# Feasibility of a Reimbursement Pathway for Mobile Medical Applications (MMA) in Australia

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By

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# Dedication

This thesis is dedicated to the people who have unconditionally loved and supported me throughout my life.

Their dedication and tenacity enabled me to dream, and achieve the unimageable.

They got a little neuro-diverse girl from Dar es Salaam, Tanzania with big dreams, to the Olympics and beyond.

## My parents

Alex and Helen Moshi

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## Thesis declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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I acknowledge the support I have received for my research through the provision of an *Australian Government Research Training Program Scholarship*.

9th of December 2019

**Magdalena Ruth Moshi** **Date**

## Publications arising from this thesis

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- Moshi MR, Tooher R, Merlin T. Suitability of current evaluation frameworks for use in the health technology assessment of mobile medical applications: A systematic review. *International Journal of Technology Assessment in Health Care*. 2018;34(5):464-75.

*Under-review*

- Moshi MR, Tooher R, Merlin T. Development of a health technology assessment module for evaluating mobile medical applications. *International Journal of Technology Assessment in Health Care*.

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- October 2018, **Poster**, Moshi* M, Tooher R, Merlin T. Assessment of mHealth apps in Australia: is current regulation adequate?, Suitable frameworks for mHealth app evaluation in Australian healthcare reimbursement*, The Annual Scientific Meeting of the Australasian Epidemiological Association*, Freemantle, Western Australia, Australia.

- May 2016, **Presentation**, Merlin* T. and Moshi M. Getting a grip on new technologies: AHTA's journey into m-health and mobile medical applications (MMAs)*, Health Technology Assessment International (HTAi) Annual Meeting*, Tokyo, Japan.

## National conferences

- September 2016, **Presentation**, Moshi* M, Tooher R, Merlin T. Determining the feasibility of reimbursing mobile health apps in Australia*, PHAA 44th Annual Conference & 20th Chronic Diseases Network Conference*, Alice Springs, Northern Territory, Australia.

## State conferences

- September 2019, **Poster**, Moshi* MR, Tooher R, Merlin T. mHealth app evaluation framework for decision-making purposes, *13th Annual Florey Postgraduate Research Conference*, Adelaide, South Australia.
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- December 2018, **Presentation,** Moshi* M, Parsons, J, Tooher, R, & Merlin, T. Assessment of mHealth apps in Australia: is current regulation policy adequate*? South Australian Population Health Conference*. Adelaide, South Australia, Australia.
    - Award: Most popular presentation

- September 2018, **Poster**, Moshi* M, Parsons J, Tooher R, Merlin T. Assessment of mHealth apps in Australia: is current regulation adequate? *12th Annual Florey Postgraduate Research Conference*, Adelaide, South Australia, Australia.

- October 2017, **Presentation**, Moshi* M, Tooher R, Merlin T. A systematic review on assessing the appropriateness of current mHealth app evaluation frameworks for the appraisal of apps in Australian healthcare reimbursement decision-making, *State Population Health Conference*, Adelaide, South Australia, Australia.

- September 2017, **Poster**, Moshi* M, Tooher R, Merlin T. Appraising the suitability of mHealth app evaluation frameworks to inform public funding decisions in Australia: a systematic review, *11th Florey Annual Postgraduate Research Conference*, Adelaide, South Australia, Australia.

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# List of abbreviations

| | |
|---|---|
| AHRQ | Agency for Healthcare Research and Quality |
| AIMD | Active implantable medical device |
| APHRA | Australian Practitioner Regulation Agency |
| ARTG | Australian Register of Therapeutic Goods |
| CADTH | Canadian Agency for Drugs and Technologies in Health |
| CER | Clinical evaluation reports |
| CNC | Clinical nurse consultant |
| COPD | Chronic obstructive pulmonary disease |
| CPD | Continual professional development |
| EEA | European Economic Area |
| eHealth | Electronic health |
| eMHPac | e-Mental health in practice |
| EU | European Union |
| EUnetHTA | European Network for Health Technology Assessment |
| FDA | Food and Drug Administration |
| FOI | Freedom of Information Act 1982 |
| GP | General practitioner |
| HIV | Human immunodeficiency virus |
| HPFBI | Health Products and Food Branch Inspectorate |
| HREC | Human research ethics committee |
| HSA | Health Sciences Authority |
| HTA | Health technology assessment |
| ICM: | Insertable cardiac monitor |
| IMDRF | International Medical Device Regulation Forum |
| IVD | *in vitro* diagnostic medical device |
| MBS | Medicare Benefits Schedule |
| MDALL | Medical device active license listing |
| MDB | Medical Device Bureau |
| mHealth | Mobile health |
| MMA | Mobile medical applications |
| MSAC | Medical Services Advisory Committee |
| NCD | Non-communicable diseases |
| OS | Operating system |

| | |
|---|---|
| PBS | Pharmaceutical Benefits Scheme |
| PICO | Population, Intervention, Comparator, Outcomes |
| RCT | Randomised controlled trial |
| SaMD | Software as a medical device |
| SES | Socio-economic status |
| STI | Sexually transmitted infection |
| TGA | Therapeutic Goods Administration |
| USA | United States of America |
| WHO | World Health Organization |

# Glossary

**Accuracy:** Nearness of the quantity's measured value to its true quantity.

**Adaptive software changes:** Preserves the MMA software within the dynamic technical environment.

**Algorithm:** A set of rules, model, or logic upon which the MMA is based on (e.g. equations, inferences engine, model-based logic, which can be affected by: reference data, criteria, knowledge base, rules).

**Analytical sensitivity:** The degree in which the input data can affect the algorithm's output.

**Analytical validity:** The ability of the MMA to accurately and reliably produce the intended output from the input data.

**Can't happen:** The programmer should check the code for situations which are expected to be 'impossible' and identify how these situations should be resolved and implement the expected process.

**Clinical equivalency:** Clinical association of MMA compared to a reference standard (e.g. predicate/ comparator device).

**Clinical utility**: The risk and benefits which result from MMA use.

**Clinical validity:** The MMA's ability to identify a particular condition.

**Corrective software changes:** Corrects existing errors or problems within the current MMA software.

**Cut-off threshold:** A scale or indices for a MMA, it should be meaningful and determined prior to validation.

**Dangerous implements:** The programmer should prevent and/or hide any code that the programme is dependent on to function properly as to code would result in the programme failing to operate as expected.

**Diagnostic MMA:** A MMA's output that is intended to diagnose and/or drive clinical management by differentiating patients or their physiological conditions (e.g. diagnostic apps).

**False negative (FN):** The ability of the MMA to wrongly identify a patient's condition as negative.

**False positive (FP):** The ability of the MMA to wrongly identify a patient's condition as positive

**Fuzzing or fuzz testing**: An automated method which can effectively identify software 'bugs' or errors in an MMA.

**Input:** Digitised content fed to the MMA (e.g. laboratory results, image, medical device data, physiological status, symptoms).

**Input:** Digitised health content which can be fed to the MMA (e.g. image, laboratory results, physiological status, medical device data, symptoms).

**Investigative MMA:** A MMA's output that is intended to diagnose and/or drive clinical management by differentiating patients or their physiological conditions (e.g. screening apps, diagnostic apps, risk predicting apps).

**Likelihood ratio:** The likelihood that a test result given by the MMA would be expected in a person with the condition compared to a person without it.

**Limit of detection:** Ability to distinguish between random patterns that distract from information and information bearing patterns of a clinical condition.

**Negative predictive value (NPV):** The likelihood that the patient does not have the condition given the MMA result is negative.

**Non-diagnostic:** A MMA that has a generic functionality which can be used across several healthcare conditions or situations (e.g. calculator app, memory test app).

**Novel association:** The MMA has a new input, algorithm, and/or output with a new target population, or a new intended target population, which are not well-known or established.

**Output:** A product of the MMA that has the ability to affect the users' health (e.g. inform, treat, diagnose).

**Paranoia:** The programmer should code defensively and check their own code to ensure that any problems within it can be detected and resolved quickly. The programmer should also not trust any programming which they did not generate themselves.

**Perfective software changes:** Recoding of MMA software to improve performance.

**Positive predictive value (PPV):** The likelihood that a patient has the medical condition if the MMA result is positive.

**Precision:** In unchanged conditions, the degree to which repeated measurements generate equal results (e.g. repeatability, reproducibility).

**Preventive software changes:** Corrects latent faults in the MMA software before they can cause operational problems.

**Receiver operating characteristic (ROC) curve**: A graphical plot that illustrates the trade-off between sensitivity and specificity.

**Reference standard:** A standard that is used and widely accepted as the benchmark for a performance and/or absence/ presence of a medical condition.

**Relevant studies:** One or multiple studies which evaluate the association between the input and the output.

**Robust:** The ability of an MMA to deal with errors occurring during software performance.

**Sensitivity:** The ability of an MMA to rightly identify the patient's condition as positive.

**Specificity:** The ability of an MMA to rightly identify the patient's condition as negative.

**Stupidity:** The programmer should assume that the end user is a novice and will have minimal to no understanding of computer programming. The program should communicate clear, concise messages to the user and be able to withstand being run in ways it was not designed to operate.

**Therapeutic MMA:** An MMA's output that is intended to treat a healthcare condition or situation.

**Valid clinical association:** A valid association between the MMA's output and the targeted medical condition (e.g. measurable, clinical outcomes).

**Validate (software validation):** The MMA accomplishes its intended purpose.

**Verify (software verification):** The MMA attains its intended purpose without interference in the form of software errors.

**Well-known association:** MMA output has well established association with health condition or physiological status in reference materials (e.g. peer-reviewed journals, clinical studies, clinical guidelines, etc.).

Source of definitions are listed below:


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# Abstract

**Introduction**

Mobile health (mHealth) applications (apps) are currently changing Australian healthcare. mHealth apps which have a therapeutic and diagnostic intended purpose are called mobile medical applications (MMA), and are being integrated into healthcare by patients and practitioners in Australia. MMAs have the potential to decrease the health burden of some chronic conditions as well as improve the delivery of healthcare. Any harms produced by the technology are mainly through the information provided and how it is used in clinical decision-making.

The nature of apps presents unique challenges (such as their rapid lifecycle) to regulatory and reimbursement processes. There are currently no policies or frameworks available that can be used to conduct a health technology assessment (HTA) on MMAs. Therefore, the aim of this research was to determine what policy changes and assessment criteria are needed to facilitate the development of a system that evaluates MMAs for regulatory and reimbursement purposes in Australia.

**Methodology**

In order to achieve this overall aim, the research was divided into four parts. Firstly, I reviewed the Australian *Therapeutic Goods Administration (TGA)* regulation of MMAs by evaluating it against international counterparts and the *International Medical Devices Regulator's Forum's (IMDRF)* guidance document for clinically evaluating medical software. This was achieved through the use of a policy analysis and case studies. The policy analysis evaluated MMA regulations internationally to determine whether the regulatory bodies of the IMDRF members addressed the IMDRF guidance on clinically evaluating software as a medical device (SaMD). The case studies reviewed how different MMAs in Australia and the United States of America (USA) were regulated to determine to what extent the *SaMD: Clinical Evaluation* (2017) guidance was applied.

The second section evaluated existing frameworks for assessing MMAs and determined whether any were suitable for use in HTA and reimbursement decision-making. This was achieved through a methodological systematic review. The systematic searches were conducted in seven bibliographic databases in order to identify literature on MMA evaluation frameworks published between 2008 and 2016. Frameworks were only eligible for inclusion in the review if they evaluated one of the HTA domains of safety, cost-effectiveness and/or effectiveness of an MMA. Once a framework had been included into the review it was evaluated to determine what other elements of an HTA the framework addressed.

The third section detailed the creation and testing of an MMA HTA evaluation module which was used to modify the current HTA guidelines in Australia. The use of the module ensures that the technology specific characteristics of apps would be properly appraised during an assessment. The module's transferability to comparable HTA jurisdictions was also assessed. This was achieved in two stages. The first stage were in-depth interviews with stakeholders (healthcare practitioners, application developers, and policymakers) to determine possible impediments and pathways to MMA reimbursement in Australia. The findings of the interviews were integrated with those from the first and second sections of this research on MMA reimbursement and regulation to create an MMA evaluation module.

The fourth and final section determined the feasibility of MMA reimbursement in Australia through the integration and synthesis of all the evidence generated from the preceding three sections.

**Results**

The research found that there were policy gaps in the regulatory and reimbursement criteria used to evaluate MMAs. Regarding current regulatory policy, the TGA does not adequately evaluate MMAs according to the IMDRF criteria. Policy changes to current regulation processes should include an assessment of the harm from misinformation as well as potential risks associated with information and connectivity compatibilities, such as cybersecurity threats. Similarly, there were a number of policy changes that could be made to support the reimbursement of MMAs in Australia.

The systematic literature review of MMA evaluation frameworks found that there was a greater need to evaluate the harms posed by MMAs (i.e. misinformation) as well as a fuller consideration of the likely comparator for the technology. Other considerations included, but were not limited to, equity of access to MMAs (i.e. by way of age, literacy, user disability, etc.), as well as the importance of secure and proper management of confidential data. Other technology specific concerns included: the possible effect of software updates on the effectiveness and safety of MMAs and possible variation in app performance on different operating systems (OS), mobile platforms, and generations of the same platform.

Interviews conducted with stakeholders sought to explore possible pathways and impediments to MMA reimbursement in Australia and, highlighted a few policy challenges. These included: clarification around where the responsibly lies regarding data ownership, cybersecurity, and professional liability in the use of app data; the digital health literacy of healthcare practitioners, patients, and any other MMA users (i.e. carers); and finally, developing evaluative measures which address the technological evolution of MMAs, such as the technology's rapid lifecycle and software updates. Contrastingly, the interviews indicated that stakeholders trust the evidence-based approach used by the Australian *Medical Services Advisory*

*Committee (MSAC)* to conduct HTAs and make public funding decisions and felt it would be an appropriate evaluation mechanism for MMAs.

Given these policy concerns, proper evaluation of MMA's is needed before they can be reimbursed in Australia. To ensure that MMAs are properly evaluated, a module was developed which could modify the current HTA framework employed by MSAC. The module addressed both regulatory and reimbursement policy concerns. This is to ensure that the regulatory issues are addressed, as the current TGA process does not properly evaluate them.

The utility of the MMA HTA evaluation module was assessed for adaptation to other comparable HTA jurisdictional bodies, such as the European Economic Area (EEA), Canada, and the United States of America (USA). Minimal modifications would need to be made to the module for it to be used by other HTA agencies in these jurisdictions. These adaptations would include the removal of any of the unique MMA items (e.g. software, updates, cybersecurity) that were already addressed by the jurisdiction's regulatory authority. Adaptations to the cost-effectiveness domain would be dependent on the individual economic evaluations conducted by the respective jurisdictional HTA agencies, and their individual healthcare contexts.

The development of the MMA HTA evaluation module, and the research that informed it, shows that MMA reimbursement in Australia is feasible. Thus, it is feasible to tailor the regulatory and reimbursement processes in Australia to evaluate MMAs properly.

**Conclusion**

In conclusion, it is possible to tailor regulation and reimbursement processes in Australia to address the evaluation of MMAs. These modifications to current processes can be made through a variety of key policy and process changes. One process change would be the adoption of the MMA evaluation module as it is capable of adapting the existing MSAC evaluation framework to assess this technology. Other policy changes would include: facilitating the digital health literacy of MMA users (i.e. healthcare practitioners, patients, carers, etc.); providing clarification around who and where the responsibility lies regarding use of MMAs (i.e. data ownership, professional liability, and cybersecurity), and, finally, stipulating evaluative procedures which address the challenges posed by the ongoing technological evolution of apps (i.e. rapid lifecycle, software updates, etc.).

# Chapter 1: Introduction

## 1.1 Introduction to thesis

Electronic health (eHealth) has been revolutionising the Australian health system. A large contributor to this transformation is mobile medical applications (MMA).(2-5) MMAs are applications (apps) that have an intended purpose which is therapeutic or diagnostic and are available on mobile devices such as smartphones, tablets, and smartwatches.(6, 7) Currently, MMAs are being both used and recommended by healthcare practitioners (i.e. general practitioners, specialists, allied health workers, etc.) in clinical consultations.(2, 4-6, 8, 9)

A possible impediment to the complete incorporation of MMAs into the Australian healthcare system is the fact that various apps can have costs attached to them.(2, 10-12) These costs can be direct or indirect. An outright cost includes the price the patient has to bear to purchase and download the MMA. Whereas, the indirect cost encompasses the in-app purchases (i.e. subscriptions) the patient has to cover in order to receive the medical services provided by the MMA for set period of time (e.g. 3 months). The direct and indirect costs associated with the MMA, may prevent some users from being able to access the medical services provided by the software. For example, a mental health MMA called *MoodKit(13)* costs AU$7.99 outright and has no in-app purchases. While, *Moodpath: Depression & Anxiety(14)* is free to download and has in-app purchases which range from AU$6.99 to AU$70.99. Some MMA have costs which may seem negligible, however, others may require in-apps purchases (i.e. subscriptions), and/or accessories such as attachments (i.e. glucometer, electrocardiogram), implantable devices (i.e. implantable cardiac monitor), and wearables (i.e. external heart rate monitor).(15-18)

In Australia, the government provides reimbursement for medical services provided or prescribed by a healthcare practitioner, through the universal health insurance system (*Medicare*). Reimbursement is available for patients and eligible healthcare practitioners. Patients are able to claim subsidies on receiving a medical service,(19-22) while healthcare practitioners can claim reimbursement for providing medical services as part of a clinical consultation.(14, 20, 21, 23-25) For medical services that involve a medical device, to be eligible for reimbursement through Medicare they have to undergo two evaluations. The first evaluation is conducted by the *Therapeutic Goods Administration (TGA)* on the medical device for regulatory purposes. The review guarantees that the medical device can be sold in Australia. The second evaluation is a health technology assessment (HTA) which is conducted by an independent organisation to inform decision making by the *Medical Services Advisory Committee (MSAC)*. A medical service is reimbursable only after it is approved by the both the TGA and MSAC and the Minister of Health agrees to fund it.(19, 22, 23, 26-28)

Currently, there is no pathway for patients or health practitioners to claim reimbursement for any MMA-based medical services, even though they are already being used and recommended in domestic healthcare.(2, 28, 29) Moreover, there are no evaluation criteria in Australia (or internationally), which can be used to review MMAs for reimbursement purposes. This is further complicated by the fact that MMAs present different harms to traditional medical devices.(22, 30-36) The dynamic nature of MMAs (i.e. software updates, rapid lifecycle and development) may require evaluative frameworks that are specific to the technology.(14, 22, 31, 32, 34-36)

Thus, this thesis explores the feasibility of tailoring regulation and reimbursement processes in Australia to the evaluation of MMAs.

## 1.2 Thesis outline

This thesis is "by publication" and is comprised of nine chapters. *Chapter 1* provides a brief introduction and background to this thesis. *Chapter 2* features a detailed background to MMA reimbursement and regulation in Australia. *Chapter 3* provides a rationale for the research and outlines the thesis aim, research questions and objectives. *Chapter 4* details the complete thesis methodology used to address the overall thesis aim and each research question. *Chapters 5, 6, and 7* discuss the findings of the research studies conducted to answer the research questions. *Chapters 5 and 6* include the articles published on MMA regulation in Australia and assessing MMAs for HTA purposes in Australia, respectively. *Chapter 7* has two sub-sections, a manuscript submitted for publication on developing an MMA evaluation module which can be used to adapt existing frameworks for HTA and reimbursement decision-making in Australia, and a small auxiliary study on the adaptability of the proposed evaluation module to comparable jurisdictions. *Chapter 8* synthesises the results from the three preceding chapters (*Chapter 5, 6, and 7*) and explores the feasibility of MMA reimbursement in Australia in the current domestic healthcare context. Finally, *Chapter 9* concludes the thesis by addressing the overall aim, answers the research questions, and provides recommendations and areas for further research.

# Chapter 2: Background

## 2.1 Introduction

This chapter provides a detailed background on MMA reimbursement and regulation in Australia.

## 2.2 About mobile health (mHealth)

Mobile health (mHealth) is a dynamic field which is developing rapidly and has great potential in Australia to change the health industry.(12, 37) A large contributor to this is the rapid penetration of smartphones and tablets throughout the country over the last decade. Currently smartphone penetration is around 89% (2018), and it is predicted that it will continue to increase until it plateaus at 95%.(12, 37-40) This combined with the increase in health and medical applications (apps), has resulted in a change within the Australian healthcare environment.

There is debate about the definitions and categorisation of mHealth, electronic health (eHealth) and telemedicine/ telehealth.(41, 42) Over the past two decades, as the fields have developed, the names for these forms of healthcare provision have been used interchangeably and definitions can slightly change depending on country.(41) Thus the definitions and categorisations of eHealth, mHealth and telemedicine used in this thesis are the ones created and recognised by the *World Health Organisation (WHO)*.(41-44) See *Appendix A* for detailed explanation of mHealth (A.1.1), eHealth and telemedicine (A.1.2).

Thus, it is important to explore the parameters of what defines mHealth apps, the different platform and operation systems the technology is available on, as well as the benefits and harms they may present to healthcare provision.

### 2.2.1 Defining mobile platforms

A mobile platform is a handheld, commercially available computing platform that may or may not have wireless connectivity. The current embodiment of a mobile platform includes smartphones, tablets, and smartwatches.(4, 42, 44, 45)

### 2.2.2 Defining operating systems

An operating system (OS) is a software that is loaded on the platform by a boot program. The software directly controls all platform processing, including other software/applications, assigning platform memory, as well as controlling output and input functions.(42-47) A few popular OSs for mobile platforms include, Android (Google), iOS (Apple), Symbian (Nokia), and Windows Phone (Microsoft).(32, 45)

### 2.2.3 Defining mobile applications

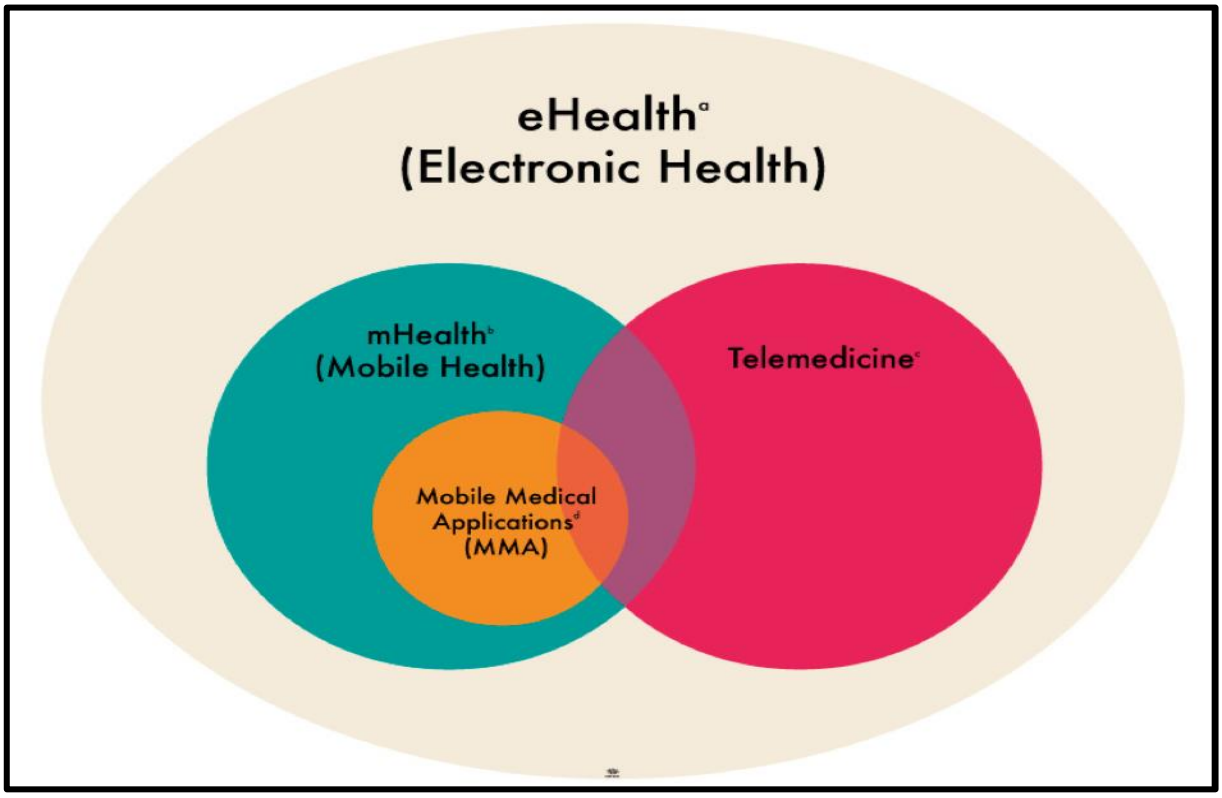
A mobile app is a type of software extension developed specifically for a mobile platform. The applications are often designed to work within the constraints of a mobile platform as well as take advantage of the

platform's specialised capabilities.(48-50) Mobile apps can be categorised into two overlapping groups of a 'native' app and/or 'web-based' apps. Native apps are software created to be executed on a mobile platform, whereas web-based software applications are tailored to mobile web browsers and are run on a server. As technology is developing there are single apps which can be categorised as both native and web-based.(48-50) This thesis focuses on native apps.

### 2.2.4 Defining mobile medical applications (MMA)

Mobile medical applications (MMA) are a subset of mHealth. The *Therapeutic Goods Administration (TGA)* defines a mobile application as meeting the regulatory authority's criterion for a medical device (explained in *Section 2.3* below).(51) Examples of MMAs in Australia are apps that are used for the diagnosis and treatment of medical conditions.(22) Thus, within this research, apps used for information, wellness (fitness, meditation, nutrition) were not considered to be MMAs as they did not have a therapeutic purpose. It is not clear how the TGA define therapeutic medical apps that have accessories. In this thesis apps that meet the TGAs definition of a medical device and have accompanying accessories were also considered MMAs. Figure 2.1 shows how MMAs fit in the broader electronic health context.

