solutions, particularly for diagnostic ultrasound in regional and remote areas of Australia. Our concern, however, lies in the provision of software that may be easily added to a phone or computer such that this will be relied upon for medical decisions without the skill set to provide this. While these regulations consider the implications of software in the medical arena, we would continue to ensure the purchase of such equipment remains in the healthcare field, and not for the purchase by a consumer for personal use.

Cybersecurity, and security in general is typically an area where systems are in place, yet often they are not well utilised. For many years ultrasound systems and reporting workstations have had the capability for users to 'log in' to ensure that the cases stored, and therefore patient data, cannot be easily accessed. This has been an area not well adhered to in general, and while not in the space of TGA specifically, further work would also be required to ensure privacy is maintained by utilising the functions already on offer.

Further work is required with regards to Artificial Intelligence, particularly the ethics and principles in which these will influence diagnostic processes, particularly considering software development.

3. Considerations relating to ultrasound

i. Technological Developments in Ultrasound Devices- *Black box technique*

Artificial Intelligence (AI) is increasingly involved in the design of medical software. AI refers to the ability of a machine to perform a task that is normally done by humans, according to the White Paper issued by Duke University Margolis Center (Daniel, Silcom, Sharma, & Wright, 2019). AI-enabled software can be divided into two categories depending on the way its programmed, namely Rules-based AI, and Data-based AI (also referred to as machine learning AI). According to the nature of different problems, different types of machine learning algorithms might be adopted. Not all algorithms might be understandable by humans or explainable to humans since some algorithms may be too complex, especially those for Data-based AI software. This creates difficulties for an overseeing process. It can be regarded as a black box algorithm.

In this submission, the term black box technique, machine learning software and data-based AI overlap and can be used interchangeably. Due to the nature of AI and its potential to provide high accuracy in performing certain tasks, we suggest that attention is needed to consider the way such algorithm to be managed.

Black box algorithms are heavily involved in the medical imaging field. A survey on deep learning in medical image analysis undertaken by a group of researchers from Radbound University in the Netherlands revealed that the relevant studies grew rapidly in 2015 and 2016 (Geert Litjens, 2017). The kind of algorithms involved include different types of neural networks and deep CNN architectures. The applied areas include brain, eye, chest, digital pathology and microscopy, breast, cardiac, abdomen, musculoskeletal and others. While we are acknowledging the development of AI technologies, we believe that AI will not replace humans, but it will instead be utilised to enhance workflow and increase efficiency (Forrest, 2018).

Regarding Ultrasound practice, early stage laboratory study shows deep thinking technology has the potential for detecting symptoms on targeted organs, for instance:

- A convolutional neural network (OxNNet) was trained using this ground-truth data set to segment the placenta, which was then used to look at predictions of small for gestational age babies (Padraig Looney, 2018);
- A generic deep learning analysis within ultrasound system may help to diagnose types of cancers better than a human reader (Anto S Becker, 2018);
- Different deep learning models may improve diagnosis for common congenital heart disease lesions, including prenatal diagnosis of Tetralogy of Fallot (TOF) and hypoplastic left heart syndrome (HLHS) of foetus (Rima Arnaout, 2018);
- Deep residual networks are used to engage in automatic classification model for anatomy recognition in placental ultrasound images (Shengfeng Liu, 2019).

ii. A New Legal Framework – *From A Comparative Perspective*

In America, the 21st Century Cures Act became law in 2016 and according to U.S. Food and Drug Administration's reading of it, certain types of clinical decision support (CDS) software is no longer considered as a medical device. (Daniel, Silcom, Sharma, & Wright, 2019). The exception is when the FDA sees a necessity to bring certain CDS software back to its jurisdiction. The overall purpose of the Act is to help accelerate medical product development and bring new innovations to patients faster and more efficiently. According to the FDA, there is some confusion regarding the difference between CDS and conventional software as a Medical Device (SaMD), and some effort has been made to reduce relevant ambiguities (U.S. Food and Drug Administration, 2017).

One would assume this effort is an attempt to overcome the drawbacks of the system, which is lacking efficiency comparing with other competing regulative models, such as directives launched by the European Union (Norman, 2016). Close examination shows that this change introduced radical reforms regarding the regulation of CDS software and was more focused on the stimulation of innovative technology and greater competition, than the peer models. Meanwhile, even the European Union is preparing for radical changes led by the development of artificial intelligence, getting ready to reduce legal obstacles to promote such development, and new medical device regulations will apply in 2020 (Lincoln Tsang, 2017).

iii. Challenges regarding Data Issue and Conformity Assessments

The nature of a machine learning device requires feeding them with large amounts of data to maintain its development and accuracy, which means more real-life data will be needed. The conventional legal framework for privacy considerations may not be the best pathway to the development of such software. This is a common problem faced by current regulations in different countries including America. Regarding the

current practice within the European Union, it is undertaking a rather restrictive approach under its General Data Protection Regulation (GDPR) in the use of personal data, and empowering individuals with further control of their own data including a right to demand explanations regarding how their data are used. Acknowledging the frustration for the health system in failing to garner the benefits of new digital technologies, the European Union has set up an agenda to change the current legal systems to maximize the potential of big analytics to use health data (Lincoln Tsang, 2017).

The White Paper recommended reforms of the current Privacy Rule and to allow individual data to be used in the development and testing of CDS software (Daniel, Silcom, Sharma, & Wright, 2019). Data issues and privacy laws might be the next issue the Australian government needs to address, following its reconsideration of the treatment of black box techniques. If supermarkets or business operators across the world are able to manipulate the way they use data, should not medical data be available for appropriate research/development bodies? If so, while this may improve the patient outcome, what controls can be put in place to protect patient data?

It might also be time to reconsider liaison to enable different research institutes to be in touch with developers to work collaboratively on the testing of relevant software. The following discussion may also show that new technology expands greatly in the medical imaging field, and the government should re-consider how to classify certain SaMD devices and the way to oversee such devices, and if reclassification of certain devices is the only way forward.

4. Would New Models of Devices Bring Potential Challenges to the Proposed Provisions?

We remain positive regarding the new changes and welcome the relevant provisions. Nevertheless, we found some confusion regarding the current provisions, with respect to ultrasound devices, considering that they could be further equipped with deep learning capacities and so able to provide direct diagnosis or screening service. Then the question will be, should these devices (SaMD) still be categorized as Class IIa, that is, as a conventional ultrasound device, or rather be classified under Class III as implicated by the proposed changes? Should the Classification of SaMD be the central focus of TGA or rather the efficient overseeing activities and support for the development of the technology?

i. Smartphone Ultrasound Devices

A new wave of smaller portable ultrasound imaging systems is entering the market. Such devices as *Butterfly IQ* that connect to a smartphone are fast gaining interest. Its company received its FDA 510(k) clearance in 2017 (Truong, 2018). The most innovative part of the technology is that it is basically a “ultrasound-on-chip”, which is capable of performing diagnostic imaging of all types including cardiac, abdominal, urological, foetal, gynaecological, and musculoskeletal systems. It is cost competitive

compared with the traditional ultrasound machines that cost 10-100 times more. This is one of a number of developments happening in the ultrasound space. While there is a clear benefit to portable systems for the use in fast and accurate diagnosis in the right hands, several challenges are of concern.

1. Who can access the software to utilise this technology? This is particularly important for a consumer/patient for reasons of safety?
2. How will new software be reviewed and managed to ensure patient care if this is a simple app upgrade?
3. What if a future software update is able to offer artificial intelligence such that a diagnosis can be made as the latest research suggests?
4. What if such a device is used for self-testing pregnancy ultrasound examinations at home? Or for scanning and providing direct diagnoses about the foetus, including any severe defects, as part of routine examinations? Or detecting ectopic pregnancy during an emergency?

Potentially less experienced medical/healthcare personnel may be better equipped to make a direct diagnosis during emergency situations, particularly in remote rural areas. Should this device be categorised as Class III as the proposed provisions suggest, as the way it is used features some Class III descriptions, including being used for diagnostic purpose during an emergency? Would the ethics and accuracy of its detection rate be managed to ensure patient safety? How easily should data be available for the purpose of post market testing to provide evidence of patient care in a variable population?

The proposed changes imply one criterion for a SaMD to be categorised as Class IIa is its capacity for providing direct diagnosis. However, a close look indicates that if a device is applied or used as a direct diagnostic tool (for practical reasons), it is considered as under Class III category. There is a lack of consistency. Alternatively, it indicates that TGA considers direct diagnosis of disease by SaMD may only occur during the listed situations, including self-testing, emergency situations or rural or remote medicine. This might not be an accurate understanding of a direct diagnosis by machines, especially not in the field of medical imaging. If SaMD can diagnose/treat patients in situations that may have otherwise required referral to specialists, as recommended by the White Paper or the latest studies, how should we characterise such practice?

ii. Workstation and System Software.