Figure 2.1: MMAs in a broader electronic health (eHealth) context




Source: [a] World Health Organisation (44), [b] World Health Organisation (42), [c] World Health Organisation (43), [d] Therapeutic Goods Administration (6)

### 2.2.5 Potential of MMAs to transform Australian healthcare

MMAs not only have the *potential* to transform Australian healthcare, they are already doing it.(2, 52-55) The potential for eHealth technology, such as MMAs, to alter the landscape of Australian healthcare has been known since the 1990s.(3)

Mobile platforms in the form of smartphones are the primary medium embodying and driving the eHealth revolution within Australian healthcare, through mHealth technologies such as MMAs.(2, 55, 56) The high penetration of smartphones is due to platform mobility, affordability, accessibility, and the available data storage, as well as the ability of installed apps to integrate with various devices and the internet. So much so, that in Australia, smartphones account for 40% (2018) of Australian internet access; compared to 49% (2018) for laptops and desktop computers.(57) The portable, personal and diverse platform has truly been embraced: within an hour of waking, over 80% of Australians will have checked their smartphone, with over half having done it within the first 15 minutes. Throughout a single day it is estimated that collectively Australians glance at their smartphone over 440 million times.(22) Even in the age group of 65 to 75 years age, where the platform has the least penetration at 68%, people check their smartphone within an hour of waking and on average will glance at it 10 times per day.(58, 59)

mHealth apps are already being used to deliver low cost health interventions to the population, particularly in rural and remote areas where there is limited health service delivery.(2-4, 60, 61) There is evidence that mHealth interventions – including those that include MMAs -- are effective in the management of chronic diseases (such as diabetes), as well as in health promotion (e.g. encouraging smoking cessation).(62, 63) MMAs could be especially beneficial as a medium to provide health services and chronic disease management, as residents of rural and remote areas are 40% more likely to have a chronic disease than those who reside in metropolitan areas.(64) Furthermore, the strain the increase in chronic health conditions has put on the domestic the health system is reflected in the increase in health expenditure.(65-67) With the average increase in health expenditure around 3.0% (2017) per year. Of this growth, approximately two-thirds was due to an increase in consumption of individual medical goods and services per person.(62) A large contributor to this increase was the broadening burden of chronic disease and the continued treatment and monitoring that accompanies the conditions.(63) The best way to reduce these increased budget pressures is through streamlined monitoring and prevention of chronic diseases. An area where MMAs can assist.(2, 10, 68)

Examples where mHealth is being used in health care include:

- *e-Mental Health in Practice (eMHPac)*(69): A programme funded by the Federal Government which teaches and encourages doctors and allied health professionals about software-based mental health resources (websites and MMAs). The programme aims to train healthcare professionals so these resources can be incorporated into primary care services to assist patients in receiving continual effective treatment regardless of time and place.(69) The programme facilitates the use of MMAs in Indigenous Australian communities, due to the high take up rates of mobile phones and social media among Indigenous young people.(70) eMHPac also provides training for doctors, nurses, and allied health workers working with Indigenous peoples.(69)

- Additionally, an eMHPac affiliated project called *StayStrong* has designed and uses an app to assist doctors, nurses, allied health workers and Aboriginal health workers in to provide culturally appropriate wellbeing support to Indigenous clientele in both a clinical and community setting.(71)

- The *Commonwealth Scientific and Industrial Research Organisation (CSIRO)* have successfully created and trialled an MMA that assists with the rehabilitation of cardiac patients.(72, 73)

- In industry, *SportsMed* a healthcare provider, orthopaedic hospital, and specialist clinic in South Australia have created and trialled an MMA to assist with the rehabilitation, treatment, and management of patients before and after hip replacements.(74, 75)

- *iBobby* is an MMA that was developed and trialled by the *Black Dog Institute*, which was aimed at providing culturally appropriate evidence-based suicide prevention to young Indigenous Australians.(70, 76)

MMAs may transform healthcare through a variety of mechanisms including: streamlining healthcare delivery (i.e. reduction of test duplication, improved coordination of the management of complex and chronic conditions); mitigation the challenges associated with treatment across distances in rural and remote areas; reducing escalating healthcare costs; remote monitoring of patients by health professionals; avoidance of hospital admissions; and a decrease in adverse events related to healthcare (i.e. through medication management and adherence).(2, 3, 10, 68, 77-79)

However, costs related to MMAs have the potential of act as a barrier to the access and provision of app-enabled healthcare. Possible cost- barriers include the purchase of MMAs, accessories or in-app purchases. For example if a doctor in Australia recommended a well-developed scientifically supported MMA like *SkinVision* –a skin-cancer detection app-- patients would have to pay between AU$5.99 to AU$41.99 every few months to monitor their skin health, due to the various in-app purchases.(80) These costs may be considered 'low', which could lead to the assumption that they are available to 'everyone'. Yet, patients (mostly low socioeconomic status) could choose to use another skin-cancer detection app which is less effective and safe but is cheaper or free.(11, 34) Furthermore, there is currently no way for healthcare practitioners (i.e. general practitioners, GPs) to claim reimbursement for using the information provided by MMAs in a clinical consultation or for reviewing, assessing, and monitoring patient data produced by an MMA.(12) This could result in medical practitioners not utilising the MMAs, charging patients privately for the extra time it takes for them to review, assess, and monitor the MMA data, or billing Medicare for longer consultations (so the patient would have to pay a larger gap payment, as well as the costs associated with the app itself). If a patient could receive reimbursement for the application through a separate Medicare item number, there would be fewer out-of-pocket costs and the usage and effectiveness of app-based management could be monitored through claims data. Conversely, if a medical practitioner was reimbursed through Medicare for the time it takes to appraise the data produced by MMAs, as well as for its use in a clinical consultation, it could assist the uptake and transmission of digital health data and spare patients' possible additional costs. Publicly funded, MMA reimbursement could ensure equitable and accessible healthcare that is provided through MMAs to all Australian residents regardless of socioeconomic status.

### 2.2.6 Potential harms

The potential harm posed by MMAs is different to that presented by traditional medical devices. Traditional medical devices pose mostly physical harms to users,(22, 36, 48) whereas the harms posed by MMAs (and similar digital health software) largely centre around the information produced and how it is used in decision-making by users.(22, 36)

A major concern is how the user applies the information produced by the MMAs to inform clinical decision-making by the healthcare practitioners or their patients. This is especially concerning when the information which underpins the MMA is outdated or not evidence based.(22, 32, 34, 36) It is not uncommon for MMA users to be exposed to misinformation. Aboms et al.(81) found low adherence to U.S clinical practice guidelines for treating tobacco use dependence among 47 mHealth apps aimed at assisting smoking cessation. A systematic review by Subhi et al.(33) concluded that mHealth apps do not adhere to medical evidence and lack expert involvement. Additionally, there is concern surrounding how the commercially

available mobile platforms' (i.e. smartphone or tablet) size and hardware features could affect the assessment and interpretation of medical information.(32, 48) For example, radiological image interpretation could be affected by the low contrast, back lighting, and screen size of device.(48) Misinformation is a serious harm. It can cause incorrect, unnecessary, or the withholding of a treatment. It can also cause patients direct psychological harm through causing unnecessary worry or indirect physical harm, through the effects of the clinical decision-making.(10, 22, 31, 34, 36, 82)

An additional harm posed by MMA relates to information security (cybersecurity). Information security is about maintaining the users' privacy and confidentiality, as well as protecting the user or their data from being the victim of malicious software. These harms are MMA-specific harms as traditional medical devices are not networked and have limited or connective capabilities. In order for a traditional medical device to be 'hacked' or for personal medical information to be sold or illegally obtained, it has to be done physically.(83) However, the dynamic and connective capabilities of MMAs results in increased vulnerablity to attacks (i.e. 'hacks') from malicious software (i.e. ransomware, viruses).(83-88) Attacks from malious software have been known to enable third party control of MMAs as well as altering the app's safety and efficacy. In either case this can threaten the health of patients. (83-89) These cybersecurity concerns increase concerns around the privacy of patient health data and who can access it. These concerns are compounded by companies that own apps who on-sell consumer data, both with and without the user's consent.(89, 90)

If MMAs become a permanent fixture in Australian clinical consultations, the software will alter how patients receive treatment. Thus there is a need for the proper integration of MMAs into the national healthcare system, starting with determining whether MMA regulation can address the technology specific harms posed by the software. This would need to be followed by deciding if MMA reimbursement as part of a clinical service is possible and feasible.

## 2.3 MMA regulation in Australia

In Australia, the first step towards a health technology with a therapeutic or diagnostic purpose being available for reimbursement is its approval by the TGA for domestic use and sale.(19, 26) Thus, for MMAs to be eligible for public funding they have to be regulated by the TGA. Currently, the TGA is attempting to regulate MMAs using pre-existing software regulation. (6, 7, 19, 26)

### 2.3.1 Therapeutic goods regulation in Australia

Therapeutic goods such as medical devices, medicines and biologicals are all subject to regulatory oversight by the TGA in Australia. The aim of regulation imposed by the TGA on therapeutic goods is to

protect public health.(6, 7) The TGA is responsible for regulating goods that are used by humans for various health related purposes that include: diagnosing, preventing, alleviating or curing a disease, injury or defect; pregnancy testing; testing of a person's susceptibility to a specific aliment or disease; or modifying, inhibiting or influencing a physiological process.(6) The TGA also regulates products that can modify or replace sections of human anatomy as well as items that are used as a component or ingredient during the manufacture of a therapeutic good.(6) The TGA regulates therapeutic goods to minimise the harm a product poses to the Australian population. In order to achieve this the organisation uses a 'risk-based' approach to guide the assessment of the product. The level of risk assigned to the product depends on its intended purpose and the manner of supply. If a therapeutic good passes the TGA's assessment for efficacy and safety, and the evaluation determines that the risks can safely be managed with the correct regulatory oversight, the product it is registered on the *Australian Register of Therapeutic Goods (ARTG)*, which is available online. Once a product is registered on the ARTG is available on the domestic market.(6, 7, 91)

### 2.3.2 Software regulation in Australia

The TGA currently regulates software as an active medical device[1]. A therapeutic good is considered a medical device if it is to be used on a human with the aim of: diagnosing, treating, alleviating, monitoring or compensating for a disability or injury; diagnosing, preventing, treating, alleviating or monitoring a disease; modifying, replacing, or investigating a physiological process or anatomy; birth control; and/or does not achieve its intended purpose of action in a human body through immunological, pharmacological or metabolic means, but could be assisted through such means.(6, 7) In specific situations software can be regulated as an *in vitro* diagnostic medical device (IVD) (see *Appendix A.1* for definition).(92, 93) There are varying ways in which the active medical device and IVD regulation policy can be applied to software; for more information see *Appendix A.2*.(6, 92)

#### Software risk-classification

Different risk-based approaches have been used to regulate and classify active medical devices and IVDs. When software is regulated as an active medical device the risk-based approach classifies devices into Classes I, IIa, and IIb. However, when Software as a Medical Device (SaMD) directly interacts (i.e. controlling, directly influencing, monitoring) with an active implantable medical device (AIMD) (i.e. cochlear implant, pacemaker, etc.), it is classified an Class III.(6) The IVD classification categorises devices into Classes 1, 2, 3, and 4.(92-95) In both risk categorisations the lowest numerical classification poses the least risk to public health.(6, 95) All medical devices and IVDs are required to meet the

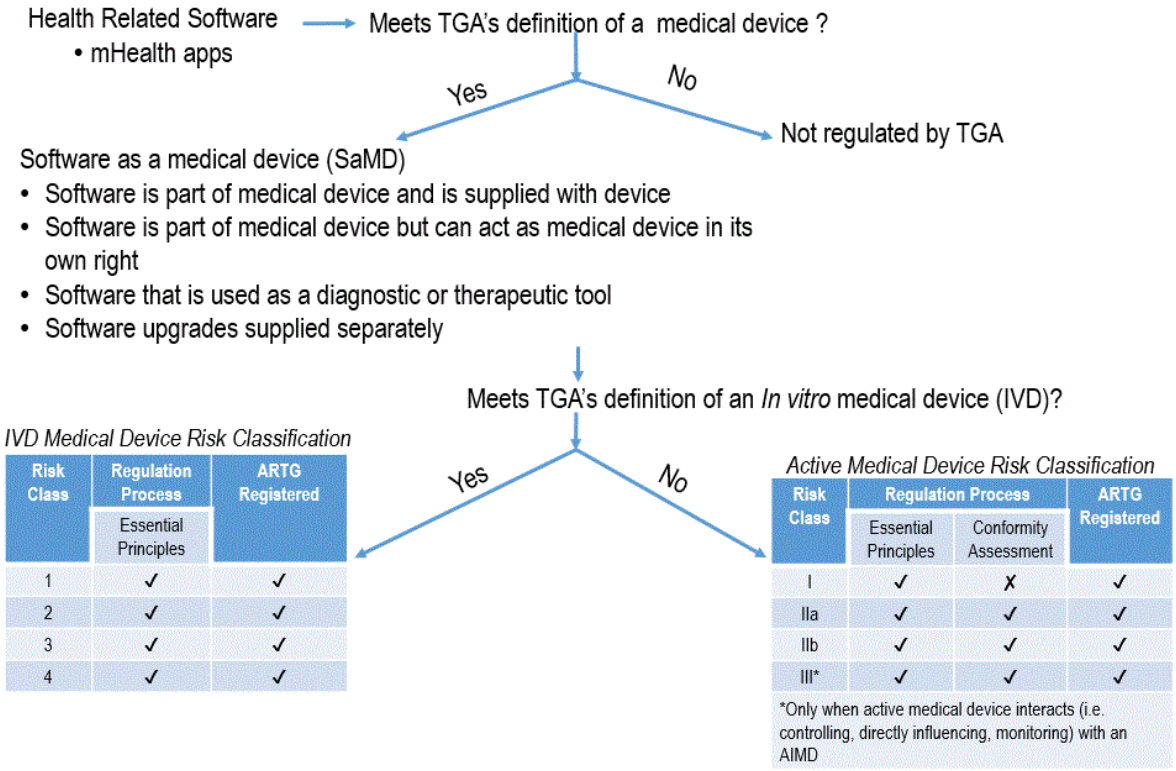
[1] The medical devices regulatory process is currently under review.(7)

Essential Principles for performance and safety characteristics.(6, 94) Device compliance with the relevant principles ensures that the health and safety of users is not compromised as the benefits of the product outweigh the risks. Non-IVD medical devices that are classified as Class II and above are required to obtain Conformity Assessment Certification, which assesses therapeutic (or diagnostic) effectiveness, as well as the Essential Principles.(6) *Appendix A.2.2* explains risk-classification, information on non-IVD medical devices and IVD risk-classification.

### 2.3.3 Current state of MMA regulation in Australia

Currently, Australia does not have any specific regulation for mobile health apps. The TGA is attempting to regulate this sub-set of mHealth application, as a software as a medical device (SaMD). As with other therapeutic goods, MMAs approved by the TGA are listed on the ARTG.(6, 7) Figure 2.2 provides a simplified depiction of how MMAs are regulated in Australia by the TGA.

Figure 1.2: Simplified overview of MMA regulation by the TGA




Source: Therapeutic Goods Administration ( 6, 7, 92, 93, 94, 95)

### Concerns with MMA Australian regulation

The regulation of MMAs as software may not be the best approach to accurately assess the risk that mobile technology poses to the population. MMAs present a different regulatory challenge compared with traditional medical software and devices. For example, with MMAs, the same app can be available on

various mobile platforms (smartphone/ tablet) as well as across various operating systems (iOS/ Android) and the app may respond differently on the different platforms or systems (see *Section 2.2.7*).(22, 32) An MMA may also pose different risks to the user on different platforms. For example, on September 12th 2016 the TGA issued a safety warning for an error that only affected *Accu-Chek Connect Diabetes Management* app on Apple's iOS, but not for the same app that is available on Google's Android platform.(96) Aside from issuing the warning, the TGA regulation is for the software but does not have any policies that account for differences across multiple platforms or operating systems. Furthermore, MMAs are regulated according to their intended purpose at the time of regulation. There are currently no clauses to address updates that could change an MMA's intended purpose after it has been approved and listed on the ARTG.(6, 7, 92) Finally, unlike other medical devices, MMAs can be created by anyone, based on any type of information and be made available direct to consumers on global scale in stores that are only monitored by multinational corporations.(48) To counteract this, in June 2016 Apple instituted guidelines that enables them to refuse to upload MMAs to their iTunes AppStore that do not have the relevant jurisdictional regulators' approval.(97, 98) The TGA has acknowledged the complexity presented by MMA regulation and is keeping up to date with medical device developments.(7)

### 2.3.4 International comparisons

The USA, the European Economic Area[2] (EEA) and Canada also regulate MMAs.(48, 101-103) Each regulatory body in these jurisdictions takes a slightly different approach to the regulation of MMAs. The EEA and Canada attempt to regulate MMAs using pre-existing policy, while the USA implemented an MMA specific approach within their current medical device regulation.(48, 101-103) In the EEA an MMA that is regulated will receive a CE marking.(101, 104) There is no registry or list of all the CE marked medical products.(101, 104) However, MMAs that have a CE marking have this in their product description, as was done with the *NaturalCycles – Contraception* app.(105, 106) In Canada only MMAs that are classified as Class ≤II are registered on the *Medical Device Active Licence Listing (MDALL)*.(102, 107) This is because Canada's *Medical Device Bureau (MDB)* does not require a medical device licence from Class I devices - Class I medical devices are monitored by the *Health Products and Food Branch Inspectorate (HPFBI)*.(102, 107-109)

[2] EEA includes the European Union(EU) member states as well as Norway, Iceland, and Liechtenstein.(99) After a referendum held on the June 23rd 2016 in which the citizens of the United Kingdom (UK) voted to leave the EU the country's continued participation in the Union or EEA is unclear.(99)

Like Australia the US FDA also provides a list of registered medical devices, called the 510k database, which can be searched.(48, 110) To address the challenges presented by MMAs, the FDA is currently piloting a new software policy and the EEA will implement one in 2020.(60, 89, 111-113)

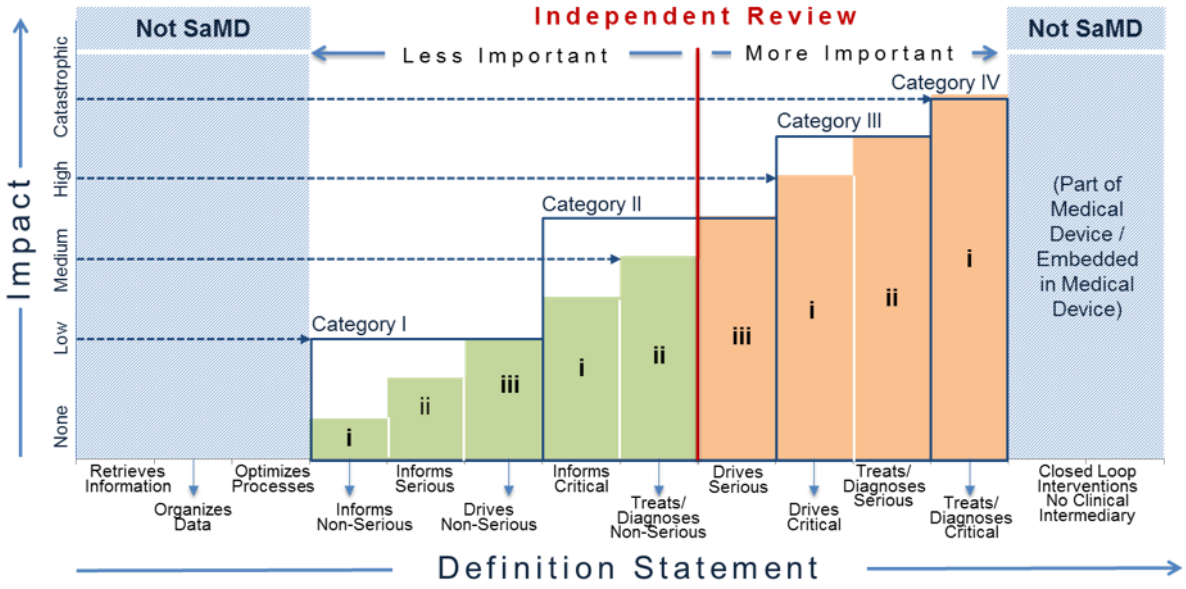
The challenge presented by software risk-classification has been noted by the *International Medical Device Regulation Forum (IMDRF)*(114). The IMDRF is a global forum for medical device regulators of which Australia, Canada, the EEA and the USA are members.(114, 115)

### 2.3.5 International medical device regulators forum (IMDRF)

In 2013 the IMDRF created a working group to develop guidance on how to support the innovation and adoption of safe and effective SaMD technology.(114) In September 2017 the IMDRF published a guidance document titled *Software as a Medical Device (SaMD): Clinical Evaluation*(22) in order to tackle the regulatory challenges presented by this technology.(22, 116)

The *SaMD: Clinical Evaluation* document applies to software that fits the definition of a medical device, irrespective of the technology used (e.g. server, mobile app).(22) The document in its current form does not apply to software that does not meet the definition of a medical device. The software excluded are ones used for retrieving information from systems or devices; optimising the workflow of healthcare through automating care protocols; collecting and organising data; or providing a closed loop intervention.(22, 116) This is demonstrated in Figure 2.3 below. Incorporated into the guidance document are other relevant IMDRF SaMD guidance documents for Risk Categorization and Corresponding Considerations, Key Definitions, and Quality Management systems. The *SaMD: Clinical Evaluation* is meant to act as a guidance document, and by no means is intended to modify or replace any existing regulatory requirements schemes already used for classification.(22)

Figure 2.3: Clinical evaluation of SaMD




Source: *SaMD: Clinical evaluation (116)*

The purpose of the clinical evidence guidance document is to simplify and to advise on the necessary level and type of clinical evidence which is needed to determine the safety and effectiveness of generic software that meets the definition of a medical device.(114) The document provides guidance on the acceptable methods for conducting a clinical evaluation of a SaMD, the relevant levels of evidence for the types of SaMD, and when an independent review of a SaMD is necessary. The guidance document also includes a SaMD framework that uses risk management principles to classify the risk posed by the software. The risk-classification for medical software has four classes; Class I, II, III, and IV. The higher the class the higher the risk posed by the software. A combination of two major factors affect the classification of the medical software; these are the significance of the information the software brings to the healthcare decision, as well as the healthcare situation or condition itself.(36, 114) How the two interact to determine the risk that the software poses to public health is shown in Figure 2.3.

The IMDRF *SaMD: Clinical Evaluation* guidance document could be used to help develop and assist in the relevant clinical evaluation of MMAs for proper MMA regulation.

## 2.4 Reimbursement of MMAs in Australia

### 2.4.1 Health services reimbursement in Australia

Australia has three overlapping avenues available for the reimbursement of diagnostic and therapeutic goods and services approved by the TGA. These are federal, state, and private.(117)

#### Federal - *Medicare* (Universal health insurance)

In 1984 the Federal Government (Commonwealth) implemented a universal health insurance scheme called Medicare to address the issue of access and equity in healthcare. In general Medicare provides Australian residents with access to hospital and medical services.(117)The insurance scheme was a response to widening the gap between different socioeconomic groups, which resulted in a large section of the population not having health insurance of any form.(20) Within Medicare there is the *Medicare Benefits Schedule (MBS)* which lists medical services that are eligible for governmental reimbursement.(20, 117) Through the MBS, Medicare provides subsided or free treatment from medical practitioners (general practitioners (GP), nurse practitioners, specialists, and optometrists). For treatment that occurs outside a hospital setting, reimbursement is available to patients for up to 100% of the MBS fee for a GP service, and up to 85% of the MBS fee for specialist services. In circumstances where a doctor bills Medicare directly ('bulk bills') the patient does not have to pay any fee for the service.(24, 117-119) Medicare also covers 75% of MBS fee for private patients in private or public hospitals.(21, 24, 119) Health professionals may charge more than the MBS fee in which case the patient must pay the gap. There are special circumstances where Medicare can provide subsidised treatment for allied health practitioners (i.e. within the Chronic Disease Management Plan) and dentists (i.e. within the Cleft Lip and Cleft Palate Scheme).(21, 24, 118)

#### State - Public hospitals

Public hospitals throughout Australia are administered by the states. State run public hospitals have a network of health services available and treatment to public patients occurs in the institutions free of charge. In 1984 an agreement was made that the States would maintain the responsibility for administration of public hospitals and that funding would be provided by the Federal Government (currently predominantly through goods and service taxation revenue). In cases where public hospital spending exceeds the allocated funding the states are responsible for difference. Conversely, if the states spend less than their allocation they are able to keep the savings.(25)

#### Private health insurance

In Australia private health insurance is available for permanent residents who choose to purchase it. The type and range of reimbursement and services available are dependent on the policy of the insurer. Private health insurance can subsidise allied health services (physiotherapy, occupational therapy,

psychology, etc.), glasses, contact lenses, hearing aids, dental treatment, dental examinations, and home nursing. Regarding hospital cover, private insurance can cover the remaining 25% of the MBS fee in a private hospital, hospital accommodation, theatre fee, prostheses, diagnostic tests, pharmaceuticals, intensive care, consumables, and any additional doctors' fees. It is important to note that private health insurance in Australia is also subsidised by the Federal Government.(21, 24, 120)

#### Deciding reimbursement eligibility

Currently, the Federal Government attempts to ensure that only evidence-based therapeutic and diagnostic services that are comparatively cost-effective, effective, and safe (in terms of health outcome) are available for governmental reimbursement through the MBS.(19, 121) In order to attain maximum health benefit at minimal expense and harm, the Federal Government uses health technology assessment (HTA) to determine if a medical service is eligible for governmental reimbursement. HTA has subsequently become a cornerstone of Medicare.(19, 25, 26, 117, 121)

### 2.4.2 HTA in Australia

In Australia HTA is the instrument used by the Federal Government to deliver financially sustainable healthcare that is both safe and clinically effective.(19, 121-123) HTA enables the provision of high quality research to inform clinical decision-making and policy development. As HTA is a multidisciplinary field, it enables an assessment of the economic, social, ethical, legal and clinical impacts of a health technology.(122-127) HTA involves the systematic evaluation of a health technology's potential impact, effect, and properties. The hallmarks of the HTA process is the evaluation and synthesis of all available evidence relating to a specific question(s) pertaining to the given health technology/intervention using a systematic and structured methodology that can easily be replicated. The HTA methodology can be adapted to different health system(s); however, the process should remain systematic, rigorous and transparent.(122, 124-127)

The Australian government uses the HTA process to help decide what health technologies should be eligible for reimbursement/ public funding. A health technology assessed for reimbursement in Australia can be a pharmaceutical, medical device, prosthesis, medical procedure, medical or surgical procedure, vaccine, and/or diagnostic technology. HTA is also used to assess health technologies that combine the use of a test and treatment/procedure such as co-dependent technologies or hybrid technologies to determine eligibility for governmental reimbursement.(19, 121) The different types of health technologies can qualify for Governmental reimbursement under the MBS or the PBS. HTA is also used to assess an intervention's eligibility for private health insurance subsidisation on the *Prostheses List*.(19, 121) The *Medical Services Advisory Committee (MSAC)* oversees the HTA of medical services (including devices) in Australia and advises the Federal Government on whether or not the respective services should be

eligible for reimbursement through the MBS.(19, 121) *Appendix A.3* has more information on MSAC. Similarly, the *Pharmaceutical Benefits Advisory Committee (PBAC)* is responsible for overseeing the HTA of pharmaceuticals and makes recommendations to the government on which products should be listed on the PBS.(121)

Apart from informing policy, the information obtained through the HTA process can be used by health professionals, consumers, and financiers, to make decisions regarding the benefits and value of the technologies and their use in specific situations.(19, 121, 124)

### 2.4.3 MMA reimbursement in Australia

Currently, reimbursement for MMAs is not available in Australia through universal or private insurance. The MBS does not have any items that cover MMAs or reimburse GPs, specialists or healthcare workers for utilising MMA capabilities or data.(2, 12) The MBS does have telemedicine items for video consultations.(121, 128-130) For further information on telemedicine reimbursement in Australia see *Appendix A.4*. Some Australian private health insurers do provide their policy holders with access to mobile apps that provide company related services (i.e. how to make a claim) or health information and prescription management.(131-133) Reimbursement under Medicare would be preferable to private health insurance as it would allow doctors, specialists and other healthcare workers (where deemed necessary) to utilise MMAs without having to worry about the cost to themselves or their patients. If MMAs were listed on the MBS it would enable the services provided to be reimbursable under Medicare and allow the benefits of the technology to be both accessible and equitable to all permanent residents of Australian irrespective of their socioeconomic status.

### 2.4.4 MMA reimbursement internationally

The USA and Germany provide MMA reimbursement within their respective health systems. Since 2013, selected US health management organisations (HMO) have reimbursed MMAs. The first MMA to be reimbursement by an HMO was an FDA approved diabetes management app called *WellDoc*.(134) Similarly, in Germany[3] multiple public health insurers reimburse MMAs.(136) The first MMA to be reimbursed in Germany was an app that had received a CE mark called *Caterna.* The app treated amblyopia (lazy-eye).(137) The health insurers in the USA and Germany that reimburse these MMAs have not published how these apps where selected or assessed for reimbursement. However, it appears likely that one of the key criteria was that the MMA had received approval from the relevant jurisdictional regulatory body.

[3] The country has a multiple insurance-based health system, where health insurance mandatory.(135)

For MMAs to be eligible for public funding through universal health insurance or some types of private health insurance they will usually have to undergo an HTA. The first step towards ensuring that the benefits and risks of MMAs are understood prior allowing equitable access to them is to determine whether it is feasible for the government to reimburse them within current HTA processes. To do this there needs to be an objective evaluation framework to assess the HTA domains of comparative safety, effectiveness and cost-effectiveness of the MMAs, as well as methods to classify the apps and assess the risk they pose to the population.

### 2.4.5 HTA evaluation frameworks for MMA

Currently, there is no MMA evaluation framework that can be used specifically for HTA purposes. Ideally, an MMA evaluation framework would address the HTA domains of effectiveness, safety and cost-effectiveness which could determine if the app is eligible for reimbursement. Nonetheless, frameworks and/or criteria that evaluate mHealth apps for a variety of different purposes have been published. Popular frameworks were developed by Stoyanov et al.(138), Martinez-Prerez et al.(139) and Reynoldson et al.(140).

## 2.5 Gap in knowledge

Unlike the USA and Germany, Australia currently does not have a method for reimbursing MMAs. In Australia, there is also no specific method to determine the comparative safety and clinical effectiveness of an app. This is concerning, as MMAs have been transforming healthcare delivery in Australia and could help in tackling the health, social and economic challenges presented by the increase in chronic diseases. Furthermore, the Australian Government and medical practitioners know the benefit of mHealth apps such as MMAs, as they are creating, recommending, and using the software. A reimbursement pathway with specific sections for MMA evaluation could help address this problem. Before MMA reimbursement can be implemented in Australia, a method or process for evaluating MMAs needs to be developed that is feasible and equally as rigorous as the current processes used to evaluate other health technologies.

## 2.6 Publications and presentation of chapter findings

### 2.6.1 Presentation(s)

- September 2016, **Presentation**, Moshi* M, Tooher R, Merlin T, Determining the feasibility of reimbursing mobile health apps in Australia*, PHAA 44th Annual Conference & 20th Chronic Diseases Network Conference*, Alice Springs, Northern Territory, Australia.

- May 2016, **Presentation**, Merlin* T. and Moshi M, Getting a grip on new technologies: AHTA's journey into m-health and mobile medical applications (MMAs)*, Health Technology Assessment International (HTAi) Annual Meeting*, Tokyo, Japan.

# Chapter 3: Research design

## 3.1 Rationale

There is currently no ability to claim reimbursement through Medicare for MMA use in Australia. Medical practitioners cannot claim the interpretation of health data derived from MMA or the use of an app during a clinical consultation. Similarly, patients cannot be subsidised through Medicare for out-of-pocket expenses (in-app-purchases or the cost of the MMA) related to the use of an MMA recommended by a medical practitioner to assist with their health condition. MMA reimbursement is not available through private health insurance providers in Australia. There is also currently no HTA method that can be used to evaluate MMAs to determine their safety, effectiveness and cost-effectiveness, to inform reimbursement decision-making. Thus, there is a need to determine if is it possible to adapt or create government reimbursement processes to include the use of MMAs by medical practitioners and patients through Medicare. The aim, research questions, and objectives are listed below, and how they interact with each other is illustrated in Figure 3.1.

## 3.2 Aim(s)

The overall aim of this thesis is to determine the feasibility of tailoring regulation and reimbursement processes in Australia to the evaluation of MMAs.

## 3.3 Research questions

1. Do changes need to be made to the current Australian regulatory model for software as a medical device (SaMD) to enable assessment of the possible health risks and benefits posed by MMAs?

2. Is reimbursement for MMAs feasible in Australia within the current health technology assessment (HTA) system?

3. What key policy changes and assessment criteria are needed to facilitate the development of a system that evaluates MMAs for reimbursement purposes in Australia?

## 3.4 Objectives

1. Assess whether the current Australian regulatory framework is suitable for the assessment of MMAs.

    - Test if the TGA regulation on SaMD is relevant for MMAs.

- Test if the IMDRF guidance for clinical evaluation of SaMD can be feasibly applied to MMAs.

- Identify the changes that would need to be made to the regulatory process in Australia to properly evaluate MMAs.

2. Review existing evaluation frameworks for MMAs and determine their suitability for use within the HTA processes currently used to inform reimbursement decision-making.

    - Determine if there are tools available to assess:
        - The clinical effectiveness and safety of MMAs,
        - The credibility of MMAs.

3. Determine whether reimbursement of MMAs is feasible in Australia and develop possible reimbursement implementation pathways.

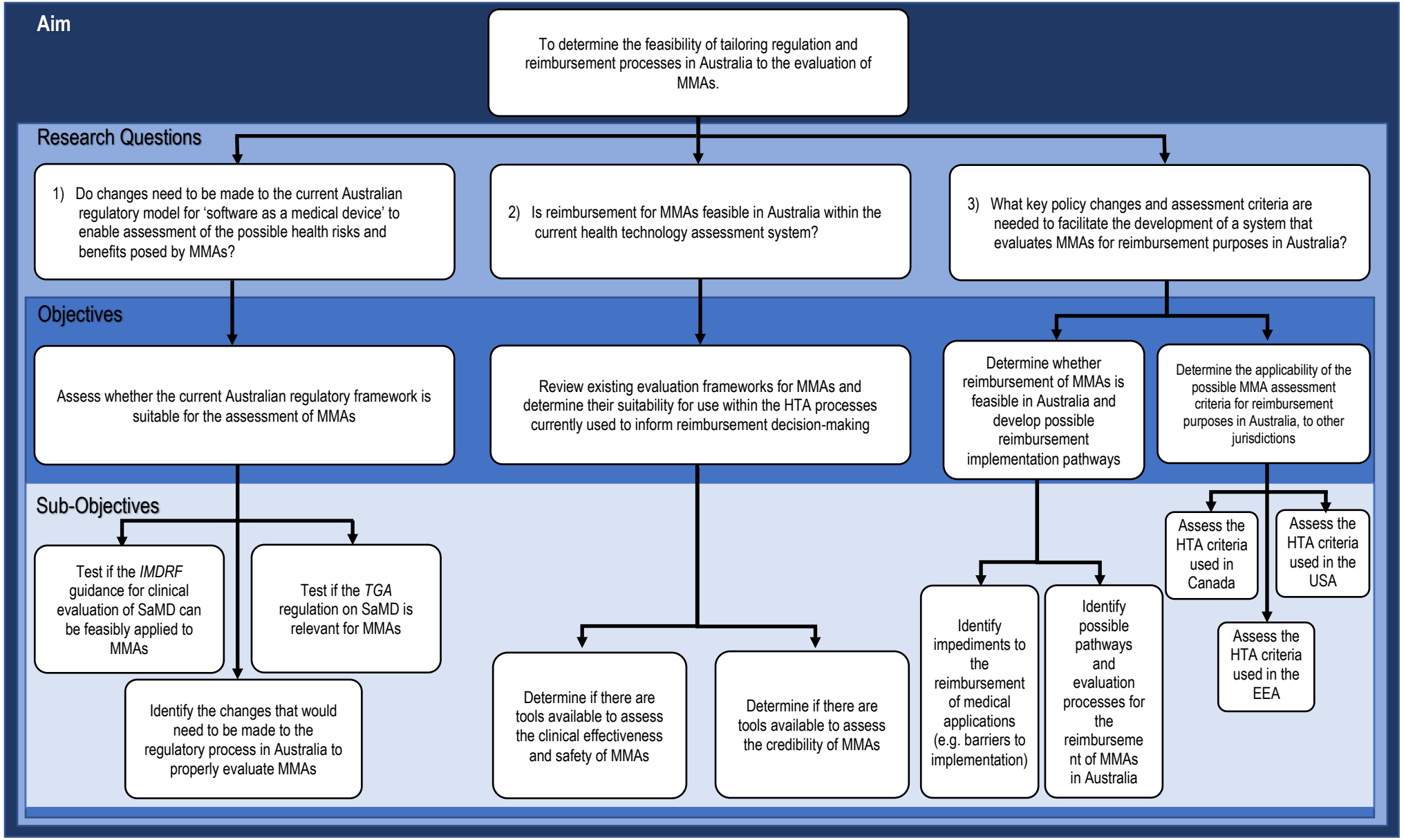
    - Identifying possible pathways and evaluation processes for the reimbursement of MMAs in Australia.

    - Identify impediments to the reimbursement of medical applications (e.g. barriers to implementation).

4. Determine the applicability of the possible MMA assessment criteria for reimbursement purposes in Australia to other jurisdictions.

    - Assess the HTA criteria used in:
        - Canada
        - European Economic Area (EEA)
        - United States of America (USA)

Figure 3.1: Structure and relationship of the thesis aim, research questions and objectives



# Chapter 4: Methodology

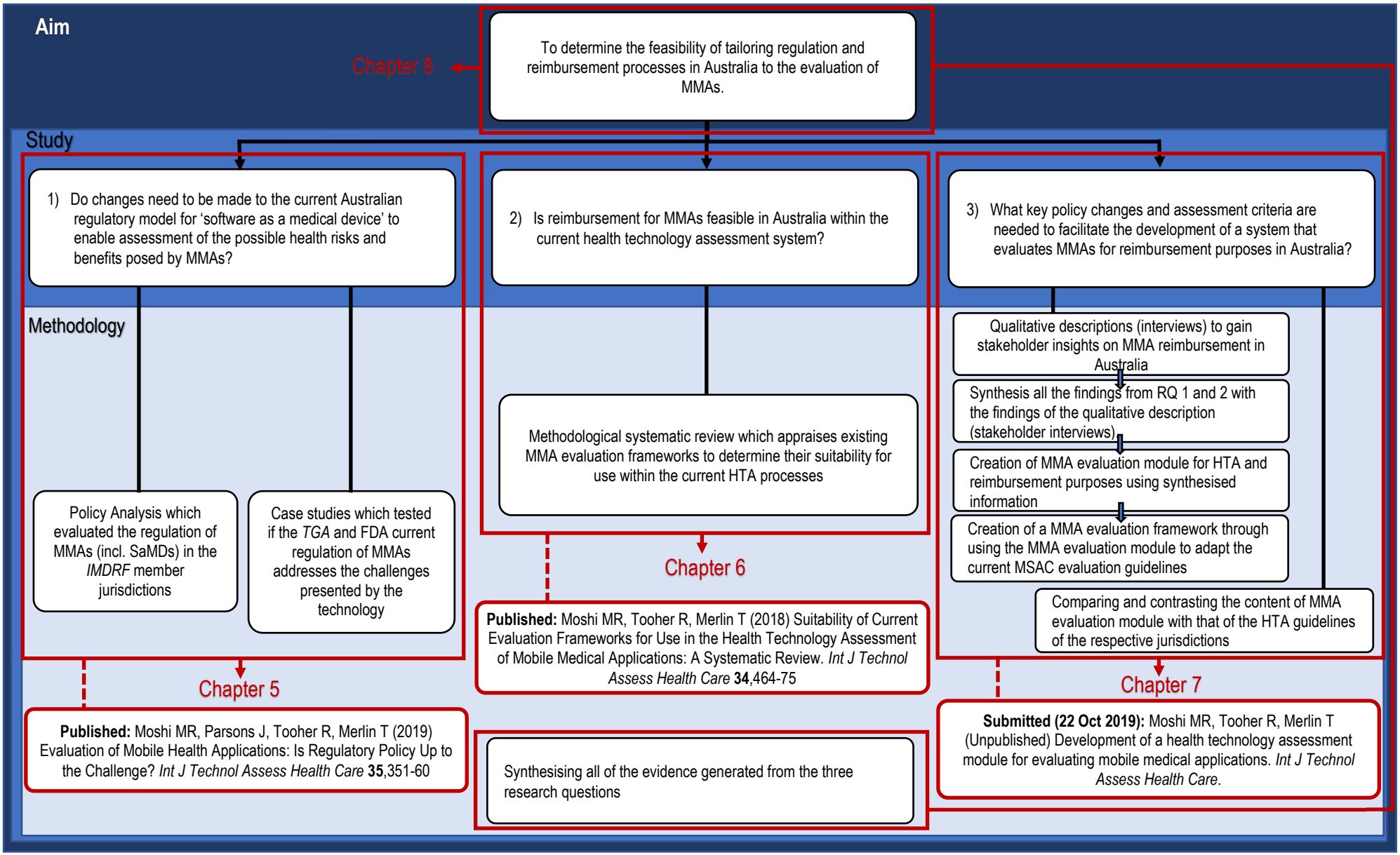
## 4.1 Framework of the research overall

In order to achieve the overall aim and address the proposed research questions, the overall project was divided into four sections. The first three sections addressed each individual research question and the corresponding objectives. While the fourth section addressed the overall aim of this thesis, which was to determine the feasibility of MMA reimbursement in Australia. Figure 4.1 illustrates the individual studies that form this thesis, and the respective methodologies undertaken to address the corresponding research question(s)/ aim. This figure also indicates which chapter addresses each respective research question(s)/ aim.

The first section (*Section 4.2*) reviews the Australian regulation of MMAs (and SaMDs) by evaluating it against international counterparts and the IMDRF guidance document for clinically evaluating medical software. The second section (*Section 4.3*), evaluates existing frameworks for MMAs and determines if any are suitable for use within HTA and reimbursement decision-making. The results of the first and second sections indicated the need for a criterion which can evaluate the MMAs for reimbursement and/or HTA decision-making purposes, as it provides a possible evaluative mechanism for MMA in Australia and in comparable jurisdictions. Thus, the third section (*Section 4.4*) of this methodology details the creation and testing of an MMA HTA evaluation module which was used to adapt the current HTA guidelines in Australia. The use of the MMA evaluation module to adapt HTA evaluation frameworks, ensures that the unique challenges apps pose would be properly appraised during an assessment. The module's transferability to comparable HTA jurisdictions (USA, Canada, EEA) and their evaluative methodologies was also assessed. The fourth (*Section 4.5)* and final section determined the feasibility of MMA reimbursement in Australia through integrating and synthesising all the evidence generated from the preceding three sections.

It is important to note, that the aim of this chapter is to summarise the methodology used to address the thesis aim and research questions. To prevent the repetition of information throughout the thesis, the details provided below are generally not present in the study manuscripts or respective chapters; where relevant, a reference to the corresponding chapter is provided.

Figure 4.1: Outline of studies and the methodologies undertaken to address the research question(s)/ aim examined



## 4.2 Evaluating the domestic regulation of MMAs

A policy analysis and a case study analysis were undertaken to critically review the regulation of MMAs in Australia.

### 4.2.1 Policy analysis

A policy analysis was conducted to determine how MMAs are evaluated for regulatory purposes in Australia and throughout the other IMDRF member jurisdictions (Brazil, Canada, EEA, Japan, Republic of Korea (south), Russia, Singapore, and the USA).(114) The MMA regulatory policies of IMDRF member jurisdictions were compared and contrasted against the *SaMD: Clinical Evidence(22)* guidance document. In situations where the SaMD guidance documents were unclear, the agencies were contacted via e-mail for further clarification. For the policy analysis, the FDA and Canadian MDB were contacted, see *Appendix B* for a summary of the correspondence. More information on the complete policy analysis method utilised is available in Moshi et al.(141) and its supplementary information in *Chapter 5*. A policy analysis was selected as the method to conduct this section of the study as it enabled the identification of potential international and domestic policy options which address MMA regulation in the English-speaking IMDRF member jurisdictions, as well as whether these options reflect the *SaMD: Clinical Evidence(22)* guidance document that they had produced - providing insight as to whether the guidance document can be practically implemented.(142, 143)

### 4.2.2 Case studies

The case studies were conducted to determine how the MMA regulatory policies identified during the policy analysis are executed by two IMDRF member jurisdictions, Australia and the USA. Each case study appraised the MMA regulatory applications that were submitted by industry, reviewed, and approved by the respective jurisdictional authorities. Case studies were used because they provided the opportunity to gain insight into how MMA regulatory evaluation is being applied in Australia and the USA.(144)

#### Acquisition of MMA regulatory submissions

Regulated MMAs and/or relevant accompanying hardware for each of the possible Australian regulatory pathways (e.g. general, AIMD, or IVD) were identified by searching the ARTG in August 2017. The regulatory submissions and/or clinical evaluation reports (CER) for the identified MMAs and/or relevant hardware were then accessed through two *Freedom of Information (FOI) Act 1982* requests to the TGA through the Australian Federal *Department of Health* in August 2017 and January 2018. Two FOI requests were submitted to the TGA, as the first request did not locate the required documents. A tabulated summary of the FOI requests made to the TGA is available in *Appendix B*.

To obtain the FDA evaluation of MMAs the FDA 510K database was searched for the same or similar MMAs to the ones identified through the ARTG. The selected MMA submissions and/or CERs were then downloaded from the 510K database.

For more information on the acquisition of MMA regulatory submission to jurisdictional agencies see Moshi et al.(141) and in *Chapter 5.*

### Data extraction

These submissions and/or CERs were assessed against a data extraction form developed from the IMDRF's *SaMD: Clinical Evaluation(22)* guidance document. The relevant data was extracted by two people to improve reliability and reduce errors. The data extraction form is available in *Appendix B*.

For more information on the data extraction methods and the creation of the aforementioned data extraction tool, see Moshi et al.(141) and its accompany supplementary material in *Chapter 5*.

## 4.3 Reviewing existing MMA evaluation frameworks and determining their suitability for use within HTA and reimbursement decision-making

A systematic literature review was conducted to provide information relevant to answering the second research question and its objectives. The overall aim of the systematic review was to review existing evaluation frameworks for MMAs and determine their suitability for use within the HTA processes currently used to inform reimbursement decision-making. The methodological systematic review was selected instead of other forms of reviews, as it enabled the identification and characterisation of all possible MMA evaluation frameworks that may be suitable for use in HTA.(145-148) A brief overview of the systematic review methods employed is outlined below.

### 4.3.1 Study eligibility criteria

Studies were included according to the following pre-defined criteria. The inclusion criteria are shown in Table 4.1.

Table 4.1: Study selection criteria

| Characteristic | Criteria |
|---|---|
| **Types of Participants** | *Anyone over the age of 18 that uses a mobile medical application (MMA)* |
| **Types of Intervention** | *Mobile medical applications (MMA)*[a] |
| **Type of Comparator** | *N/A – methodological systematic review* |
| **Outcome Measure** | *Framework(s)* [a] *that assess MMA effectiveness, cost-effectiveness and/or safety* |
| **Language** | *All literature was limited to English language only* [b] |

**Explanatory note(s)**

[a] Previously defined *Section 2.2*,

[b] *Article outcomes that are not reported in English will be excluded.*

If one framework was presented in several articles, the publications were collated and included as single study.

The full study eligibility criteria and reasoning behind it, is available from Moshi, Tooher, & Merlin(149) in *Chapter 6*.

### 4.3.2 Literature search methods

The published literature searches were conducted in the electronic bibliographic databases listed in Table 4.2. The searches had a cut-off date of 31st of October 2016. The minimum search date was the 1st of January 2008 (the first online application store opened in 2008).(10)

Table 4.2: Electronic bibliographic databases

| Electronic Database | Source | Time Period |
|---|---|---|
| *Medical sciences bibliographic databases* | | |
| Cumulative Index to Nursing and Allied Health Literature (CINAHL) | http://web.a.ebscohost.com.proxy.library.adelaide.edu.au/ | 31th October 2016 |
| Embase | http://www.embase.com.proxy.library.adelaide.edu.au | 31th October 2016 |
| PubMed (including MEDLINE) | https://www-ncbi-nlm-nih-gov.proxy.library.adelaide.edu.au/ | 31th October 2016 |
| Psych INFO | http://ovidsp.tx.ovid.com.proxy.library.adelaide.edu.au/ | 31th October 2016 |
| *The Cochrane Library* | http://onlinelibrary.wiley.com/cochranelibrary/search/ | 31th October 2016 |
| *Engineering bibliographic databases* | | |
| Business Source Complete | http://web.b.ebscohost.com.proxy.library.adelaide.edu.au/ehost/search/advanced?sid=44187681-5977-443a-b76a-e8d266c3c643%40sessionmgr106&vid=0&hid=125 | 31th October 2016 |
| Compendex | https://www-engineeringvillage-com.proxy.library.adelaide.edu.au/search/quick.url | 31th October 2016 |

#### Search terms and strategy

#### Search terms

The search terms included terms for MMA, mobile platforms, and evaluation. The search terms and strategy are explained in the supplementary document of Moshi, Tooher, & Merlin(149) in *Chapter 6*.

#### Search strategy

To identify the relevant published literature within the various databases the broad search only included keyword and indexing terms for MMAs and mobile platforms. 'Evaluation' and 'framework' related terms were not included in the search string because MMA assessment is an emerging field and it was expected there would be a variety of different synonyms used and limited or idiosyncratic ways in which

methodological frameworks would be indexed. I was concerned that additional terms would limit the searches, which could risk excluding relevant articles.

The engineering bibliographic databases, *Compendex* and *Business Source Complete*, favour 'key word' searches over 'indexing terms'. The lack of indexing resulted in the use of a slightly different strategy. The search strategy included key words for: mHealth applications and evaluation (assessment). The use of evaluation instead of smartphone related terms narrowed the search results to relevant literature.

The search strategy used in *PubMed* (including MEDLINE) and *Compendex* are available in the supplementary document of Moshi, Tooher, & Merlin(149) in *Chapter 6*. The search strategies used in the remaining databases are available in Table C.1-C.5 in *Appendix C*.

Grey literature searches were conducted to identify MMA evaluation frameworks that were not available in the published literature. The full strategy is available in the supplementary documents of Moshi, Tooher, & Merlin(149) in *Chapter 6*.

### 4.3.3 Study selection

*There were seven stages to the study selection.*

1. Search results accompanying abstracts were downloaded from the included databases and imported into *Endnote X7(150)*.

2. Duplicates of references were removed.

3. The citations and abstracts were exported from *Endnote X7(150)* to a screening database in *Rayyan(151)*. This enabled blinded consideration of the eligibility of evidence by two independent screeners.

4. The selection of a study in the database for inclusion in the systematic review was dependent on whether the citation or abstract information met the pre-defined eligibility criteria developed to address the research question (see *Chapter 6*).

5. I (MM) applied the study eligibility criteria to all the database and this was checked by a second screener (TM). The second screener reviewed 10% of the yielded literature to determine whether there was consistency in the interpretation of the inclusion criteria.