Software on both ultrasound equipment and workstations continues to develop to gain efficiencies and accurate diagnosis. Typically, a workstation is in the hands of a medical professional and therefore a supplement to the expertise already assisting in the care and management of the patient. One example of this is the Samsung S-Detect™ for Breast is AI based software which analyses breast lesions using ultrasound images and has been implemented into Samsung's ultrasound systems. It assists in standardizing reports and classification of suspicious breast lesions by incorporating BIRADS® ATLAS* (Breast Imaging-Reporting and Data System, Atlas)

(Samsung Brings Together Medical Imaging and AI for Radiologists at RSNA 2018, 2018). Its application to FDA 510(k) for clearance is still pending.

Samsung highlights the way S-Detect provides automated results with a result of lesions' analysis, a further reading reveals that it carefully withdrew the description as a computer-aided tool. There is no doubt that companies always strategically change the wording of device descriptions in marketing materials and their actual manuals, which may raise legal concerns (Vreugdenburg, 2014).

The proposed provisions indicate that, regarding screening devices, the potential degree of *harm* brought about by misdiagnosis or delay of diagnosis determines its classification. Within the domain of breast cancer screening, we know some devices can ignore cancerous situations as caused by its false negative readings. Because of this, it is likely that a S-Detect could be classified as Class III. On the other hand, according to the proposed provisions Samsung and the medical community may well argue that the intended use is to aid a clinician in making a diagnosis, and so should be classified as Class IIa.

Does this mean that TGA should give further guidance on the specific kind of screening device it is considering? Is the particular kind of misdiagnoses or harm to be considered to determine the classification? Should different diseases or conditions be listed? How do we ensure those utilising this equipment for medical practice are sufficiently trained in the use and limitations? Alternatively, TGA could focus on the accuracy (and therefore potential risk) of the machine learning capacity to consider its classification?

Comparative FDA regulations: Most medical imaging devices are classified as Class II. Concerning breast imaging systems, a latest change brought by FDA in June 2018 is, that computer-aided detection (CAD) devices are classified according to the way risks could arise due to the way these devices operate. It is suggested that the devices used to direct the clinician's attention to portions of an image will be classified as Class II, but those intended to assess disease risk, specify disease type, severity, or stage and/or recommend an intervention will be classified as Class III, including the ones with deep learning capacities, and this brought some previously classified III devices down to Class II (Lovells, 2018). Accordingly, it is reported that the FDA is taking a "risk-based" approach to the regulation of Health IT and addressing the nature of CAD products (Javitt, 2018). Risk is a comparable concept to harm, but with more focus on the nature of IT technology than an actual harm analysis.

One factor relating to the harm issue is concerning the false negative rate. This is an essential issue within the medical imaging system, when the proposed reclassification was announced. The FDA was expecting the use of special controls to address such an issue, rather than relying on the general control under the conventional Class III pathway. Regarding false negative readings, it was expected that design verification and validation should include detailed descriptions of image analysis algorithms, detailed descriptions of study protocols and datasets, labelling for the device must include detailed descriptions of patient population, the intended reading protocol, the intended user and user training, warnings, limitations and so on (Radiology Devices Reclassification of Medical Image Analyzers, 2018).

5. Conclusion

ASUM agrees with the current concerns of the TGA and support the proposed changes to ensure patient safety while remaining on the cutting edge of healthcare provision, which is a complex space.

There are some open questions triggered by the current consultation paper for the TGA to consider. Is it time to consider provisions to stimulate innovative technology as part of this discussion, as well as new assessment methods to manage new technologies, including machine learning SaMDs, if Australia is ambitious and not willing to fall behind with technological development?

This submission pointed out some forthcoming differences between the FDA classification of some medical imaging devices and the changes proposed by TGA. The question will be left to TGA regarding how to address the difference if a device is moved from Class III down to Class II by the FDA and how TGA may adopt such standards via its current proposed provisions. We also recommend additional consideration regarding the assessment of such devices, with a focus on accuracy, and expect further guidance on some definitional issues, including *what is a direct diagnosis from an AI-enabled medical device*.

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