6. The studies that addressed the research question were exported from *Rayyan(151)* back to *Endnote X7(150)*.

7. I (MM) retrieved the included articles from stage 5 in full. The full text articles were screened against the pre-defined inclusion criterion in order to determine if they were eligible to be incorporated in the systematic review. Full-text articles were reviewed by a second researcher (TM) if eligibility was unclear.

8. Reference lists of the included studies were reviewed and screened for any potentially relevant studies that could have been missed in the electronic database searches. Any studies that are identified were reviewed according to stages 4 and 6.

The systematically reviewed evidence base consisted of articles selected from the sixth and seventh stages. Any disagreement in the selection process was resolved by the two reviewers through discussion. If consensus could not be reached, a third researcher (RT), was consulted to make the final decision. A PRISMA(152) diagram was used to illustrate the selection process. The list of included studies and the PRISMA diagram is available from Moshi, Tooher, & Merlin(149) in *Chapter 6*.

### 4.3.4 Data collection and analysis

Data extracted from the included studies was done using a pre-defined table detailed in Table C.6 in *Appendix C*). The information extracted included: author, year of publication, name of criteria/framework, outline of criteria/ framework, study methodology, intended user population, and the HTA domains addressed (current use of the technology, characteristics of the technology, effectiveness, safety, cost-effectiveness, organisational aspects, legal aspects, social aspects). More information is available from Moshi, Tooher, & Merlin(149), in *Chapter 6.*

To standardise the data extraction a checklist was created by MM. The use of this checklist enabled the traditional HTA domains addressed by each of the included MMA evaluation frameworks to be identified. The data extraction checklist was informed by Busse et al.(51) and Merlin et al.(153). The checklist was trialled and tested by myself (MM) and an HTA expert (DT) and found to have acceptable inter-reliability (Kappa 0.77). The full checklist is available in *Appendix C*. More information is available from Moshi, Tooher, & Merlin(149), in *Chapter 6*.

#### Critical appraisal of evidence

Since this was a methodological systematic review the included studies reporting on the evaluation frameworks were not critically appraised.

## 4.4 Creating an evaluation module and framework capable of conducting an HTA on MMAs

Various steps were undertaken to address the third research question and its underlying objectives. Thus, the overall aim of this section was to determine what policy changes and assessment criteria are needed to facilitate the development of a system that evaluates MMAs for reimbursement purposes in Australia. The first step was to gain stakeholder (healthcare practitioners, app developer, and policymakers) insights on MMA reimbursement in Australia using semi-structured in-depth interviews. The second step was to synthesise all the information gained from the assessment of MMA regulation (Moshi et al.(141) in *Chapter 5*), and, the systematic review of existing MMAs evaluation frameworks to determine their suitability to inform reimbursement decision-making (Moshi, Tooher & Merlin(149) in *Chapter* 6) with the stakeholder insights. This synthesised information was then used to create an MMA evaluation module which can be used to adapt current HTA frameworks so that they can be condut a HTA that will inform on whether an MMA is suitable for public funding.

### 4.4.1 Qualitative description using in-depth stakeholder interviews

Stakeholders were interviewed to identify any pathways and/or impediments to MMA reimbursement in Australia. The broad methodological approach used was a qualitative description. This approach is regularly used in the health sciences and creates a rich description of an event experience in the participants' language. This enabled the data to reflect participants' perceptions, sensitivities, inclinations and sensibilities.(154) The interviews were used to gain insight into stakeholders' views and opinions on the use of MMAs in clinical practice and the technologies' domestic future.(144, 154)

#### Ethical considerations

The ethical clearance (H-2017-039) for the in-depth interviews with stakeholders was received from the *University of Adelaide Low Risk Human Research Ethics Committee (HREC).* A copy of the ethical approval received is available in *Appendix D*.

The main risk associated with participation was the potential for reputational and/or professional risk through disclosure of information about clinical or regulatory practices. To minimise this risk, steps were taken to maintain participant confidentiality and anonymity. For more information on the ethical consideration related to the in-depth interviews see Moshi, Tooher & Merlin(155) in *Chapter* 7.

#### Recruitment

Stakeholders were recruited purposively from stakeholder groups that were able to provide a rich insight and understanding of the topic.(144, 154) The stakeholder groups included healthcare practitioners, (general practitioners (GP) and allied health workers) policymakers, and mobile application developers. From each individual stakeholder group participants were recruited via email, using passive snowballing

(see *Appendix D* for the recruitment email and participant information sheet). An information power approach (instead of attempting to reach data saturation), guided sampling as participants could only be included if they could provide meaningful information on the topic.(27, 28, 156) The stakeholders were not offered any remuneration for their participation in the study and they were free to withdraw at any time prior to the completion of the publication(155). For more information about the recruitment process and information power, see Moshi, Tooher & Merlin(155) and the supplementary information in *Chapter 7*.

### Data collection

I collected the data using semi-structured interviews. The interview structure enabled the use of open-ended questions and subsequent follow up and probing to further explore a topic when the interviewer deemed it necessary.(144, 154) The interview schedules were informed by the results of Moshi et al.(141) in *Chapter 5* and Moshi, Tooher & Merlin(149) in *Chapter 6*. Different interview schedules were developed and used for the three stakeholder groups. I conducted the interview in person or via teleconference (phone/ videoconferencing). The interview schedules are given in *Appendix D*. Written and verbal consent was collected prior to the start of each interview. Examples of the consent forms used are given in *Appendix D*. Each interview was recorded using an electronic audio-recorder. All communication with participants, before and after the in-depth interview, was done solely via email. Detailed information about the data collection process is available in Moshi, Tooher & Merlin(155) and the supplementary information in Chapter 7.

### Data analysis

A professional transcriber (Nicola Bennett) was employed to transcribe the interviews verbatim from the recordings. I analysed the interview transcriptions using thematic analysis (Braun and Clarke (157)) within the epistemology of pragmatism. *NVivo 11*(QSR international Pty Ltd)(29) was used to assist in the coding and the analysis, as well as to keep a log of the analysis and how and why decisions were made. The log was time and date stamped. Data triangulation was achieved using various quotes to demonstrate a finding as well as using participants from different jurisdictions throughout Australia.(30, 144) For more information on the data analysis process and the epistemology, see Moshi, Tooher & Merlin(155) and its supplementary information in *Chapter 7*.

### Reflexivity and context

All of the interviews and the overall research project were based in Adelaide, Australia. I was born in Adelaide to an Australian born parent and another parent who migrated to Australia. I am a biracial woman and thus am always aware of my minority status and increased vulnerability to acts of discrimination in any given situation throughout the world. These lived experiences make me hyperaware and sensitive to power dynamics.

I spent the majority of my childhood and formative years living as an expatriate with my parents overseas. All of my tertiary education has been conducted in Australia at a *Group of 8* (research-intensive) University. I am a native English-speaker and it is my primary medium of communication. I also received all my primary, secondary, and tertiary education in English. The fact that I am a native English speaker meant that I was able to identify any subtleties in a conversation and/ or the transcripts that were assessed. During interviews, this meant I was able to understand the 'subtext' of a conversation as well as to naturally probe. It also resulted in an ability to correctly recognise humour and understand colloquialism. This enabled me to build rapport and trust with the interviewees.

Given this was my first professional involvement in qualitative research, the entire process was a learning experience. Thus, there were a variety of factors which could have influenced my interpretation of the interviews. My main research training and experience within medical sciences is in HTA; a subset of evidence-based medicine. This resulted in a bias towards quantitative research, as well as being objective and detached from the research. It also meant that I had minimal experience and knowledge of theoretical paradigms and how to apply them. I kept a diary and wrote an entry after every individual interview of how I felt it went. Then with my meetings with my supervisor (Tooher) we would discuss how I felt during the interviews and review the audio-recording and transcripts to see if there was anything I could change in the next interview, such as probe in specific areas or use silence more effectively. My limited experience may have impacted the interpretation and analysis of the interviews as this was the first time I had used this method and I initially struggled to get into the 'head space' necessary to achieve a thorough analysis. I also worked with my supervisor on how to be subjective and aware of my biases as I undertook planning, data collection, and data analysis components of the qualitative description section of this thesis.

My personal lived experiences may have created an unconscious bias during the interviews and analysis. Prior to the start of this research project I did not have any prior experience or training, with the design, development, or assessment of MMAs or eHealth technologies outside of being an end-user. Though, when I was conducting the interviews, there were moments when I did not understand specific terms or phrases and had to determine the concept from the context. This may have affected my interviews as I could have missed an opportunity to expand, probe, and/or seek clarification on a specific issue. I also could have developed unconscious biases towards eHealth technologies throughout my life, through my parents' professions. One of my parents is a retired South Australian-trained electronics engineer, who throughout my childhood and formative years, worked with some of the largest technology and software companies in the world (at the time). So, I was exposed to the digital revolution from a unique perspective and learnt from a young age how its rapid evolution would disrupt multiple industries, as well as alter how people throughout the world lived and communicated. My other parent is a South Australian-trained and practicing Clinical Nurse Consultant (CNC). I have witnessed how their role in the healthcare workforce

and continual professional development (CPD) has dramatically changed with the healthcare industry's adoption of eHealth technology.

It is possible that my parent being a CNC who is actively involved in eHealth integration into the Australian healthcare system, unconsciously shaped my views on the technology and its adoption. I tried to keep their views separate when conducting interviews with healthcare practitioners. However, when they mentioned specific topics sometimes, I remembered my parent cited the very same issue, and I would use that opportunity to probe. Similarly, this occurred when interviewing application developers, as prior to the start of this thesis, majority of my understanding of apps, was shaped from the perspective of my parent- someone who worked in the industry.

Finally, during the interview(s), the issue of ethnicity and race occurred, where the research participant expressed discriminatory views. As an Australian biracial woman, I have developed the ability to look past a person's biases and continue on a conversation with complete professionalism. However, after the interview I was shaken by the experience. I worked hard to limit how that experience could have affected my analysis and interpretation of the transcript(s) from the interview(s).

### 4.4.2 Development of the MMA HTA evaluation module and framework for reimbursement purposes

The results were integrated through prioritising and synthesising the research generated in the preceding sections (*Sections 4.2, 4.3, and 4.4.1*). A list of options to evaluate MMAs for HTA and reimbursement purposes was generated from the findings of the policy analysis, case studies, systematic review, and stakeholder interviews. These findings were synthesised to create the MMA HTA evaluation module. The MMA module was considered capable of adapting current HTA reimbursement assessment frameworks to ensure that the unique challenges apps present are properly appraised.

#### Development of MMA HTA evaluation module

In order to create the MMA HTA evaluation module that can be used for modifying current HTA frameworks, the key policy changes had to be identified. The policy changes were identified by synthesising and evaluating the findings from *Chapters 5 and 6* with the results from the qualitative description detailed above in *Section 4.3.1*.(149, 155) The complete module and its detailed creation is available in Moshi, Tooher & Merlin(155) in *Chapter 7*.

#### Development of MMA HTA evaluation framework

The MMA HTA evaluation module was used to adapt the current MSAC technology evaluation guidelines to create an MMA evaluation framework for HTA and reimbursement purposes. A detailed description of

the steps taken to develop the evaluation framework is available in Moshi, Tooher & Merlin(155) and the supplementary information in *Chapter 7* (*Section 2).*

### 4.4.3 Applicability of MMA HTA evaluation module to comparable jurisdiction

The applicability of the new MMA HTA evaluation module to comparable HTA jurisdictions (USA, EEA, Canada) was examined thorough comparing and contrasting its content with the that of the HTA guidelines of these jurisdictions. The USA, Canada, and EEA were selected as comparable jurisdictions as they have consolidated and comprehensive HTA guidelines available in English. The complete and detailed method is available in *Chapter 7* (*Section 3*).

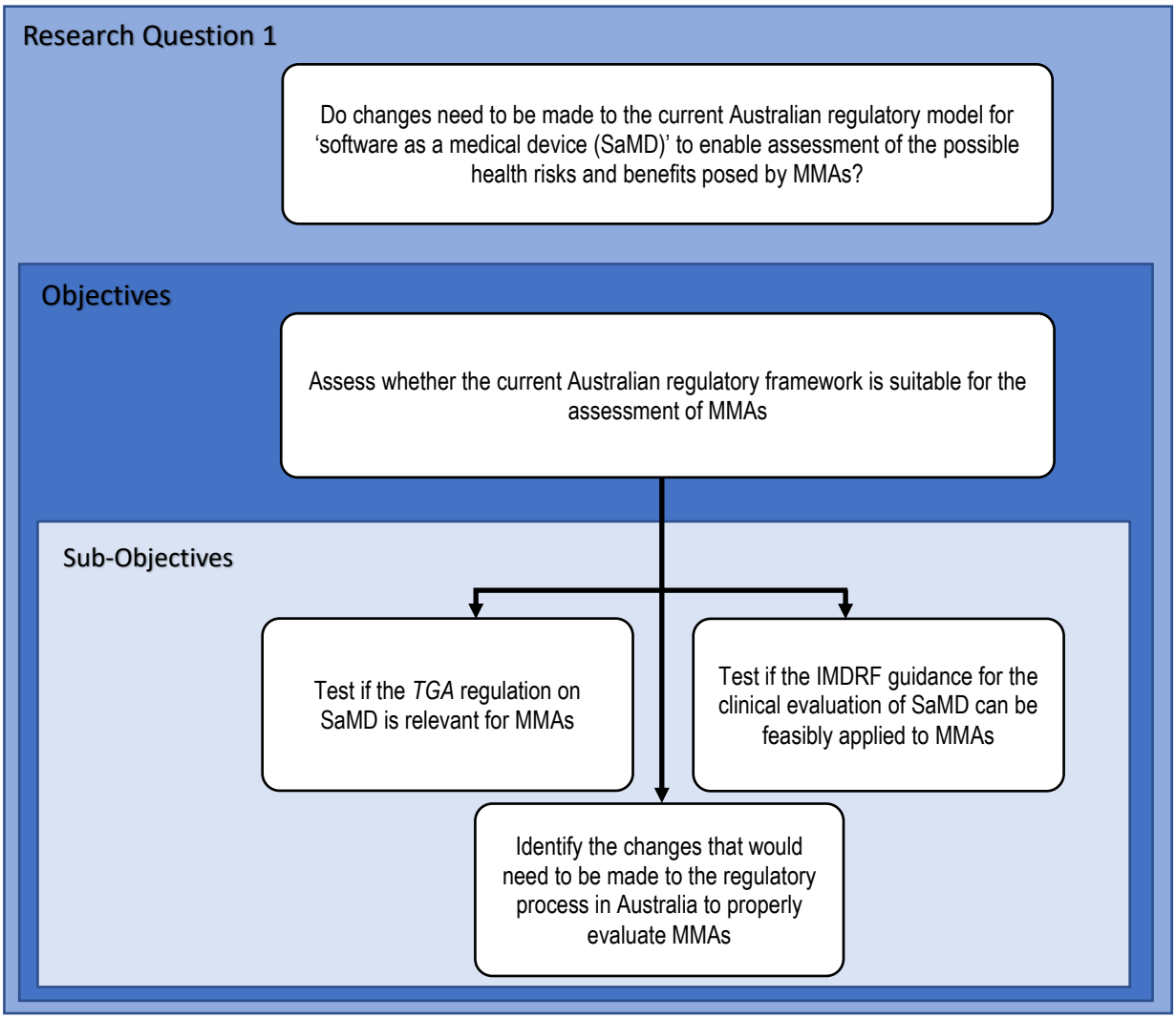
# Chapter 5: Regulation of mobile medical applications (MMAs) in Australia

## 5.1 Preface

This chapter assesses the adequacy of TGA regulation of MMAs in Australia by investigating if changes need to be made to the current Australian SaMD regulatory model. To determine if the current domestic regulatory framework was suitable to address the challenges presented by MMAs, it was reviewed against the policies of international regulatory counterparts, and the IMDRF guidance document for the regulation of the technology.

This chapter addresses the first research question and its respective objective(s) (listed below in Figure 5.1). How this section relates to the overall thesis aim and other objectives and research questions is illustrated in Figure 3.1 in *Chapter 3*.

Figure 5.2: Structure of *Chapter 5's* research question and objectives



This chapter addresses the above research question and objectives using a policy analysis and case studies detailed in the publication by Moshi et al.(141) and its corresponding supplementary documentation (see *Section 5.2*). For additional information on the methods used in Moshi et al.(141) see *Chapter 4 Section 4.3.*

A tabulated summary of my correspondence with the jurisdictional regulatory agencies used during the policy analysis section of Moshi et al.(141) is supplied in *Appendix B*. Regarding the case studies, a table summarising the FOI requests as well as the data extraction form are also in *Appendix B*.

## 5.2 Publication

| | |
|---|---|
| **Title** | The evaluation of mobile health applications: is regulatory policy up to the challenge? |
| **Journal** | *International Journal of Technology Assessment in Health Care* |
| **Publication Date** | 16th of July 2019 |
| **DOI** | https://doi.org/10.1017/S0266462319000461 |
| **Conditions of publication reuse** | "5.1.2 The Contributor may reproduce the Contribution or an adapted version in any format in any work authored or edited by the Contributor, subject to appropriate acknowledgment"(158) |
| **Version presented in thesis** | Presented as published |

## 5.2.1 Statement of authorship

# Statement of Authorship

| | |
|---|---|
| Title of Paper | Evaluation of Mobile Health Applications: Is Regulatory Policy Up to the Challenge? |
| Publication Status | ☒ Published ☐ Accepted for Publication<br>☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style |
| Publication Details | Moshi MR, Parsons J, Tooher R, Merlin T. Evaluation of Mobile Health Applications: Is Regulatory Policy Up to the Challenge? International Journal of Technology Assessment in Health Care. 2019;35(4):351-60 |

### Principal Author

| | |
|---|---|
| Name of Principal Author (Candidate) | Magdalena Ruth Moshi |
| Contribution to the Paper | I contributed to the conception of the study and study design. I conducted the policy analysis, case studies. I prepared all Freedom of Information (FOI) requests and was responsible for all communication with domestic and international regulatory bodies. I prepared the manuscript and acted as the corresponding author. I was also responsible for all major and minor revisions. |
| Overall percentage (%) | 80% |
| Certification: | This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper. |
| Signature | Date 26-09-2019 |

### Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

| | |
|---|---|
| Name of Co-Author | Jacqueline Parsons |
| Contribution to the Paper | J. Parsons assisted in the data extraction in the case studies as well as the interpretation of data the extracted data. She provided feedback on the manuscript, and evaluated the revised manuscript against reviewers' comments. |
| Signature | Date 9/10/19 |

| | |
|---|---|
| Name of Co-Author | Dr Rebecca Tooher |
| Contribution to the Paper | R. Tooher contributed to the conception of the study as well as study design. She was also assisted in the interpretation of data and results. She provided feedback on the manuscript, and evaluated the revised manuscript against reviewers' comments. |
| Signature | Date 1/10/19 |

| | |
|---|---|
| Name of Co-Author | Professor Tracy Merlin |
| Contribution to the Paper | T. Merlin contributed to the conception of the study as well as study design. She assisted in the interpretation of data and results. She provided feedback on the manuscript, and evaluated the revised manuscript against reviewers' comments. |
| Signature | Date 30/9/19 |

## 5.2.2 Complete journal article

### Title

The evaluation of mobile health applications: is regulatory policy up to the challenge?

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## Abstract

**Objective**

To determine whether the approach used in Australia to regulate mobile medical applications (MMA) is consistent with international standards and is suitable to address the unique challenges of these technologies.

**Method**

The policies of members of the *International Medical Device Regulator's Forum* (*IMDRF)* were analysed, to determine whether these regulatory bodies address IMDRF recommendations for the clinical evaluation of software as a medical device (SaMD). Case-studies of varying types of regulated MMAs in Australia and the US were also reviewed to determine how well the guidance in the IMDRF's *SaMD: Clinical Evaluation* (2017) document was operationalised.

**Results**

All included jurisdictions evaluated the effectiveness of MMAs and addressed the majority of the key sub-categories recommended in the IMDRF guidance document. However, safety principles concerning information security (cybersecurity) and potential dangers of misinformation (risk-classification) were generally not addressed in either the case-studies or in the policy documents of international regulatory bodies. Australia's approach was consistent with MMA regulation conducted internationally. None of the approaches used by global regulatory bodies adequately addressed the risk of misinformation from apps and the potential for adverse clinical consequences.

**Conclusion**

The risks posed by MMAs are mainly through the information they provide and how this is used in clinical decision-making. Policy in Australia and elsewhere should be adjusted to follow IMDRF risk-classification criteria to address this potential harm as it examines the danger of misinformation. Australian regulation should also be updated to so it can comprehensively evaluate the harm posed by cybersecurity and the risk posed by connectivity capabilities.

## Keywords

Mobile applications, health policy/standards, technology assessment, mobile health

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## Conflict of interest

None

## Introduction

Mobile medical applications (MMA) are software applications (apps) with a therapeutic or diagnostic purpose(1). MMAs are a part of larger group of software known as software as a medical device (SaMD); a class of medical software which can act as a medical device(1). These apps are increasingly being used globally by patients and health practitioners to treat and monitor chronic health conditions (such as diabetes)(2,3). Currently, software - including MMAs - in Australia is regulated as a general medical device, or an *in vitro* diagnostic (IVD) medical device, and when applicable as an active implantable medical device (AIMD)(2,4). MMAs are also subject to pre and post market regulatory oversight by the Australian federal regulatory agency, the *Therapeutic Goods Administration (TGA)*(2). All devices regulated in Australia are listed on the *Australian Register of Therapeutic Goods (ARTG)*(5).

MMAs pose similar regulatory challenges to other forms of contemporary digital health software. These technologies are characterised by different methods for determining whether their intended purpose is achieved (software validation), as well as a fast and iterative design and development process, compared to more traditional forms of medical software and/or hardware(6-10). However, unlike traditional software forms, MMAs are easily accessible and installable software, and can be deployed on readily available non-specialised hardware (off-the-shelf) over various platforms. These platforms may also be interconnected with other datasets, systems and devices, via the internet and other networks(6-9).

Current software regulation used by the TGA in Australia focuses on assessing the risks presented by traditional forms of software and/or hardware - predominantly direct physical harms such as infection(2). However, the risks posed by apps are mainly indirect, through the information they provide, and are thus more challenging to regulate(9). In this, MMAs resemble *in vitro* diagnostic medical devices (tests) as they do not directly improve health outcomes, but the output they provide has the ability to alter the management of the patient(11). Other jurisdictional regulatory bodies such as the *United States (US) Food and Drug Administration (FDA)(3)* and that of the *European Commission(12)* have experienced similar challenges with MMAs. In response, in 2013 the FDA implemented an MMA specific approach to regulatory evaluation(3).

The regulatory challenges presented by MMAs and other contemporary software led the *International Medical Device Regulator's Forum* (*IMDRF)* - to which Australia and the US are signatories - to create a working group aimed at harmonising the regulation of standalone medical device software(13). In 2017 the IMDRF published a final guidance document on *Software as a Medical Device (SaMD): Clinical Evaluation*(13,14). The guidance document provides the level and type of clinical evidence needed to appraise software for regulatory purposes(13).

This study explores the regulation of MMAs in various international jurisdictions, and tests whether the approach used in Australia by the TGA to regulate MMAs (and/or accompanying hardware) is consistent with international standards and suitable to assess the challenges that MMA technology presents.

## Methods

Two methods were used to critically review international approaches to the regulation of MMAs and to benchmark the Australian approach against its international counterparts: a policy analysis and a review of case studies.

### Policy analysis

The aim of the policy analysis was to identify policies for the evaluation of MMAs in the regulatory setting developed in the nine IMDRF member jurisdictions. These policies were then compared and contrasted relative to the *SaMD: Clinical Evidence(13)* guidance document (Supplementary material)(13,15).

To identify documents for the policy analysis, documents available on the relevant jurisdictional regulatory agencies' websites were reviewed (Supplementary material). Other relevant policy documents were identified through the snowballing of sources.

### Inclusion criteria

The included policy documents had to be in English as well as published in or after January 2013 (IMDRF published its first SaMD guidance document in 2013) and before April 2018. The policy documents were limited to guidance documents that directly or indirectly addressed the regulation of MMAs and/or software within the IMDRF member countries. Legislative documents or Acts were excluded as they had not been enforced by the relevant jurisdictional regulatory agency (e.g. *TGA*).

### Case studies

The case studies were used to assess to what extent these regulatory policies had been enacted in Australia and the US. The US was selected as companies' regulatory submissions to the FDA were accessible. The case studies evaluated MMA applications which had been submitted, reviewed, and approved by the relevant jurisdictional regulators. Data were extracted from these documents using a form identifying elements of the IMDRF's *SaMD: Clinical Evaluation(13)* guidance document (Supplementary material). The data extraction form is available upon request.

### Acquisition of submissions to regulatory bodies

The *ARTG* was searched in August 2017 to identify MMAs and/or the accompanying hardware that were representative of each type of regulation pathway (i.e. general medical device, IVD and AIMD). Subsequently, *Freedom of Information Act 1982 (FOI)* requests to the Australian *Department of Health* in August 2017 and January 2018 to obtain the regulatory evaluation/ individual document but with sponsor and manufacturer information redacted.

The corresponding FDA evaluation of these MMAs were obtained through searching their 510K database and downloading the approved submissions(16). Unlike the TGA, the FDA reviewed the MMAs and/or any accompanying hardware together.

### Evaluation of submissions to regulatory bodies

The TGA and FDA evaluation documents of the MMAs and/or their accompanying hardware (where applicable) that were used as case studies are listed in Table 1. Relevant information was extracted into to the data extraction form and by the first (MM) and second (JP) authors to determine what the regulatory bodies did and did not assess. Any disagreements between the evaluators was resolved by discussion, and if consensus was not achieved, a third author (TM) was consulted.

Table 1: Included MMAs and accompanying hardware (where applicable)

| Medical Device Name | | | Entry Number | | Sponsor | | Medical Device Type | Medical Device Intended Purpose | Risk-Classification | |
|---|---|---|---|---|---|---|---|---|---|---|
| Commercial | ARTG (TGA) | 510K Database (FDA) | ARTG (TGA) | 510K Database (FDA) | ARTG (TGA) | 510K Database (FDA) | | | ARTG (TGA) | 510K Database (FDA) |
| *DANA* | | *DANA(43)* | | K141865 | | AnthroTronix, Inc. | Standalone software | Diagnostic | | Unclassified |
| *iHealth Align Glucose Meter* | *Clinical chemistry substrate IVDs (iHealth Align Gluco-Monitoring System) (45)* | *iHealth Align Gluco-Monitoring System (BG1) (46)* | 239352 | K153286 | Propell Pty Ltd ATF Propell Trust | Andon Health Co., Ltd | IVD | Therapeutic | IVD Class 3 | Class II |
| | *Software IVDs (iHealth Gluco-Smart App) (44)* | | 279064 | | Propell Pty Ltd ATF Propell Trust | | Software IVD | Therapeutic | IVD Class 1 | |
| *Reveal LINQ Insertable Cardiac Monitoring (ICM) System* | *Reveal LINQ Model LNQ11 – Implantable cardiac monitor (48)* | *Reveal LINQ Insertable Cardiac Monitor (Model LNQ11) (49)* | 218791 | K150614 | Medtronic Australasia Pty Ltd | Medtronic Inc. | Active Implantable | Therapeutic | AIMD | Class II |
| | *LINQ Programmer Application Model MSW001 – Implantable cardiac monitor programming application software (47)* | | 274712 | | Medtronic Australasia Pty Ltd | | Software | Therapeutic | Class III | |
| *SkinVision* | *SkinVision-Skin Cancer Detection App (42)* | | 279238 | | Emergo Asia Pacific Pty T/a Emergo Australia | | Standalone software | Diagnostic | Class I | |

**Explanatory note:**

AIMD – Active implantable medical device

ARTG (Australian Register of Therapeutic Goods) – the databases used to catalogue all registered medical devices in Australia

IVD -- *In vitro* diagnostic medical device

MMA -- mobile medical applications

510K Database – the database used to catalogue all registered medical devices in the USA

## Results

### Policy analysis

Nine of the ten included regulatory bodies had policy guidance information on medical software regulation available, however only five were in English(2,3,17-23). The jurisdictions of Australia, Canada, the European Economic Area (EEA), Singapore and the US were included in the analysis(2,3,17-19).

### Independent review (e.g. internal non-conflicted experts, third parties, external experts)

Policy documents from Australia, the EEA, and Singapore all recommend that the clinical evaluation of a medical device should be performed by a qualified individual(s). This is consistent with IMDRF SaMD clinical evaluation recommendations. The regulatory bodies also state the applicants should justify the choice of clinical evaluator(s) as well as provide evidence of the expert(s) experience and/or proficiency(24-26). The US and Canadian guidance documents did not include any clause to indicate that the submission to the jurisdictional regulatory body should involve a clinical evaluator(3,18,27,28).

### Continuous learning using real world performance data

Also, in line with IMDRF guidance the five jurisdictional regulatory agencies require post-market surveillance of medical devices, encouraging the manufacturers to monitor the performance and safety (e.g. adverse events) of medical devices (29-33). However, contrary to the recommendation in *SaMD: Clinical Evaluation(13)* these regulatory agencies do not review the device surveillance approach taken by the manufacturers, assess how burdensome the approach is, nor determine how the collected information could be integrated into the functionality of the regulated software in pre-market assessments.

### Description and current use of the technology

All five regulatory agencies appraised the intended purpose of MMAs(1-3,17,24-26,28,34). However, only the EEA considered the input (e.g. physiological status, laboratory results, images, etc.), output (e.g. treat, diagnose, inform, etc.), and/or algorithm (e.g. model based logic, equations, rules, etc.), used by the app(13,17,35). The TGA requires a statement of both the intended purpose and the manner of supply of the apps(2).

### Effectiveness

All of the guidance documents recommend assessing the clinical effectiveness of SaMDs, in terms of *clinical association* and *product performance*. It was difficult to determine whether particular evidence was specifically required for the evaluation of MMAs, as this was not stated. Regarding *clinical association,* all jurisdictions require a literature review, information on clinical equivalency of the product, any research

that has been conducted on the product, and any performance data that the manufacturer possesses on the device (e.g. post-market data)(1-3,17,24-26,28,34). Regulatory bodies in Australia, Singapore, and the US verify whether the app/software meets the requirements of its specifications and whether it has been validated through testing as fulfilling its intended purpose(24,26,28,35).

### Safety

Like Australia, the other jurisdictional members of the IMDRF use a physical risk-based (Table 2) approach for medical device software which aims to minimise the effect of physical harm from the device by balancing this against the benefits of its intended purpose. In all these jurisdictions, the higher the risk the medical devices poses, the more regulatory controls that are applied to the technology and the more systematic the clinical evaluation (Figure 1)(1-3,17,18,24-26,28,34,36-39). The system (risk-classification) recommended by the IMDRF to classify the dangers posed by SaMDs, assesses the harm posed by comparing the impact the software output will have on clinical decision-making against the severity of the condition being treated by the software(9,14). However, none of the included jurisdictions used the risk-classifications suggested in the IMDRF's *SaMD: Clinical Evaluation(13)* guidance document.

Similarly, none of the regulatory bodies included any aspects of information security (cybersecurity) for software as recommended by the IMDRF(13).

Table 2: Risk classification of medical devices in included jurisdictions

| Jurisdiction | Regulatory Authority | Type of Medical | Risk Posed | | | |
|---|---|---|---|---|---|---|
| | | | Low | Moderate | High | Serious |
| Australia | *Therapeutic Goods Administration (TGA)* | Non-IVD | I | IIa | IIb | III |
| | | IVD | 1 | 2 | 3 | 4 |
| | | Active Implantable | | | | AIMD |
| Canada | *Medical Devices Bureau (MDB)* | Non-IVD | I | II | III | IV |
| | | IVD | I | II | III | IV |
| | | Active Implantable | | | III | IV |
| European Economic Area (EEA) | *European Commission* | Non-IVD | I | IIa | IIb | III |
| | | IVD | General IVD | | High risk IVD | |
| | | Active Implantable | | | | AIMD |
| Singapore | *Health Science Authority (HSA)* | Non-IVD | A | B | C | D |
| | | IVD | A | B | C | D |
| | | Active Implantable | | | | D |
| United States American (USA) | *Food and Drug Administration (FDA)* | All | I | II | | III |

**Explanatory note:**
AIMD – Active implantable medical device
IVD -- *In vitro* diagnostic medical device
Non-IVD -- A medical device that is neither an AIMD nor IVD

### Technical characteristics

Australia, Singapore, the US, and the EEA all clarify in their guidance documents that their jurisdictional influence only applies to MMA software and/or any relevant attachable hardware(1-3,17,19,27,34). These jurisdictions clearly conveyed that their jurisdictional authority does not extend to the mobile platforms (e.g. smartphone, etc.) or the devices' operating system (e.g. Android, etc.) that interacts with the app and/or hardware (1-3,17,19,27,34).

### Summary of findings

Regulatory agencies in Australia, the EEA, and Singapore all to some extent addressed four of the five recommendations within the *SaMD: Clinical Evaluation(13)* guidance documents. The USA, and Canada did not assess if an independent reviewer (clinical evaluator) is necessary to appraise submissions. Canada was the only jurisdiction that did not assess technical characteristics of SaMD. Each of the five jurisdictions did not assess safety - as defined by the *SaMD: Clinical Evaluation(13)* guidance documents - both in terms of how risk is classified for software and in terms of cybersecurity.

### Case-studies

We could not identify any standalone software versions of MMAs that were regulated by both Australian and American regulatory agencies. For Australia we selected the *SkinVision* skin cancer detection app (Class I), and for the US we selected *DANA* (unclassified), an MMA that assesses a person's medical and psychological state(40,41). These MMAs where selected as they were two apps that acted as a medical device using solely a mobile platform and did not require an attachment and/or any additional

hardware. For software that related to the IVD and implantable MMA regulatory pathways, we were able to identify apps that were regulated in both jurisdictions. We selected the *iHealth Align Glucose Meter* for the IVD pathway and the *Reveal LINQ Insertable Cardiac Monitoring (ICM) System* for the implantable MMA pathway. In Australia the TGA classified the MMA and the attachable hardware of *iHealth Align Glucose Meter* as IVD Class 1 and IVD Class 3 respectively(42,43). The FDA classified the app and hardware together as Class II(44). As with the glucometer, the TGA classified the MMA and ICM hardware as Class III and AIMD respectively(45,46), while the FDA classified the devices together as Class II(47). See Table 1 for more information.

### Independent review

The use of an independent reviewer in the case studies was only used by the TGA for high risk software and hardware submissions. The low risk TGA submissions of Class I (*SkinVision*) and IVD Class1 (*iHealth* app) did not require independent review of the device. These applications to the TGA were generally accepted within 24 hours of submission. The higher risk devices such as Class III (*ICM* app), IVD Class 3 (*iHealth Align Glucose Meter*), or AIMD (*ICM System*), were all reviewed by TGA reviewers as well as professionals with clinical expertise whose *curriculum vitae* (CV) was provided with the submission (40,42,43,45,46). Regarding submissions to the FDA it was unclear if the reviewers had direct involvement with the development and/or testing of the product, or if the FDA ever reviews their CVs.

### Continuous learning using real world performance data

Only the TGA considered how real world experience data could be integrated into the lifecycle of the medical device software and hardware within pre-market evaluations. In the Class III (*ICM* app) and AIMD (*ICM System*) submissions the TGA only assessed whether the manufacturers would continue to monitor the software after market authorisation(45,46). The TGA did not fully comply with IMDRF recommendations and examine if the MMA product performance was inferior or superior to the metric stated in the submission, and/or if the data could be used to enable or disable functions in the software. Unlike Australia, the FDA did not integrate any real world data into the jurisdictional regulatory process.

### Description and current use of the technology

The TGA's and FDA's appraised submissions all reviewed the intended purpose of the software and hardware, the intended population, and output(s) of the technology (e.g. inform, treat, diagnose)(40-47). From the selected submissions, the TGA did not enquire about the input (e.g. digitized content such as laboratory results, symptoms, images). However, the TGA did review the software output (e.g. inform, treat, diagnose) for IVD Class 1 (*iHealth* app) and Class I (*SkinVision*) software, AIMD (*ICM*) and IVD Class 3 (*iHealth Align Glucose Meter*), but not the Class III (*ICM* app) software(41,44,47). The FDA

reviewed the input for Class II (*ICM* and *iHealth Align Glucose Meter*) software and devices as well as the software's algorithm (e.g. equations, model based logic, rules, knowledge base, reference base) (41,44,47). However, the FDA only reviewed the output for IVD MMAs (*iHealth Align Glucose Meter)*, not for the active implantable (*ICM*) or standalone (*DANA*) MMAs(41,44,47).

### Effectiveness

Effectiveness in terms of *clinical association* or *product performance* (Table 3) was not assessed by the TGA in any of the software classified as Class I (*SkinVision*), or devices in IVD Class 1 (*iHealth* app)(40,42). Unlike the TGA, each MMA assessed by the FDA did evaluate valid *clinical association* and *product performance* in all submissions to some extent, including reviewing the clinical equivalency of all included MMAs. The FDA also examined if any scientific validity studies had been conducted on IVD (*iHealth Align Glucose Meter)* and active implantable (*ICM*) devices(41,44,47). The TGA evaluated the *clinical association* domain through the use of a literature review and experience data for its active implantable devices (*ICM*), whereas the FDA did not(41,44-47). Regarding *clinical validation,* the FDA reviewed the relevance of the data used to demonstrate MMA effectiveness for all of the selected device types(41,44,47). Neither the TGA nor FDA assessed *analytical validity* for low risk (*SkinVision* and/or *iHealth* app) or unclassified devices (*DANA*). Only Class II (*ICM* and *iHealth Align Glucose Meter*) and above medical devices in either jurisdiction had their performance verified and validated(41,43-47).

Table 3: SaMD: Clinical Evaluation categories and sub-categories addressed by each submission

| Medical Device Submission(s) | Risk Classification | Independent Review | Description and current use of the technology | Effectiveness | | | Safety | | | Technical Characteristics | Continuous learning using real world performance data |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Product Performance | | Risk-Classification | | Information security to safety consideration | | |
| | | | | Clinical Association | Clinical validation | Analytical/ Technical validation | State of healthcare situation/ condition | Significance of information provided by the MMA to the healthcare decision | | Socio-technical and system environment | |
| *Therapeutic Goods Administration (TGA)* | | | | | | | | | | | |
| [a] SkinVision-Skin Cancer Detection App (42) | Class I | ✗ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ~ | ✗ |
| [a] BG1 Gluco-Smart (44) | IVD Class 1 | ✗ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ~ | ✗ |
| [a] LINQ Programmer Application Model MSW001 – Implantable cardiac monitor programming application software (47) | Class III | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✓ | ✓ | ✓ |
| [b] Clinical chemistry substrate IVDs (iHealth Align Gluco-Monitoring System) (45) | IVD Class 3 | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✓ | ~ |
| [b] Reveal LINQ Model LNQ11 – Implantable cardiac monitor (48) | AIMD | ✓ | ✓ | ✓ | ✓ | ~ | ✗ | ✗ | ✗ | ✗ | ✓ |
| *U.S. Food and Drug Administration (FDA)* | | | | | | | | | | | |
| [c] DANA (43) | Unclassified | ✗ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✓ | ✗ |
| [c] iHealth Align Gluco-Monitoring System (BG1) (46) | Class 2 | ✗ | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✓ | ✗ |
| [c] Reveal LINQ Insertable Cardiac Monitor (Model LNQ11) (49) | Class 2 | ✗ | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✓ | ✗ |

**Explanatory note:**

✓ Domain was addressed, ~ Domain was partially addressed, ✗ Domain was not addressed
[a] Software, [b] Hardware *(attachment to platform)*, [c] Software and hardware combined as a single device,
AIMD -- Active implantable medical device,
IVD -- *In vitro* diagnostic medical device
Non-IVD -- A medical device that is neither an AIMD nor IVD
SaMD-- Software as a medical device

### Safety

The case-studies demonstrated that information required by the TGA and FDA changed depending on the risk-classification and the intended purpose of the device. For IVD Class 3 (*iHealth Align Glucose Meter)* devices the TGA determined whether the sponsor and/or manufacturer had been transparent with their information as well as if the device could withstand being configured in unintended ways. Unlike the FDA, the TGA also inquired about how the information is displayed by the software and how the technology could affect workflow for Class III (*ICM* app) devices.

With respect to information security (cybersecurity), the TGA reviewed transmission data and if software could resist system interactions for Class III (*ICM* app) devices. The FDA did not appraise MMA cybersecurity in any form.

### Technical characteristics

The case-studies demonstrated that there was limited consideration of information about the mobile platform or operating system. In Australia, for some classes of MMAs (not including hardware), the regulatory agency required information about the platform that the software was run on. However, for Class I (*SkinVision*) and IVD Class 1 (*iHealth* app) MMAs the submissions only stated that the devices were medical software, inferring use of an off-the-shelf device. The FDA assessed whether MMAs were run on non-specialised medical platforms (e.g. smartphones) for all the included devices. For the IVD device the FDA inquired about the type of platform and operating system that the attachment and app were to use.

### Summary of challenges

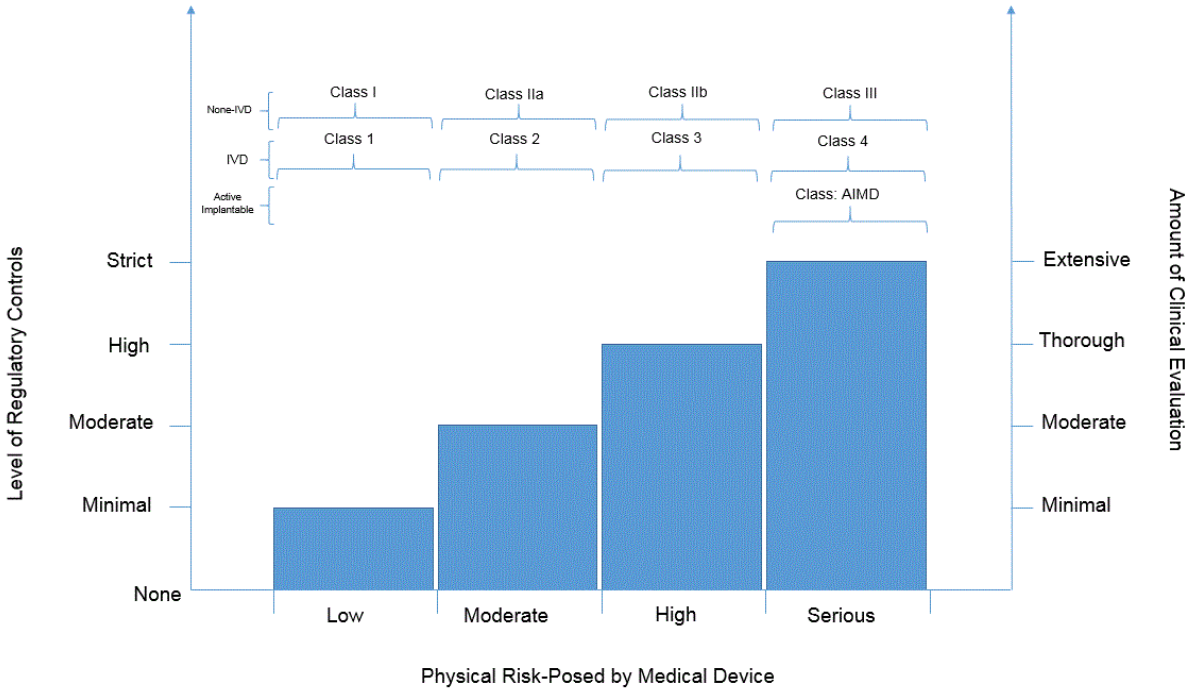
The case studies have highlighted a number of challenges faced by Australian regulations of MMAs. When compared to IMDRF recommendations, the challenge revolves around how the Australian system should change its risk-classification system so that it is based on MMA content and information, instead of the physical risk it poses. Another challenge is integrating technology specific items (e.g. cybersecurity, analytical validity, etc.) into current regulation and ensuring that MMA regulatory submissions undergo independent clinical review– not just for devices that are Class II and above.

## Discussion

In English speaking IMDRF jurisdictions the current regulatory oversight of MMAs and/or accompanying hardware does not completely comply with the IMDRF *SaMD: Clinical Evaluation(13)* guidance on the regulation of software.

However, the Australian software regulation is consistent with the approaches used internationally. Most jurisdictions utilise a physical harm based risk-classification system, which determines how extensive and thorough (Figure 1) the clinical evaluation a MMA should be(2,3,24,26,30,36,37). Figure 1 illustrates the current Australian physical based risk classification. It is concerning that none of the IMDRF member jurisdictions review software safety using the method that they have recommended, i.e. that the risk-classification should be based on the consequences to patients of the information supplied by the software (output). Much like medical tests, MMAs can produce health consequences for patients indirectly, if the patient takes a course of action (e.g. treatment) based on the information provided. The credibility of this information is critical.

Figure 1: The relationship between the application of Australian regulatory controls and risk-classification



The challenges presented by digital health software to current device regulation is resulting in changes in regulatory processes internationally. In April 2017 the European Commission adopted new medical device legislation (implemented in 2020) to ensure that regulatory processes can adapt to the significant progress in technology and science that has occurred in the past two decades, and which will likely to continue in the future(12).

Furthermore, the US has had to explore a different way of regulating SaMDs to address the unique challenges they present (3). The FDA is currently piloting a new method to regulate software (including MMAs)(10). It explores a pre-certification (based on *SaMD: Clinical Evaluation*) approach which assesses the SaMD developer for their software testing, designs, and other matters(7,10,48-50). The reason for exploring this new approach is because the existing method was considered inappropriate for the regulation of SaMDs, given the technology is easily adaptable with a fast life-cycle(10,50).

Unlike the *European Commission* and the FDA, the TGA has not altered its approach to MMA regulation, but it does acknowledge the complexity of MMA regulation(51). Like the other regulatory agencies, the main reason that the TGA approach to regulation of MMAs is not compliant with *SaMD: Clinical Evaluation(13,14)*, is because of the risk-classification approach used. Software has no direct physical interaction with the user (e.g. exchange or administer energy and/or supply energy for imaging, monitoring physiology processes), so the devices are generally classified as Class I (Figure 1)(2,26). Thus, submissions for MMAs will only have to provide a minimal level of evidence. An MMA which has direct interaction with an AIMD is automatically a Class III (this explains why the *Reveal LINQ ICM* app is Class III instead of Class I)(2,52). If the TGA measured the risk posed by software by reviewing the impact of the MMA content on the user, instead of its physical harm, as the IMDRF recommended for SaMD, the clinical evaluations and regulatory controls applied to medical apps may be more extensive. With regard to hardware that accompany MMAs, the current 'physical risk' approach of the TGA may be appropriate as these devices generally have direct contact with patients and as such pose physical harms(2).

### Technical considerations

The TGA regulatory approach does not assess information security in MMAs or the applicable hardware. However, the TGA issued a *Medical Devices Safety Update(53)* in 2016 on medical device cybersecurity, in which it "*advises medical device sponsors and asset owners to perform risk assessments by examining the specific clinical use of potentially affected products in the host environment*"(53). Traditionally medical devices did not have the networking or connective capabilities and could only be 'hacked' through being physically altered(54). However, with the networked and connective nature of MMAs and applicable hardware, these devices are now vulnerable to ransomware and other forms of malicious software(54-

59). This is particularly concerning as software enables third parties to remotely control the device (e.g. in 2017 the FDA issued a *Safety Communication* about cybersecurity vulnerabilities in Abbott's implantable cardiac pacemaker), as well as alter the programming(54,56,57,60,61). The ability of malicious software to affect the safety and efficacy of the device could ultimately endanger the life of a patient(54,56,57,61).

### Areas for future research

The development of a risk-classification process that can assess the downstream harms posed by SaMDs and accompanying hardware is needed. Methods for evaluating the cybersecurity of MMAs/SaMDs and accompanying hardware are also urgently required. Research would also be helpful on the impact of commercially accessible non-specialised platforms on MMAs. Finally, further research could be conducted to investigate if our study findings are applicable to non-English language regulatory agencies.

In the long term, research could explore the barriers to more robust regulation of MMAs to protect the Australian population from preventable harm. Better regulation of MMAs in Australia could also potentially create a pathway to reimbursement, as it is the first step to a device being eligible for government reimbursement schemes(62). If MMAs and/or the accompanying hardware are not properly regulated, it may prevent a device that could potentially provide benefits to the populations' health from being publicly funded. This raises the question of how a health technology assessment (HTA)
would be conducted on an MMA for reimbursement purposes, given the indirect impact of MMA information on patient health outcomes(63). Perhaps methods used in the evaluation of *in vitro* diagnostics could be adopted.

### Limitations

There were various limitations to this research. Due to the policy analysis being limited to jurisdictional documents available in English, potentially important information was excluded. Furthermore, the case studies did not include FDA Class I or III software. However, according to regulatory policy, the clinical evaluations conducted for FDA Class I or III are almost identical to the ones that we reviewed. The study used the *SaMD: Clinical Evaluation(13,14)* as the benchmark (gold standard) to measure the regulation of SaMDs, and there may be differing views on the validity of this standard.

## Conclusion

The Australian TGA's regulation of MMAs is consistent with approaches used by similar international regulatory agencies. These approaches all focus on evaluating the physical risks posed by traditional

medical devices. However, unlike risks posed by traditional medical devices, the main harm posed by MMAs relate to the information provided and how this is subsequently used in clinical decision-making. At present, none of the approaches used by international regulatory agencies adequately assess the harms and risks posed by potential misinformation in apps. In order to protect the Australian public as well as global app users from the threats posed by MMAs - which mimic the challenges of IVDs – proper regulation that addresses the unique challenges of this technology is required.

### Policy implications

To address the unique challenges presented by software as a medical device, the Australian TGA should adopt the risk-classification approach recommend by the IMDRF. Any hardware that accompanies the MMA should continue to be regulated in accordance with current TGA evaluation and risk classification. The TGA should also create a method for evaluating the information security of the apps, and other software and hardware with connectivity capabilities, due to cybersecurity threats. Other IMDRF jurisdictions should consider similar changes to their regulation of MMAs and medical device software more generally. With a clearer understanding of the information and connectivity risks and benefits associated with MMAs, there is a greater potential for the development of reimbursement pathway for these technologies.

If the FDA's software pre-certification program is successfully implemented and integrated into the US regulatory environment, the TGA could also consider trialling a similar system in Australia.

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### 5.2.3 Supplementary material

## IMDRF member jurisdictions

Table S.1: Regulatory authorities' websites for IMDRF member jurisdictions

| Jurisdiction | Regulatory Authority | Website |
|---|---|---|
| Australia | *Therapeutic Goods Administration (TGA)* | https://www.tga.gov.au/ |
| Brazil | *Agência Nacional de Vigilância Sanitária (ANVISA)* | http://portal.anvisa.gov.br/english |
| Canada | *Medical Devices Bureau (MDB)* | https://www.canada.ca/en/health-canada/corporate/about-health-canada/branches-agencies/health-products-food-branch/therapeutic-products-directorate.html |
| China | *China Food and Drug Administration (CFDA)* | http://eng.sfda.gov.cn/WS03/CL0755/ |
| European Economic Area (EEA) | *European Commission* | https://ec.europa.eu/commission/index_en |
| Japan | *Pharmaceutical and Medical Device Agency (PMDA)* | https://www.pmda.go.jp/english/ |
| Russia | *Roszdravnadzor (Federal Service for Surveillance in Healthcare)* | http://www.roszdravnadzor.ru/en/ |
| Singapore | *Health Sciences Authority (HSA)* | www.hsa.gov.sg |
| Republic of Korea (South) | *Ministry of Food and Drug Safety (MFDS)* | http://www.mfds.go.kr/eng/index.do |
| United States of America (USA)[a] | *U.S. Food and Drug Administration (FDA)* | https://www.fda.gov/ |

**Explanatory note:**

[a] The FDA was directly contacted in April 2018 to clarify what regulations applied to medical apps, due agency being in a period of policy reform.(54)

## Sources of data extraction form

The data extraction form also incorporated elements from the IMDRF guidance document *SaMD: Possible Framework for Risk Categorization and Corresponding Considerations(9)* when these details were referenced in the *SaMD: Clinical Evaluation(13)*. The data extraction form excluded recommendations relating to the IMDRF guidance document *SaMD: Application of Quality Management Systems(16)* as these were not health system specific considerations.

## 5.3 Postface

### 5.3.1 Chapter summary

This chapter addressed the first research question, which was to assess whether the TGA regulation of MMAs in Australia, using the current SaMD approach, properly assesses these technologies. This was achieved through a policy analysis and a review of case studies, which compared the Australian regulation of MMAs to its international counterparts and the IMDRF guidance document for SaMD regulation. Both analyses found that Australia and its international counterparts do not properly regulate MMAs. This is because the approaches used to regulate MMAs are the same as used to evaluate traditional medical devices and MMAs pose different challenges to usual technologies. The differences are related to the harms posed by the app, as well as how secure it is. The harms posed by MMAs are not physical, but are related to the information the apps produce and how this information is consequently used in clinical decision making. The security of a MMA is important as the technology's connectivity, compatibility, and networking capabilities pose a threat to a patient's personal medical information. Threats such as ransomware, and other types of malicious software, could affect the app's safety and efficacy. In conclusion, the current TGA regulatory framework does not properly evaluate MMAs and the challenges the technology presents. Changes need to be made to the current TGA regulation of MMAs. Regulatory processes should address the harm of misinformation as well as the possible risks associated with information and connectivity compatibilities (cybersecurity threats). Improving Australian regulation of MMAs may facilitate a pathway for the technology being reimbursed within the domestic healthcare system.

### 5.3.1 Update

After the submission of Moshi et al.(141) to the *International Journal of Technology Assessment in Health Care* in November 2018, the TGA opened a consultation into proposed changes to SaMD regulation in Australia.(159, 160) The proposed changes to regulation were released in February 2019, and included changes on how to classify the risk posed by the technology, prevent personal importation of SaMDs, as well as to ensure that the performance and safety of SaMDs are properly evaluated.(159, 160) The consultation period closed at the end of March 2019, with a TGA brief summary of the findings relased in November 2019.(159, 160) The TGA will conduct additional consulations on the regulations in 2020.(159) Currently, is unclear if the consultation will conform with the findings of Moshi et al.(141)

### 5.3.3 Publications and presentation of chapter findings

Between July 16th 2019 and December 5th 2019 --according to *Cambridge University Press*—Moshi et al.(141) has accumulated an *Altmetric* of 11, 107 full PDF views, 11 HTML views, and 789 abstract views.(161)

#### Publication(s)

- Moshi MR, Parsons J, Tooher R, Merlin T. Evaluation of Mobile Health Applications: Is Regulatory Policy Up to the Challenge? (2019). *International Journal of Technology Assessment in Health Care*, 35(4), 351-360.

*Conference proceedings*

- Moshi M, Parsons J, Tooher R, Merlin T, editors. OP143 Assessment of mHealth Apps: Is Current Regulation Policy Adequate? HTAi 2019 Annual Meeting; 2019; Cologne, Germany: Health Technology Assessment International

#### Presentation(s)

- June 2019, **Presentation**, Moshi* MR, Parsons, J, Tooher, R, & Merlin, T. Assessment of mHealth apps: is current regulation policy adequate? *Health Technology Assessment International (HTAi) Annual Meeting*. Cologne, Germany.
    - Award: Short listed for best student presentation

- December 2018, **Presentation**, Moshi, MR., Parsons, J., Tooher, R., & Merlin, T. Assessment of mHealth apps in Australia: is current regulation policy adequate? *South Australian Population Health Conference*, Adelaide, South Australia.
    - Award: Most Popular Presentation

- September 2018, **Poster**, Moshi* MR, Parsons J, Tooher R, Merlin T. Assessment of mHealth apps in Australia: is current regulation adequate? 12th Annual *Florey Postgraduate Research Conference*, Adelaide, South Australia.

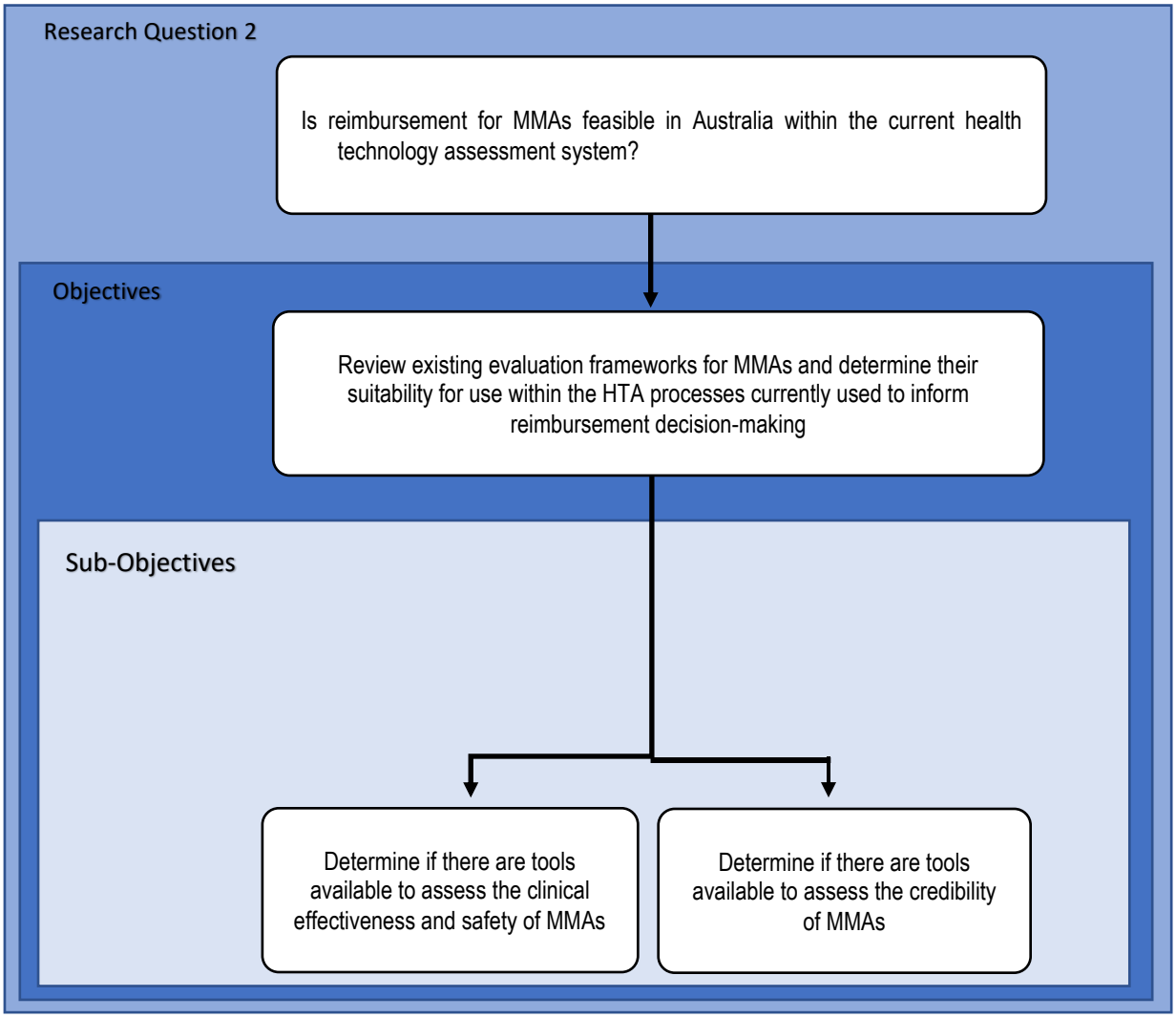
# Chapter 6: The suitability of mobile medical application (MMA) evaluation frameworks for reimbursement purposes

## 6.1 Preface

This chapter explores if reimbursement for MMAs is feasible in Australia within the current HTA system. It achieves this by examining existing MMA evaluation frameworks --available prior to 31st October 2016— to determine if they are suitable to be used for HTA purposes, specifically reimbursement decision-making.

The chapter is aimed at addressing the second research question and its respective objective(s) (see Figure 6.1 below). Figure 3.1 in *Chapter 3* demonstrates how this section relates to the aim of this thesis and the research questions and objective(s).

Figure 6.3: Structure of *Chapter 6's* research question and objectives



This chapter addresses the above research question and objectives using a methodological systematic review detailed in the publication by Moshi, Tooher & Merlin(149) and the corresponding supplementary document (see *Section 6.2*). For additional, information on the methods used in Moshi, Tooher & Merlin(149) see *Chapter 4, Section 4.3*.

The full search strategies used in the included bibliographic databases are described in *Appendix C* and the supplementary information of Moshi, Tooher & Merlin(149). Additionally, the data extraction standardisation tool, as well as a template of the data extraction table, are available in *Appendix C*.

## 6.2 Publication

| | |
|---|---|
| **Title** | The suitability of current evaluation frameworks for use in the health technology assessment of mobile medical applications: a systematic review |
| **Journal** | *International Journal of Technology Assessment in Health Care* |
| **Publication Date** | 11th of September 2018 |
| **DOI** | https://doi.org/10.1017/S026646231800051X |
| **Conditions of publication reuse** | "5.1.2 The Contributor may reproduce the Contribution or an adapted version in any format in any work authored or edited by the Contributor, subject to appropriate acknowledgment"(158) |
| **Version presented in thesis** | Presented as published |

## 6.2.1 Statement of authorship

# Statement of Authorship

| | |
|---|---|
| Title of Paper | Suitability of current evaluation frameworks for use in the health technology assessment of mobile medical applications: A systematic review |
| Publication Status | ☒ Published ☐ Accepted for Publication<br>☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style |
| Publication Details | Moshi MR, Tooher R, Merlin T. Suitability of current evaluation frameworks for use in the health technology assessment of mobile medical applications: A systematic review. International Journal of Technology Assessment in Health Care. 2018;34(5):464-75 |

### Principal Author

| | |
|---|---|
| Name of Principal Author (Candidate) | Magdalena Ruth Moshi |
| Contribution to the Paper | I contributed to the conception of the study, study design, systematic literature review, as well as manuscript preparation and drafting. I also acted as the corresponding author and was responsible for all major and minor revisions. |
| Overall percentage (%) | 80% |
| Certification: | This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper. |
| Signature | Date: 26-09-2019 |

### Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

| | |
|---|---|
| Name of Co-Author | Dr Rebecca Tooher |
| Contribution to the Paper | R. Tooher contributed to the conception of the study as well as study design. She was also assisted in the interpretation of data and results. She provided feedback on the manuscript, and evaluated the revised manuscript against reviewers' comments. |
| Signature | Date: 4/10/19 |

| | |
|---|---|
| Name of Co-Author | Professor Tracy Merlin |
| Contribution to the Paper | T. Merlin contributed to the conception of the study as well as study design. She assisted in the interpretation of data and results. She provided feedback on the manuscript, and evaluated the revised manuscript against reviewers' comments. |
| Signature | Date: 30/9/19 |

## 6.2.2 Complete journal article

### Title

The suitability of current evaluation frameworks for use in the health technology assessment of mobile medical applications: a systematic review

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### Short title

Assessing mobile medical app evaluation frameworks

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## Abstract

### Objective

To identify and appraise existing evaluation frameworks for mobile medical applications (MMA) and determine their suitability for use in health technology assessment (HTA) of these technologies.

### Methods

Systematic searches were conducted of seven bibliographic databases to identify literature published between 2008 and 2016 on MMA evaluation frameworks. Frameworks were eligible if they were used to evaluate at least one of the HTA domains of effectiveness, safety, and/or cost and cost-effectiveness of an MMA. After inclusion, the frameworks were reviewed to determine the number and extent to which other elements of an HTA were addressed by the framework.

### Results

A total of 45 frameworks were identified that assessed MMAs. All frameworks assessed whether the app was effective. Of the 34 frameworks that examined safety, only seven overtly evaluated potential harms from the MMA (e.g. the impact of inaccurate information). Only one framework explicitly considered a comparator. Technology specific elements should be addressed in an HTA of MMAs.

### Conclusion

None of the evaluation frameworks could be used, unaltered, to guide the HTA of MMAs. To use these frameworks in HTA they would need to identify relevant comparators, improve assessments of harms and consider the ongoing effect of software updates on the safety and effectiveness of MMAs. Attention should also be paid to ethical issues, such as data privacy and technology specific characteristics.

### Implications

Existing MMA evaluation frameworks are not suitable for use in HTA. Further research is needed before an MMA evaluation framework can be developed that will adequately inform policymakers.

## Keywords

Technology assessment, health policy/standards, mobile health, mobile applications

## Acknowledgements

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## Funding

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## Conflict of interests

None

## Introduction

Mobile health (mHealth) has the potential to change health systems and how care is delivered.(1) One form of mHealth is mobile medical applications (MMAs), also known as 'apps'. These are a type of software available for mobile platforms (e.g. smartphone, tablet, smartwatch).(1) In a medical context, MMAs may be used by patients to self-manage and/or screen medical conditions, rather than presenting at hospitals or clinics for additional appointments. MMAs may also allow for medical practitioners and/or allied health workers to remotely monitor, screen and manage their patients.(2,3)

A potential barrier to the successful integration of MMAs into health systems is that many come at a cost to the patient, or require in-app purchases, which some patients are unable to afford. While some MMAs may have a negligible costs - and thus will not warrant public funding - others may require subscriptions or come with accessories, such as wearables and implantable devices. Furthermore, medical practitioners and allied health workers that use MMA-based services during a clinical encounter are often unable to claim reimbursement for the interpretation of MMA output or for treatment guided by MMA results.

Health Management Organisations (HMO) in the USA have reimbursed some MMAs since 2013.(4) Similarly, since 2014 private health insurers have reimbursed specific MMAs in Germany.(5,6) It is unclear how these apps were selected for reimbursement, although this may have depended on whether the MMA was approved by the relevant regulatory authority (e.g. the *U.S. Food and Drug Administration (FDA))*.

Countries with tax funded universal healthcare like Australia and Great Britain currently do not reimburse the use of MMAs. However, the *National Institute for Health Care Excellence (NICE)* in Britain is currently investigating ways to assess MMAs and provide guidance on their use.(7,8) If the use of MMAs becomes routine in clinical consultations, MMA-guided care will need to be formally assessed.

This systematic review is part of a larger research project to develop or adapt an evaluation framework for MMAs and determine the feasibility of a reimbursement pathway for MMAs in Australia. The aim of our review was to identify and appraise existing evaluation frameworks for MMAs and determine their suitability for use in health technology assessment (HTA). In this context an evaluation framework was defined as a method for determining an MMA's effectiveness, safety and/or cost, cost-effectiveness.

## Methods

### Literature search

We searched PubMed (MEDLINE), EMBASE, CINAHL, PsychINFO, *The Cochrane Library,* Compendex, and Business Source Complete between January 1st 2008 (when the first publicly accessible online application store opened) and October 31st 2016.(9) We used a broad search strategy including terms for MMAs (e.g. mHealth app*, telehealth app*), mobile platforms (e.g. cellular phone, mobile device) and evaluation (e.g. criteri*, apprais*). Grey literature sources were also searched to identify any relevant material that may have not been identified through the database search. The full search strategy is given in supplementary item 1.

### Study eligibility criteria

Papers were selected for inclusion if they met the pre-determined eligibility criteria. The population of interest were participants aged 18 years or over that used an MMA. The intervention of interest was an MMA evaluation framework. This included frameworks that assessed all mHealth apps, as MMAs are a subset of these. MMAs were defined as mobile apps (including accompanying accessories or attachments) available on various platforms (smartphone, tablets, smart watches etc.) that have a therapeutic or diagnostic intended purpose. Framework(s) aimed solely at assessing pregnancy, health promotion, or disease prevention apps (e.g. medication management, smoking cessation, and weight management) were excluded as the apps' intended purpose was not diagnostic or therapeutic. The outcomes of interest were the core HTA evaluation domains of effectiveness, safety, and/or cost, cost-effectiveness. There was no comparator as the aim of the systematic review was not to determine the effectiveness of these evaluation frameworks but, rather, to identify the HTA domains that they address. Only frameworks available in English were included. Frameworks that were duplicated in several articles were collated and reported as a single record.

#### *Study selection*

Two reviewers *(MM and TM)* screened the literature separately and applied the inclusion criteria. MM reviewed all title and abstracts retrieved from the searches, while TM assessed 10%. The full text articles were screened against the inclusion criteria by MM. Any articles in which MM was unsure of eligibility, were discussed with TM and a consensus decision made. The reference lists of included papers were pearled to identify any additional relevant references.

### Data extraction

The data extracted from the papers included: Author and dates of publication, source affiliation, country of origin, name of framework, study design, description of framework, intended audience/user, type of

MMA, framework scoring system, and HTA domains addressed. The included papers were not critically appraised for study quality as this was a methodological systematic review.

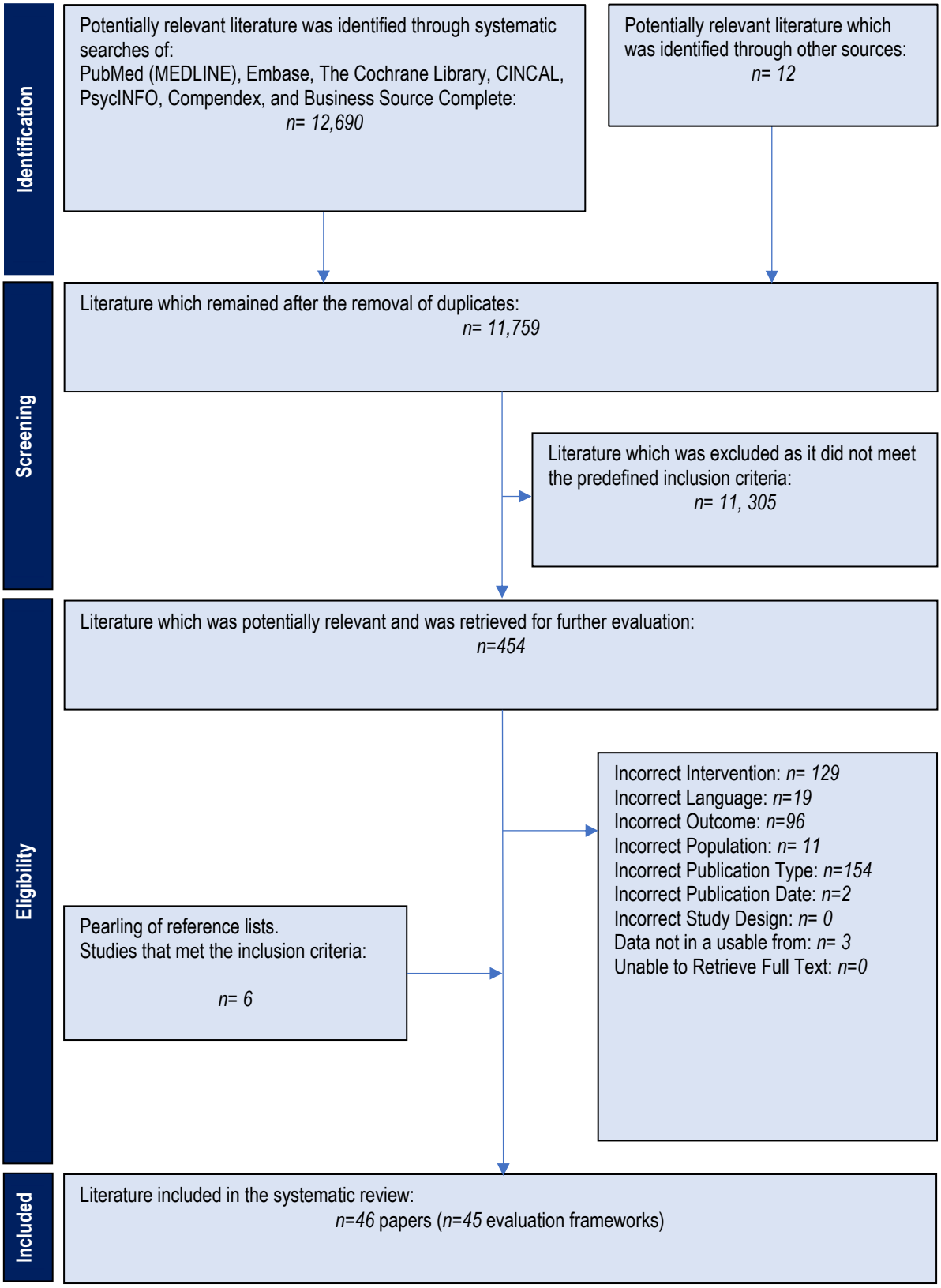
### Framework assessment

A checklist was created to act as a tool to standardise data extraction. Using the checklist, each framework was assessed to determine if it included any of nine traditional HTA domains - six core domains considered essential for full HTA: current use of the technology; description and technical characteristics; effectiveness; safety; cost and cost effectiveness; organisational aspects - and three optional domains: legal aspects; ethical aspects; social aspects.(10,11) The checklist was trialled and tested by an HTA expert and MM and was found to have reasonable inter-rater reliability (Kappa=0.77).

## Results

The systematic searches retrieved 12,690 citations. An additional 12 papers were identified from grey literature sources. Six additional frameworks were identified through the pearling of the included publications' reference lists. Three frameworks were excluded as the information provided was not in a usable form. An evidence base of 46 papers met the inclusion criteria, and two of these papers published on the same framework. Thus, 45 frameworks were identified that assessed whether MMAs are safe, effective and/or cost-effective. Figure 1 illustrates the complete study selection process. Table 1 and Table 2 provide details on all 45 MMA evaluation frameworks.

Figure 4: PRISMA Flow-chart of literature selection



### Overview of frameworks

All of the included frameworks addressed mHealth applications, with 73% (n=33) explicitly assessing MMAs. Most of the frameworks that evaluated MMAs were sourced from universities. The remaining 27% (n=12) were developed by private organisations, institutes, medical schools, or governmental organisations.

The frameworks originated from three geographical regions. Most (49%, n=22) came from North America, while Europe contributed 40% (n=18) and the remaining 11% (n=5) originated from the Asia-Pacific region.

The frameworks that assessed MMAs came in a variety of different formats. Some of these formats included questionnaires, data extraction criteria, flow charts, and varying types of lists. Due to the variety of formats, it was difficult to categorise the frameworks into types. Less than half of the frameworks had a scoring system (Table 1).

Table 1: Description of frameworks

| Author, date | Intended audience | Type of mobile application | Source affiliation[1] | Scoring system in framework | Country of origin[1] |
|---|---|---|---|---|---|
| Albrecht, Von Jan & Pramann (20), 2013 | Patients | MMA | Institute | No | Norway |
| Anxiety and Depression Association of America (ADAA) (38), 2016 | Quality assurance for user protection | MMA | Private organization | Yes | USA |
| Arnhold, Quade & Kirch (57), 2014 | Quality assurance for research setting | MMA | University | Yes | Germany |
| Aungst et al. (32), 2014 | Health professionals | MMA | University | No | USA |
| Basilico et al. (41), 2016 | Quality assurance for research setting | MMA | University | Yes | Italy |
| Beatty, Fukuoka & Whooley (15), 2013 | Patients, health professionals | MMA | University | No | USA |
| BinDhim et al (58), 2015 | Regulators | mHealth | University | Yes | Australia |
| Brooks et al. (39), 2015 | Patients | MMA | University | No | USA |
| Chan et al. (18), 2015 | Patients, health professionals | MMA | University | No | USA |
| Chomutare et al. (59), 2011 | Quality assurance for research setting | MMA | University | No | Norway |
| Demidowich et al.(60), 2012 | Quality assurance for research setting | MMA | Medical school | Yes | USA |
| Drinic et al. (16), 2016 | Patients | MMA | University | No | USA |
| Fairburn & Rothwell (33), 2015 | Quality assurance for research setting | MMA | University | No | UK |
| Ferrero-Alvarez-Rementeria (36), 2013 | All stakeholders in mHealth | mHealth | Governmental organization | No | Spain |
| Gautham, Iyengar, & Johnson, C. W (30), 2015 | Health professionals | MMA | University | No | UK |
| Gibbs et al.(25), 2016 | Quality assurance for research setting | MMA | University | No | UK |
| Grundy et al. (26), 2016 | Patients, health professionals, and app developers | mHealth | University | Yes | Australia |
| Hacking Medicine Institute (HMi) (34), 2016 | Quality assurance for user protection | MMA | Institute | Yes | USA |
| Hoppe, Cade & Carter, (61) (2016) | Patients | MMA | University | Yes | UK |
| Huckvale et al. (27), 2015 | Quality assurance for research setting | MMA | University | Yes | UK |
| IMS Institute for Healthcare Informatics(62), 2013 | Quality assurance for user protection | mHealth | Institute | Yes | USA |
| Jin & Kim (63), 2015 | Health professionals | mHealth | University | Yes | Republic of Korea |
| Kassianos et al.(21), 2015 | Quality assurance for research setting | mHealth | University | No | UK |
| Lalloo et al.(47), 2015 | Quality assurance for research setting | MMA | University | Yes | Canada |
| Lee et al.(42), 2015 | Patients, health professionals, and app developers | MMA | University | No | New Zealand |
| Martinez-Perez et al. (28,29), 2013/2015 | Patients, health professionals | MMA | University | Yes | Spain |
| McMillan et al. (19), 2016 | Quality assurance for research setting | MMA | University | Yes | UK |

| | | | | | |
|---|---|---|---|---|---|
| mHIMSS App Usability Work Group (31), 2012 | Health professionals | mHealth | Private organization | No | USA |
| Mobasheri et al. (64), 2014 | Quality assurance for research setting | MMA | University | No | UK |
| Murfin (24), 2013 | Health professionals | mHealth | University | No | USA |
| Pandey et al.(22), 2013 | Quality assurance for research setting | MMA | University | No | USA |
| Portelli & Eldred (17), 2016 | Quality assurance for research setting | MMA | University | Yes | UK |
| Powell et al.(14), 2016 | Patients, health professionals | MMA | Private organization | Yes | USA |
| Psyber Guide (65), | Quality assurance for user protection | MMA | Private organization | Yes | USA |
| Reynoldson et al. (43), (2014) | Patients | MMA | University | Yes | UK |
| Robustillo Cortes et al. (12), 2014 | Patients | MMA | University | No | Spain |
| Schnall et al. (44), 2015 | Quality assurance for research setting | MMA | University | Yes | USA |
| Shah, Jonassiant & Castro(66), 2014 | Patients | MMA | University | Yes | USA |
| Shaia et al. (45), 2016 | Patients | MMA | Medical school | Yes | USA |
| Shen et al. (46), 2015 | Quality assurance for research setting | MMA | University | No | Canada |
| Singh et al.(37), 2016 | Quality assurance for research setting | MMA | University | No | USA |
| Social Wellth (67), 2016 | Quality assurance for research setting | mHealth | Private organization | Yes | USA |
| Stoyanvo et al. (13), 2015 | Quality assurance for research setting | MMA | University | Yes | Australia |
| Walsworth (40), 2012 | Patients | mHealth | University | No | USA |
| Yasini & Marchard (23), 2015 | Quality assurance for user protection | mHealth | Private organization | No | France |

**Explanatory note:**

[1] Based on first author affiliation.

### Intended audience

The included frameworks had different intended audiences or purposes, such as: MMA developers (n=3), used for quality assurance for user protection (n=13), for patients (n=17), or used for quality assurance in a research setting (n=18). All of these frameworks assessed the HTA domains concerning the current use of the technology, description and technical characteristics, effectiveness, safety, and ethical aspects.

### Intended health condition

The majority of the frameworks were aimed at evaluating MMAs that focused on the treatment, management or diagnosis of chronic health conditions. Diabetes and mental health were the most commonly addressed conditions with 13% (n=6) of the frameworks focused on MMAs for each condition. Cancer and pain were the next most frequently addressed conditions (7%, n=3, each). Three frameworks (7%) were aimed at MMAs managing sexuality transmitted infections (STI), with two of these focused specifically on the human immunodeficiency virus (HIV).

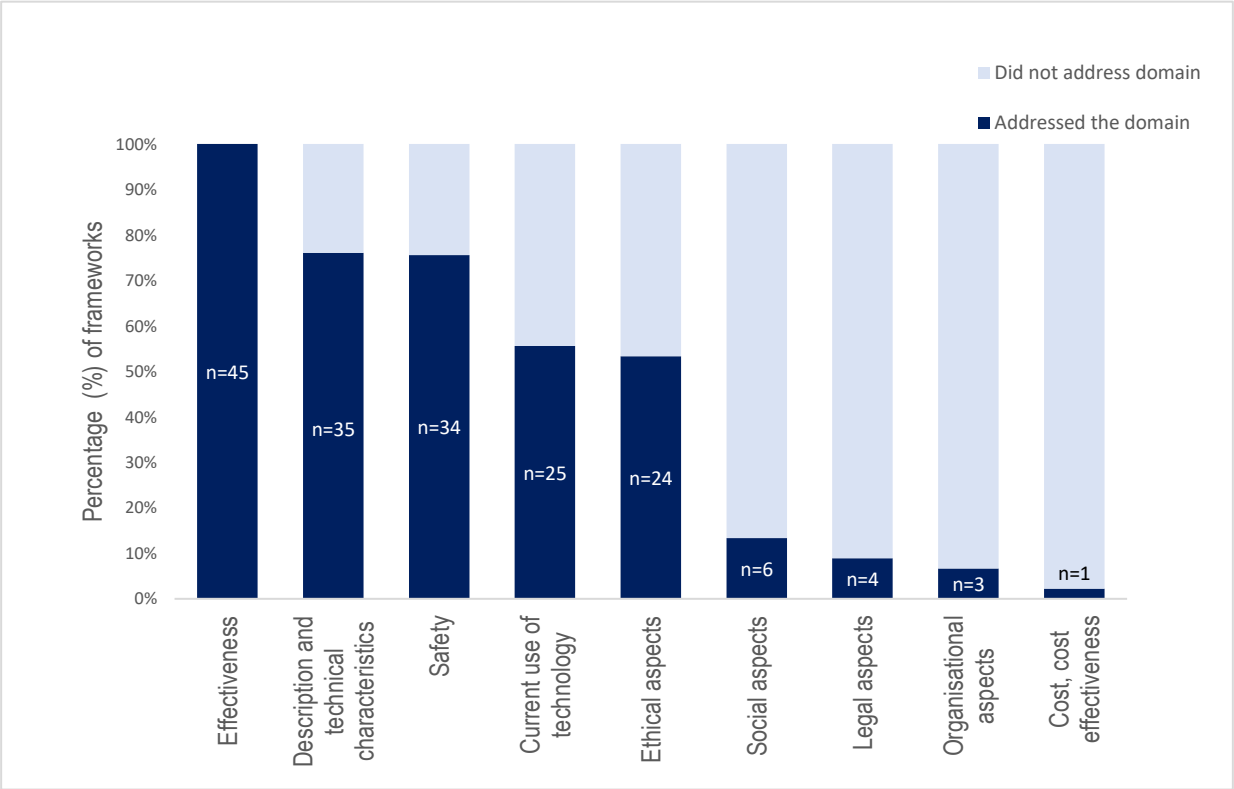
### Critical appraisal of the evidence-base underpinning the MMA

The credibility of the information included in an MMA was assessed by 15 (33%) frameworks, including through: level of evidence or grade of the recommendation (12,13); assessment in a randomised controlled trial (RCT) (13-15); study design (i.e. clinical trial, controlled trial) (16,17); improved health outcomes (18); sample size, intervention fidelity and evaluation design (19); and publication in peer-reviewed journals (20-23). Powell et al.(14), Beatty et al.(15), and Stoyonavov et al.(13) specifically question if the MMA was clinically tested using RCTs. Stoyonaov et al.(13) asked whether, the MMA has been verified through trialling/testing, ranking the responses with the lowest being no RCTs and the highest being multiple RCTs. One framework considered whether a systematic review or meta-analysis had been conducted about the MMA and topic area.(24) Furthermore, 27 (60%) of the included frameworks asked about the MMA's source of information.

### Health technology assessment (HTA) domains

More than half of the assessed frameworks included the following HTA domains: MMA effectiveness; description of technical characteristics; safety; current use of the technology; and ethical aspects (Figure 2). Five frameworks assessed 6 domains,(19,25-29) whereas two frameworks only assessed a single domain (Table 2).(30,31) The average number of domains addressed was four ($\bar{x} = 3.9$).

Figure 2: The proportion of frameworks that address each HTA domain




### Core HTA domains

#### Effectiveness

Every framework assessed the effectiveness of MMAs in some capacity. Eleven frameworks (24%) evaluated user satisfaction. Thirty (67%) frameworks evaluated the technical efficacy of MMAs. Beatty, Fukuokam & Whooley.(15), Drinic et al.(16), and McMillan et al.(19) appraised efficacy of the applications, but did not provide any further detail of what they meant; it could interpreted as both therapeutic and/or diagnostic effectiveness. Only one framework explicitly considered comparative effectiveness.(32) Aungst et al.(32)'s framework asked whether an MMA already exists for the current reference condition (clinical tool used in practice).

Table 2: HTA domains addressed by each framework

| Author, date | Health technology assessment (HTA) domains | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Domains addressed in a full HTA | | | | | | Auxiliary domains addressed in a full HTA | | |
| | Current use of the technology | Characteristics of the technology | Effectiveness | Safety | Cost, cost-effectiveness | Organisational aspects | Legal aspects | Ethical aspects | Social aspects |
| Albrecht, Von Jan & Pramann (20), 2013 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✓ | ✗ |
| Anxiety and Depression Association of America (ADAA) (38), 2016 | ✗ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Arnhold, Quade & Kirch (57), 2014 | ✗ | ✗ | ✓ | ✗ | ✗ | ✗ | ✗ | ✓ | ✗ |
| Aungst et al. (32), 2014 | ✗ | ✗ | ✓ | ✓ | ✗ | ✓ | ✗ | ✗ | ✗ |
| Basilico et al. (41), 2016 | ✓ | ✓ | ✓ | ✓ | ~ | ✗ | ✗ | ✗ | ✗ |
| Beatty, Fukuoka & Whooley (15), 2013 | ✗ | ✓ | ✓ | ✓ | ~ | ✗ | ✗ | ✗ | ✓ |
| BinDhim et al (58), 2015 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Brooks et al. (39), 2015 | ✗ | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Chan et al. (18), 2015 | ✗ | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✗ |
| Chomutare et al. (59), 2011 | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Demidowich et al.(60), 2012 | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Drinic et al. (16), 2016 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Fairburn & Rothwell (33), 2015 | ✓ | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Ferrero-Alvarez-Rementeria (36), 2013 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✓ | ✗ |
| Gautham, Iyengar, & Johnson, C. W (30), 2015 | ✗ | ✗ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Gibbs et al.(25), 2016 | ✓ | ✓ | ✓ | ✓ | ~ | ✗ | ✓ | ✓ | ✗ |
| Grundy et al. (26), 2016 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✓ | ✓ | ✗ |
| Hacking Medicine Institute (HMi) (34), 2016 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✓ | ✗ |
| Hoppe, Cade & Carter, (61) (2016) | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Huckvale et al. (27), 2015 | ✓ | ✓ | ✓ | ✓ | ~ | ✗ | ✓ | ✓ | ✗ |
| IMS Institute for Healthcare Informatics(62), 2013 | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Jin & Kim (63), 2015 | ✗ | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✓ | ✗ |
| Kassianos et al.(21), 2015 | ✗ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Lalloo et al.(47), 2015 | ✗ | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✓ |
| Lee et al.(42), 2015 | ✓ | ✓ | ✓ | ✓ | ~ | ✗ | ✗ | ✓ | ✗ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Martinez-Perez et al. (28,29), 2013/2015 | ✗ | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ |
| McMillan et al. (19), 2016 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✓ | ✓ |
| mHIMSS App Usability Work Group (31), 2012 | ✗ | ✗ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Mobasheri et al. (64), 2014 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✓ | ✗ |
| Murfin (24), 2013 | ✗ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✓ | ✗ |
| Pandey et al.(22), 2013 | ✓ | ✗ | ✓ | ✓ | ~ | ✗ | ✗ | ✓ | ✗ |
| Portelli & Eldred (17), 2016 | ✗ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✓ |
| Powell et al.(14), 2016 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✓ | ✗ |
| Psyber Guide (65), | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✓ | ✗ |
| Reynoldson et al. (43), (2014) | ✓ | ✓ | ✓ | ✓ | ~ | ✗ | ✗ | ✓ | ✗ |
| Robustillo Cortes et al. (12), 2014 | ✗ | ✓ | ✓ | ✓ | ✗ | ✗ | ✓ | ✓ | ✗ |
| Schnall et al. (44), 2015 | ✓ | ✓ | ✓ | ✗ | ~ | ✗ | ✗ | ✗ | ✗ |
| Shah, Jonassiant & Castro(66), 2014 | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Shaia et al. (45), 2016 | ✓ | ✓ | ✓ | ✓ | ~ | ✗ | ✗ | ✓ | ✗ |
| Shen et al. (46), 2015 | ✓ | ✓ | ✓ | ✓ | ~ | ✗ | ✗ | ✓ | ✗ |
| Singh et al.(37), 2016 | ✗ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✓ | ✓ |
| Social Wellth (67), 2016 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✓ | ✗ |
| Stoyanvo et al. (13), 2015 | ✓ | ✓ | ✓ | ✓ | ~ | ✗ | ✗ | ✓ | ✗ |
| Walsworth (40), 2012 | ✓ | ✗ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ |
| Yasini & Marchard (23), 2015 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |

**Explanatory note:**

✓ Domain was addressed; ~ Domain was partially addressed ; ✗ Domain was not addressed

### Investigative MMAs

The diagnostic accuracy of MMAs was assessed by 29% (n=13) of the frameworks. Martinez-Perez et al.(28,29) reviewed the accuracy of an MMA's calculations. Stoyanov et al.(13), Powell et al. (14), Fairburn & Rothwell(33), Gibbs et al.(25), and Murfin(24), all assessed the accuracy or specificity of the information given in the MMAs, while HMi(34) reviewed the MMA's clinical credibility. Powell et al.(14) included four response options which rated how the MMA was designed to improve a specific condition, whereas Gibbs et al.(25) ranked the accuracy of the information also using four options. None of the 13 frameworks assessed subsequent changes in patient or decision-making management associated with use of the MMA (a necessary domain for determining the effectiveness of investigative interventions).(35) Furthermore, none of the included frameworks assessed the clinical utility of MMAs, i.e. the health impacts of an MMA that provides diagnostics information.

### Therapeutic MMAs

Therapeutic effectiveness was assessed by 71% (n=32) of the frameworks. Three frameworks addressed primary patient-relevant outcomes including quality of life and mortality,(16,18,19) whereas, 25/32 (78%) made provision for the reporting of surrogate outcomes (e.g. physiological, biochemical, and/or behaviour change parameters); for example, a diabetes management MMA that could log glucose (HbA1C) readings, or an HIV management app that could track T-cell counts.

### Safety

Safety was addressed in 34 (76%) frameworks with 27 (79%) of these assessing the source of the information used by the MMA, and three appraising how the information sources were selected. Only seven frameworks evaluated the harms of the app itself (e.g. adverse events).(14,18,19,26,32,36,37) Six frameworks addressed whether the MMA had been trialled or tested and whether safety concerns had been identified during the process.(15,16,20,22,38,39)

### Cost, cost-effectiveness

Only one framework assessed the cost-effectiveness domain by asking whether a health economic evaluation had been conducted.(40) However, this domain was partially addressed by 11 (24%) frameworks that reviewed the cost of MMAs in terms of the price to download the application or to undertake in-app purchases.(13,15,22,25,27,41-46)

### Current use of the technology

The current use of the technology was assessed by 25 (55%) of the frameworks. Seventeen assessed (68%) usage of the MMA (e.g. rates, utilisation, trends), 16 (64%) assessed the intended user population and 15 (60%) considered the intended purpose of the app (e.g. diagnosis, management, or treatment).

### Description and technical characteristics

Technical characteristics of MMAs were assessed by 78% (n=35) of the frameworks. The type of device (e.g. mobile platform, operating systems, software versions) was evaluated in 23 (67%) frameworks and 19 (54%) evaluated whether experts were consulted during the development of the app. Eleven (31%) assessed whether the MMA had communicative capabilities (e.g. communication with personal health records, communication with electronic health records, and healthcare provider-patient communication), and 8 (23%) considered whether the MMA had personalisation capabilities.

### Organisational aspects

Only three (7%) of the included frameworks assessed whether the MMA would have organisational implications. Two of the frameworks recorded if any training was needed to use the application and if adopting the MMA would alter the utilisation of existing services.(18,28,29) One framework assessed whether the MMA would alter the daily practices of clinicians.(32)

### Optional HTA domains

#### Legal aspects

Four (9%) of the identified frameworks assessed the legal implications of MMAs.(12,25-27) Three of these determined whether there were legal implications by asking whether the MMA had a disclaimer concerning clinical accountability.(12,25,26) Two of the frameworks required consideration of the possibility of copyright infringement.(26,27)

#### Ethical aspects

Ethical considerations were examined by 24 (53%) frameworks. Of these, 18 (75%) recorded whether the MMA had a privacy policy (though only four considered the individual content of the privacy policy); 18 (75%) evaluated patient confidentiality provisions in the app; and 14 (58%) assessed conflicts of interest (e.g. affiliation, funding, third party sponsorship). Four (17%) frameworks appraised equity (e.g. socioeconomic status, disability, language, and age),(13,18,27,43) and an additional four (17%) frameworks assessed MMA accessibility (e.g. geographical location).(19,27-29,42)

### Social aspects

Six (13%) frameworks assessed how the MMA provides social support to the users, (15,17,28,29,37,47) for example, whether the MMA provides psychosocial support, if the MMA can provide support through social media, or if access to social support is facilitated.

## Discussion

None of the included frameworks could be used "off the shelf" to evaluate MMAs in a full HTA requiring assessment across all six core HTA domains. Frameworks by Grundy et al.(26), Hacking Medicine Institute (HMi)(34), Huckvale et al.(27), Martinez-Perez et al.(28,29), and McMillan et al.(19) all assessed six HTA domains, but none of these addressed all of the six core domains. Ethical, social and legal considerations are frequently omitted in typical HTAs. However, we found that, for MMA specific evaluations, ethical issues were often addressed, whereas organisation of care, and cost and cost-effectiveness domains, together with legal considerations, were the least likely to be addressed.(11)

## Safety

Nearly a quarter of the evaluation frameworks did not assess safety in any capacity. Only five (16%) frameworks explicitly considered the MMA's ability to cause harm or adverse events. None of the frameworks explicitly assessed the comparative safety of the MMA with reference to other MMAs or current clinical practice without use of an MMA. It is possible that evaluators of MMAs do not find safety as important a concern as the effectiveness this technology. MMAs with attachments (such as glucometers, oximeters, or electrocardiogram leads) that have the potential to physically harm, may be more obvious candidates for safety assessment, rather than the individual MMA itself.

A further concern regards the source of information on which the assessment of safety was based. We found that only one quarter of frameworks checked this factor. Lack of attention to information sources is problematic because of the potential harms caused by misinformation. The *International Medical Device Regulators Forum (IMDRF)(48)* states that the greatest risks and benefits posed by software which acts as a medical device (SaMD) - such as an MMA - relates to its output and how it impacts on a patient's clinical management or other healthcare related decisions, not from direct contact with the device itself. Apps which utilise poor/weak evidence bases could present a range of clinical harms. For example, chronically ill patients using medication incorrectly due to inaccurate feedback from the MMA; rehabilitation patients doing inappropriate exercises; or, potentially more seriously, the long-term consequences to health of receiving a false negative diagnosis from an investigational MMA. However, both the physical harm and risks associated with misinformation are of interest in an HTA and may affect subsequent policy decisions, regarding access to, or reimbursement of MMAs.

## Effectiveness

Normally to assess the effectiveness of an intervention in an HTA, the results of the intervention are compared to current practice or an existing intervention. However, only one of 45 frameworks considered in this systematic review referred to the availability of a comparator MMA or to the current management

of the condition without the MMA. Without a comparator identified it is impossible to adequately assess the effectiveness of an MMA or conduct a full HTA that could inform policy decision making.

### Investigative MMAs

The safety and effectiveness of an investigative medical service can be determined through direct or linked evidence.(35,49-51) None of the included frameworks appeared to use a direct evidence approach to evaluate an MMA. Frameworks did address the diagnostic accuracy of an MMA, however, none linked this to subsequent changes in management or healthcare decision-making. In any case, those frameworks that assessed the diagnostic accuracy of MMAs did not collect sufficient information to enable a full assessment.

### Therapeutic MMAs

In the evaluation of a therapeutic medical service safety and effectiveness can be determined through direct randomised trials (preferred), indirect comparisons of randomised trials, or non-randomised trials, and observational studies. The purpose of this evidence is to identify the best available clinical evidence for the primary indication relative to the main comparator.(50,51) None of the included frameworks adequately addressed the key elements evaluated to demonstrate the therapeutic effectiveness of an MMA, with only seven frameworks considering the quality of the evidence base (such as whether clinical trials were considered or what health outcomes eventuated from use of the MMA).

### Cost and cost-effectiveness and organisational Issues

The frameworks did not consider the impact that the direct costs of an MMA would have on the current health system, or the potential effect on other medical services or devices (Table 2). Only one framework, by Walsworth(40), addressed cost and cost-effectiveness and it only assessed if the value of the MMA justified the cost. Formal economic evaluations of the value for money associated with the use of the MMA was not required by any of the identified evaluation frameworks. It may be that the cost impact of MMAs is considered to be trivial and therefore cannot justify a formal economic evaluation; the cost of some MMAs is small. However, costs do not just relate to the unit price of the MMA but also to downstream costs associated with behaviour affected by the MMA.

Although no single framework addressed all of the information necessary for an HTA of an MMA, there were elements considered across the frameworks that if combined could produce a comprehensive evaluation framework. Technology-specific characteristics are particularly relevant.

### Technology specific considerations

There are a number of technology specific considerations that may need to be addressed when conducting an HTA on an MMA.

The first is a requirement to assess ethical aspects, specifically data privacy. Over half of the frameworks identified had assessed ethical issues concerned with MMAs. Connectivity to the internet, networks and other devices through a portable handheld device (i.e. smartphone or tablet) is a unique vulnerability of apps that are used for medical purposes. If the MMA is jeopardised (e.g. hacked or viruses), there is the potential to compromise sensitive personal health information.(52,53) The *IMDRF(54)* regards security concerns relating to the privacy and confidentiality of data (of an SaMD) as safety concerns. The accessibility, availability, and integrity of the device output are crucial for patient treatment and diagnoses.(54) A further concern is that companies have been known to sell consumer data.(55) The *FDA*(52,53) has attempted to address cybersecurity concerns by publishing pre and post market guidance documents which provide recommendations for the management of cyber threats to medical devices.

Secondly, compatibility and connectivity concerns are important for the evaluation of MMAs. MMA performance may vary between different platforms (i.e. smartphone, tablet, or smartwatch), with different operating systems (i.e. Android vs iOS), and for different generations of the same device (i.e. iPhone 5 vs iPhone 6). Additionally the impact of software updates must also be allowed for, as MMAs are a dynamic technology which is constantly changing. One update that makes an incremental change to the MMA may not alter its intended purpose. However, multiple subsequent incremental updates may change the intended purpose of the MMA.(56) As highlighted by the IMDRF(54), if not managed systematically, any modification (e.g. updates) to the software throughout its lifecycle – including maintenance - poses a risk to the patient. A full HTA that is used to inform policy decisions regarding an MMA may need to assessing these compatibility and connectivity concerns to ensure that the app is consistent across various platforms, operating systems, and devices, as well as identify when software modifications such as updates, should trigger reassessment of the MMA.

### Key components of an MMA evaluation framework

MMA evaluation frameworks intended to appraise apps for HTA purposes should include: consideration of a comparator; a complete assessment of safety and harms from misinformation; a more detailed evaluation of ethical issues such as equity and secure management of confidential data; a consideration of the impact of software updates on the safety and effectiveness of the MMA. It is difficult to determine from this systematic review whether social, legal, and organisational aspects, or the cost and cost effectiveness of MMAs should be evaluated. It would be helpful to identify indicators that could trigger an assessment of these factors. More research is needed to determine the concepts that should be included

in an MMA evaluation framework for HTA purposes and what structure the framework could take. For example, would the structure of such a framework follow the HTA domains or use another categorisation method which is more suitable to address the unique challenges presented by MMAs (e.g. development quality, information security, technical considerations).

The second stage of our research project is to conduct interviews with MMA developers, health professionals and policy makers to identify factors important in the use, assessment and reimbursement of MMAs.

### Limitations

As with any systematic review there were some limitations with the research. There is a risk of publication bias, although we attempted to limit this by conducting grey literature searches and including all frameworks in the review that met the selection criteria. Another possible limitation was that the checklist we created to standardise and identify which HTA domains the frameworks addressed, could have been idiosyncratic. The tool was pilot tested by an HTA expert and found to have fair inter-rater reliability. The use of the core HTA domains to assess the MMA evaluation frameworks may have limited the concepts identified. To address this, we have also highlighted a number of technology-specific considerations that would need to be included in a HTA of MMAs.

## Conclusion

In conclusion, none of the 45 identified frameworks could be used, unaltered, to assess an MMA in a full HTA to inform a policy decision. While several of the identified MMA evaluation frameworks addressed up to six of the HTA domains, there was a lack of detail that would be required to undertake a full HTA. To adapt these frameworks for use in the HTA of MMAs there would need to be greater consideration of the comparator, and a fuller assessment of the harms associated with MMAs. Our results also indicate that an HTA of an MMA should pay particular attention to the ethical issues associated with the technology, in particular to the secure handling of confidential data. The impact of MMA updates on overall conclusions of safety and effectiveness would also need consideration.

## Policy implications

This research has various policy implications. Firstly, there is a need to develop an MMA evaluation framework that is compatible with HTA and addresses all of the relevant policy concerns. Further information is needed from developers and users of apps about the technology-specific characteristics of MMAs that would need to be addressed in a HTA evaluation framework to inform policy decisions on MMAs. Secondly, due to technology specific considerations, such as the app development cycle, varying platforms, and cybersecurity risks, regulatory and reimbursement authorities may need to work collaboratively with each other if MMAs are to be safely integrated into clinical practice and healthcare delivery.

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### 6.2.3 Supplementary material

## Literature search terms and strategy

### Search strategy

The search strategies used in all electronic bibliographic databases were based on the search terms described below. The search strategy in Table S.1 is an example of a strategy that was used in medical bibliographic databases and Table S.2 is an example of the one used in engineering databases.

### Search terms for mobile medical applications (MMA)

Several search terms were used for mobile medical applications (MMA). These included terms used to describe MMAs, mobile health (mHealth) apps, and mobile apps in general. Search terms for telemedicine (including telehealth) and electronic health (eHealth) were also included as they are sometimes used interchangeably with mHealth.(1)

### Search terms for mobile platforms

A variety of search terms were used for mobile platforms. Similar to the MMA strategy several terms were used to describe the devices. These terms include various names for cell phones, 'smart' devices, the operation systems the platforms run, and the commercial names of popular devices. It was important to include a wide array of search terms for cell phones and related devices as indexing terms for smartphones in some databases were only added recently (2016). Indexing terms for mobile phones were implemented in 2003 – predating the 2008 cut-off.(2,3)

### Search terms for evaluation

Additional search terms were included for evaluation (assessment).

Table S.1: Search strategy for *PubMed (MEDLINE)*

| Mobile Medical Applications (MMA) | Mobile Platform |
|---|---|
| (mobile applications[mh] OR mobile app*[tw] OR portable electronic app*[tw] OR mHealth app*[tw] OR portable software app*[tw] OR mobile medical app*[tw] OR mobile health app*[tw] OR telemedicine[mh] OR telemedicine app*[tw] OR telehealth app*[tw] OR electronic health app*[tw] OR eHealth app*[tw]) | AND (cell phones[mh] OR cell phone*[tw] OR cellular phone*[tw] OR cellular telephone*[tw] OR mobile phone*[tw] OR mobile[tw] OR mobile device*[tw] OR mobile platform*[tw] OR smartphone[mh] smartphone*[tw] OR smart phone*[tw] OR android*[tw] OR ipad*[tw] OR iphone*[tw] OR apple watch*[tw] OR smart watch*[tw] OR tablet*[tw] OR iOS[tw] Blackberr*[tw] OR windows[tw] OR Microsoft[tw] OR google[tw] OR apple OR HTC[tw]) |

Table S.2: Search strategy for *Compendex*

| Mobile Medical Applications (MMA) | Evaluation | Other |
|---|---|---|
| ("mobile medical app" OR "mobile health app" OR "mobile health application" OR "mobile health app" OR “telemedicine app” OR “telemedicine application” OR “mHealth app” OR “mhealth application” OR “eHealth app” OR “eHealth application” OR “telehealth app” “telehealth application”) | AND (evaluat* OR criteri* OR apprais*) | AND medic*<br><br>(tool* OR framework*) |

## Grey literature search strategy

*In addition to the literature searches in electronic bibliographic databases several grey literature sources were searched to identify any relevant MMA related evaluation frameworks that were not available in the published literature. These sources are listed in Tables S.3, S.4, and S.5.*

Table S.3: Internet

| Source | Location |
|---|---|
| *IMS Institute for Health Informatics* | http://www.imshealth.com/ |
| *MIT Hacking Medicine Institute* | http://hackingmedicine.mit.edu/ |
| *Mobihealthnews* | http://www.mobihealthnews.com/ |
| *Mobile World Capital* | *http://mobileworldcapital.com/* |
| *Sax Institute* | https://www.saxinstitute.org.au/ |
| *Science.gov* | *http://www.science.gov/* |
| *The Commonwealth Fund* | http://www.commonwealthfund.org/ |
| *World Health Organisation (WHO)* | http://www.who.int/en/ |

Table S.4: Speciality websites

| *Source* | *Location* |
|---|---|
| *Indigenous Australian HealthInfoNet* | *http://www.healthinfonet.ecu.edu.au/* |
| *International Medical Device Regulator Forum (IMDRF)* | *http://www.imdrf.org/index.asp* |

Table S.5: Sub-jurisdictional

| Source | Location |
|---|---|
| *National Health Services (NHS), England* | http://www.nhs.uk/Pages/healthappslibrary.aspx |
| *Victorian Health Promotion Foundation (VicHealth)* | https://www.vichealth.vic.gov.au/media-and-resources/vichealth-apps |

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## 6.3 Postface

### 6.3.1 Chapter summary

The systematic review addressed the second research question of this thesis which was aimed at determining if it is feasible to evaluate MMAs within the current Australian HTA system. It achieved this by reviewing the existing MMA evaluation frameworks --available prior to 31st October 2016— to determine if any are suitable to be used to inform HTA purposes and/or reimbursement decision-making. The systematic review found that from the 45 MMA evaluation frameworks included, none of them could be used without any alterations to conduct a full HTA on apps. Of the frameworks which did review up to 6 HTA domains, none of them evaluated MMAs with enough detail to properly undertake an assessment of the wider health and societal implications of apps. This was due to the lack of consideration of the harms presented by MMAs (i.e. misinformation) and the need for fuller consideration of a comparator (i.e. comparative safety, comparative effectiveness and comparative cost-effectiveness).

The research also found that not only are current MMA frameworks unsuitable for conducting a HTA on MMAs, but, the current HTA system in Australia may also need to be adapted to properly review the dynamic nature of MMAs. A large proportion of the technology specific MMA considerations identified related to ethical concerns. These considerations include, but are not limited to, concerns around the proper and secure management of confidential data. Additional technology specific concerns which need to be considered, are the effect of software updates on the safety and effectiveness of MMAs as well as how the app performance may be altered on different OS, platforms, and generations of the same platform.

In conclusion, using current HTA processes in Australia, decision making regarding MMA reimbursement would be based on insufficient and potentially misleading information. The collation of current MMA evaluation frameworks has highlighted technology-specific information that is not incorporated in existing HTA guidance in Australia. Unfortunately, none of the identified MMA evaluation frameworks are fit-for-purpose for informing policy decisions – the target audience was different. Changes need to be made to current Australian HTA processes to ensure that the methodology evaluates some of the technology specific challenges presented by MMAs.

### 6.3.2 Update

Since the publication of Moshi, Tooher & Merlin(149), no other systematic review has been conducted that reviews the suitability of MMA evaluation frameworks for use in HTA.

### 6.3.3 Publications and presentation of chapter findings

Between September 11th 2018 and December 5th 2019 --according to *Cambridge University Press*-- Moshi, Tooher & Merlin(149) has accumulated an *Altmetric* of 5, 347 full PDF views, 48 HTML views, and 1153 abstract views. On December 5th 2019 Moshi, Tooher & Merlin(149) had 3 citations and was the second highest *Altmetric* of the 5th issue of the 34th volume of the *International Journal of Technology Assessment in Health Care*.(162)

#### Publication(s)

- Moshi MR, Tooher R, Merlin T. Suitability of current evaluation frameworks for use in the health technology assessment of mobile medical applications: A systematic review. *International Journal of Technology Assessment in Health Care*. 2018;34(5):464-75.

#### Presentation(s)

- October 2018, **Rapid Fire Presentation**, Moshi* M, Tooher R, Merlin T, Assessment of mHealth apps in Australia: is current regulation adequate?, Suitable frameworks for mHealth app evaluation in Australian healthcare reimbursement*, The Annual Scientific Meeting of the Australasian Epidemiological Association*, Freemantle, Western Australia, Australia

- October 2018, **Poster**, Moshi* M, Tooher R, Merlin T, Assessment of mHealth apps in Australia: is current regulation adequate?, Suitable frameworks for mHealth app evaluation n Australian healthcare reimbursement*, The Annual Scientific Meeting of the Australasian Epidemiological Association*, Freemantle, Western Australia, Australia

- October 2017, **Presentation**, Moshi* M, Tooher R, Merlin T, A systematic review on assessing the appropriateness of current mHealth app evaluation frameworks for the appraisal of apps in Australian healthcare reimbursement decision-making, *State Population Health Conference*, Adelaide, South Australia, Australia.

- September 2017, **Poster**, Moshi* MR, Tooher R, Merlin T, Appraising the suitability of mHealth app evaluation frameworks to inform public funding decisions in Australia: a systematic review, *11th Annual Florey Postgraduate Research Conference,* Adelaide, South Australia.

# Chapter 7: Evaluative module for assessing mobile medical applications (MMA)

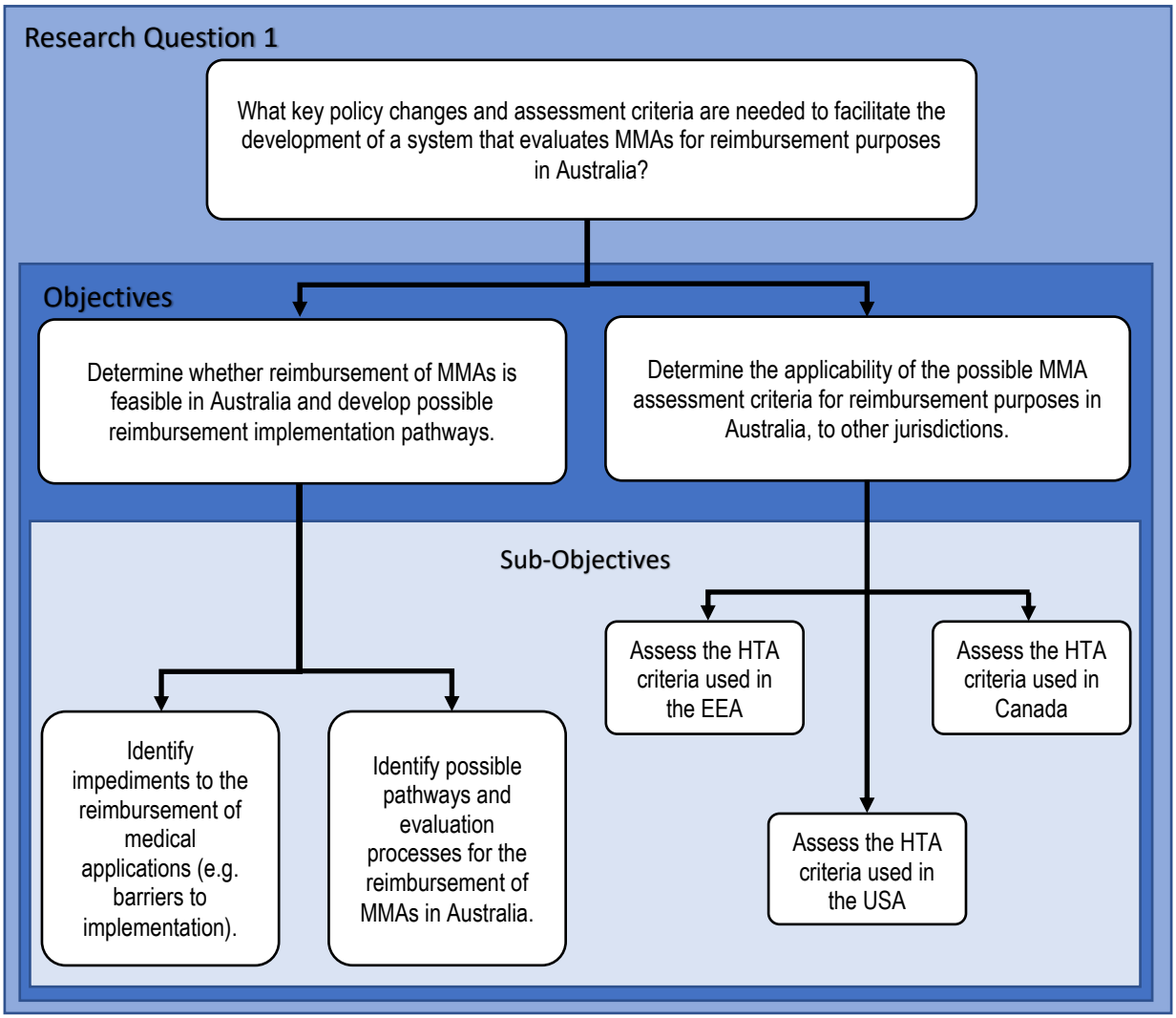
*Development of a health technology assessment (HTA) evaluative module for assessing MMAs for reimbursement and decision-making purposes*

## 7.1 Preface

This chapter explores the policy changes and assessment criteria needed to facilitate the development of a process for evaluating MMAs for reimbursement purposes in Australia. It achieves this through synthesising the findings from *Chapters 5 and 6* with the results of newly conducted stakeholder (app developers, policymakers, healthcare workers) interviews. The findings of the synthesis and interviews were then used to create an evaluation module that could be used to adapt the current Australian HTA evaluation framework for the assessment of MMAs.

This chapter is aimed at answering the third research question and its respective objective(s) as given in Figure 7.1. How the third research question and objectives relate to the other research questions is illustrated in Figure 3.1 in *Chapter 3*.

Figure 7.1: Structure of *Chapter 7's* research question and objectives



The publication included in this chapter combines and synthesises the results from *Chapters 5 and 6* with the results of in-depth interviews undertaken to identify stakeholder groups' (medical practitioners, application developers, and policymakers) views on possible pathways and impediments to MMA reimbursement in Australia. Moshi et al.(141) in *Chapter 5* reviewed the Australian regulatory model for MMAs and identified the changes that are needed to properly assess the possible health risk and benefits posed by the technology. Moshi, Tooher, and Merlin(149) in *Chapter 6* determined whether reimbursement of MMAs is possible within the current Australian HTA system. The findings from both of these chapters were used to scaffold interviews held with stakeholder groups to elicit their views on the feasibility of MMA reimbursement in Australia. The findings from *Chapter 5*, *Chapter 6*, and the stakeholder interviews were integrated to create an MMA module for evaluating MMAs for reimbursement and decision-making purposes.

The interview schedules for the different stakeholder groups, the ethical clearance, the recruitment email, participant information sheet, as well as templates for consent forms for teleconference and in-person interviews are given in *Appendix D*.

The second section of this chapter (*Section 7.3*) explores the second objective and explores the possibility of the MMA module being applied internationally. The focus was determining if the MMA HTA evaluation module developed for the domestic healthcare context could be transferred and applied to evaluate apps for reimbursement and decision-making purposes in jurisdictions similar to Australia.

## 7.2 Manuscript submitted for publication

| | |
|---|---|
| **Title** | Development of a health technology assessment module for evaluating mobile medical applications |
| **Journal** | *International Journal of Technology Assessment in Health Care* |
| **Date submitted for publication** | 22nd of October 2019 |
| **Status of manuscript** | Under-review |
| **Conditions of publication reuse** | "5.1.2 The Contributor may reproduce the Contribution or an adapted version in any format in any work authored or edited by the Contributor, subject to appropriate acknowledgment"(158) |
| **Version presented in thesis** | Presented as submitted |

### 7.2.1 Statement of authorship

# Statement of Authorship

| | |
|---|---|
| Title of Paper | Development of a health technology assessment module for evaluating mobile medical applications |
| Publication Status | ☐ Published ☐ Accepted for Publication<br>☒ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style |
| Publication Details | Moshi MR, Tooher R, Merlin T. Development of a health technology assessment module for evaluating mobile medical applications. International Journal of Technology Assessment in Health Care. |

## Principal Author

| | |
|---|---|
| Name of Principal Author (Candidate) | Magdalena Ruth Moshi |
| Contribution to the Paper | I contributed to the conception of the study and study design. I recruited all interview participants. I then conducted all the in-depth interviews and analysed them. Additionally, I developed and tested the module. I then, prepared the manuscript and am the corresponding author. I will be responsible for all major and minor revisions. |
| Overall percentage (%) | 80% |
| Certification: | This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper. |
| Signature | Date 3-12-19 |

## Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

| | |
|---|---|
| Name of Co-Author | Dr Rebecca Tooher |
| Contribution to the Paper | R. Tooher contributed to the conception of the study as well as study design. She was also assisted in the interpretation of data and results. She provided feedback on the manuscript, and evaluated the revised manuscript against reviewers' comments. |
| Signature | Date 3/12/19 |

| | |
|---|---|
| Name of Co-Author | Professor Tracy Merlin |
| Contribution to the Paper | T. Merlin contributed to the conception of the study as well as study design. She assisted in the interpretation of data and results. She provided feedback on the manuscript, and evaluated the revised manuscript against reviewers' comments. |
| Signature | Date 3/12/19 |

### 7.2.3 Complete manuscript

## Title

Development of a health technology assessment module for evaluating mobile medical applications

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## Abstract

**Objective**

The aim of this study was to develop a module which could be used to facilitate the assessment of mobile medical applications (MMA) for regulatory and reimbursement purposes.

**Methods**

In-depth interviews were conducted with policymakers, healthcare practitioners, and application developers to determine possible pathways and impediments to MMA reimbursement. These findings built upon with our previous research on MMA reimbursement and regulation in order to create a module which could be used with existing HTA methodological frameworks to guide the evaluation of MMAs.

**Results**

Stakeholders indicated that they *trust* how traditional medical devices are currently appraised for reimbursement and would like something similar for MMAs. They were concerned that there was a lack of clarity regarding which entity was responsible for app quality. There were also concerned about the *digital health literacy* of medical practitioners and patients. When evaluating MMA software changes, connectivity and cybersecurity of the app need to be considered. Additionally, the credibility of the information presented in apps must be assessed as it could potentially mislead patients and clinicians. Poor assessment of software reliability may also be an issue.

**Conclusion**

An MMA evaluation module was created to adapt an existing HTA process for MMA technology. The adaptations included making provisions for an assessment of cybersecurity, consideration of the impact on MMA clinical utility of software updates, and compatibility issues. Items to address concerns around practitioner responsibility and the potential for app misinformation were also incorporated into the module.

## Keywords

Technology assessment, health policy/standards, mobile health, mobile applications

## Acknowledgements

The authors would like to acknowledge Ms Nicola Bennett for transcribing the interviews and Ms Jacqueline Parsons for reviewing the *Framework for health technology assessment (HTA) of mobile medical applications (MMA) for reimbursement purposes*.

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## Conflict of interest

None

## Introduction

Electronic health (eHealth) technologies such as mobile health (mHealth) applications (apps), electronic health records (EHR), and telemedicine are increasingly being used in healthcare(1-3). Apps with a diagnostic or therapeutic purpose are known as mobile medical applications (MMA) and have been growing in popularity over the past few years (4-7). MMAs are now being used and recommended by healthcare practitioners within clinical consultations (4-7).

In Australia, government reimbursement of clinical encounters and prescribed interventions is available to healthcare practitioners (e.g. general practitioners (GP), medical specialists, allied health workers, dentists, optometrists) and patients through the national health insurance scheme called the *Medical Benefits Schedule (MBS)* (8,9). For a medical service or intervention to be reimbursable through the MBS, it has to first be approved by the *Therapeutic Goods Administration (TGA),* and then undergo a health technology assessment (HTA) to ensure it is safe, effective and cost-effective (5,6,9). After a medical service has undergone an HTA conducted by an independent body --under the guidance of the Australian *Medical Services Advisory Committee (MSAC)*-- and approved by the Federal Minister of Health, it is given an item number and listed on the MBS for reimbursement (8,9). Currently, there is no mechanism for MMAs to be reimbursed through the MBS, although other eHealth technologies, such as telemedicine, are reimbursed (10-12).

MMAs pose different harms and risks than traditional medical devices or eHealth technologies, and therefore evaluation of them requires consideration of different dimensions than those used in a typical medical services evaluation (13-17). Unlike other technologies, MMAs: have a fast life cycle; are available on non-specialised off-the-shelf devices; are available on various operating systems (e.g. Android or iOS) and operating platforms (e.g. smartphone, smart watches, tablets); have software updates; can provide real-time post-market performance data or 'real world data'; and connect to various databases and data systems via the internet and have other networking capabilities (14-17).

MMAs do not currently undergo HTA evaluations in the Australian healthcare system (13). The aim of this study, therefore, was to develop evaluation criteria (a module) that could be used to adapt current HTA frameworks for the assessment of MMAs.

## Methodology

The need for a module capable of adapting HTA processes to enable them to properly evaluate MMAs has been described previously (Moshi, Tooher & Merlin(13), and Moshi et al.(18)). A module was

developed by synthesising the results of the two previously mentioned studies with insights generated from semi-structured in-depth interviews with a range of stakeholders (healthcare practitioners, app developers, and policymakers). The interviews sought stakeholder views on possible pathways and impediments to MMA reimbursement in Australia in order build on the findings from the two preceding studies and inform the creation of the HTA evaluation module. Patients were not interviewed as they are the end-users of the proposed HTA process.

Since the complete methodologies utilised in the first two studies are available in their respective publications, only the methods related to the interviews and the creation and testing of the module are described below.

## In-depth interviews

In depth interviews were undertaken with a sample of key stakeholders to support and inform the creation of the MMA evaluation module and to provide insight into issues identified in the two preceding studies. The study was not designed as a standalone qualitative study.

### Recruitment

The stakeholders were purposively recruited by email (between April and December 2017) from those who have experience with MMAs in their professional careers. Potential participants were identified by scoping done by the first author (MM), as well as through contacts of the second (RT) and third (TM) authors. Passive snowballing via email was then used to identify further participants. All participants were emailed the participant information sheet in English prior to agreeing to the interview. The participants participated in the study on a voluntary basis and were free to withdraw prior to this publication. Adopting an information power approach, participants were only recruited if we identified that they could substantially add to the range of views about this topic (see Supplementary material A for more information) (19-21).

### Data collection

The data were collected through semi-structured in-depth interviews with key stakeholders. The interviews were conducted by the first author (MM) in-person or via teleconference. The interviews were recorded using an audio-recorder. Verbal and written consent was sought before the start of each interview. In the case of in-person interviews, written consent was obtained before the interview, whereas with teleconferences a completed written consent form was returned via email before the start of each interview. The participants were not renumerated for their participation in the study.

### Data analysis

The interviews were transcribed verbatim by a professional transcriber and were analysed through thematic analysis (Braun & Clarke(22)) using the epistemology of pragmatism (see Supplementary material A for more information). The assistive software *NVivo 11* (QSR international Pty Ltd)(23) was used by the first author (MM) to aid in the analysis. The coding and analysis were checked by the second author (RT). Data source triangulation was achieved through the use of multiple participants with different expertise from five Australian jurisdictions (24-26). Quotations from participants are used below to illustrate the findings.

### Ethical considerations

The stakeholder interviews (from the larger research project) were approved (H-2017-039) by the *University of Adelaide Human Research Ethics Committee (HREC) Low Risk Human Research Ethics Review Group.*

To minimise any risk of reputational damage to the participants through disclosure of information about clinical or regulatory practices, we took extra steps to ensure that participants or their organisations could not be identified from any data extracts used as quotation(s), or from any example(s) included in this written publication.

### Development and testing of MMA evaluation module

The module was developed by synthesising the results from the two aforementioned studies (8; 18) with the findings from the stakeholder interviews. This was achieved by the identification of the key policy changes and assessment criteria needed to enable the appraisal of MMAs. For example, Moshi, Tooher, & Merlin (2018) identified the key considerations for conducting an HTA on MMAs for reimbursement and decision-making purposes (Table 1) (8). Moshi et al. (2019) identified critical regulatory considerations for MMAs which are not addressed the Australian regulatory authority (*Therapeutic Goods Administration (TGA)*) or by the other IMDRF member jurisdictions (Table 1) (18). On the basis of these studies, and informed by the insights generated from the interviews with stakeholders (Table 1), a module was developed.

### Pilot testing of the MMA evaluation module

The MMA evaluation module was tested by applying it to the current HTA evaluation frameworks used by the Federal Department of Health to appraise medical services for public funding decisions. These included the MSAC technical guidelines for both therapeutic and investigative medical services.

# Results

## Stakeholder Interviews

### Interview characteristics

Nine semi-structured in-depth interviews were conducted between September and December 2017. The duration of each interview was approximately 1 hour.

The participants included four healthcare practitioners (general practitioner(s) (GP), nutritionist(s), physiotherapist(s)), three policy makers, and two developers of health apps. Three different interview schedules were used, one for each type of stakeholder.

### Themes

Stakeholders, particularly the healthcare practitioners, expressed *trust* in the HTA approach used by the MSAC. *Trust* in these processes is an enabler for the reimbursement of MMAs in Australia, as it aids in the creation of *evidence-based policy*. It requires that there be a *rationale for use* for the intervention in question.

*"So I think, if an app was listed on the MBS [Medicare Benefits Schedule] I think that would for me would indicate to me that oh well I would assume that there had been…it would be evidence based, there had been [a] quality check done on I guess the content and the process"*

Healthcare practitioner, 1

The interviews reflected that there are unclear lines of *responsibility* with respect to jurisdictional oversight and practitioner accountability for MMAs.

*"I think one of the biggest challenges we have is actually working out what it is that we can regulate and we are able to regulate and I am aware that there are lots of complexities to this including kind of where it is that the actual app is being sold from impacts our ability to actually regulate things."*

Policymaker, 1

The ownership of the heath data produced by an MMA is a significant stakeholder concern as it affects patients' rights to data privacy and confidentiality. For example, if the app data are owned by the company that developed the MMA, would they have the right to sell the patients' (or users') private medical data?

*"there is an issue around who actually owns the data and monitors the data and is responsible for contacting the patient and/or their GP, if there is a marker that says you know they might have had an episode"*

Policymaker, 2

Stakeholders were also concerned about the impact of app use on the relationship between clinicians and their patients, including the clinician's duty of care, and whether this would affect professional indemnity. The stakeholders suggested that bringing MMAs into the standard technology regulatory framework would help to address these concerns.

*"if there is a proper accredited process then that's all you really need to know and then you are comfortable if your apps yeah put up to against the accredited process and passes then you know I think from a professional indemnity point of view you would have been seen to have done the…gone through the appropriate processes do it."*

Healthcare practitioner, 4

The stakeholder interviews also identified that the *digital health literacy* of both practitioners and patients is important. Healthcare practitioners were particularly concerned that the efficacy and safety of an MMA might depend on the fidelity of data entered by the user (i.e. patient) into the app and, further, that patient self-management might be compromised by a lack of knowledge about how to interpret the app's output.

*"I'd still want to verify the data that has been inputted into it by the user I suppose, I guess my preference to sort of use my clinical judgement perhaps isn't so much about the quality and strength of that app but more so the quality and completeness of the raw data that the clients inputting."*

Healthcare practitioner, 1

*"user error you know often just by putting in say 100 kilograms instead of a 100 grams you know you can appreciate that could make a big difference"*

Healthcare practitioner, 2

*"I think it* [digital health resources] *gives people worry sometimes they get more confused rather than more enlightened ."*

Healthcare practitioner, 3

The stakeholder interviews also highlighted the need for post-market surveillance of MMAs. These concerns were due to MMA's fast lifecycle and the rapid *technological evolution* of digital health technologies.

*"The technologies are evolving fast and the policy just doesn't have a chance to catch up"*

Policymaker, 1

Stakeholders were particularly concerned about how post-market data and software updates might lead to changes which effectively created a new app or function that was not the subject of the original evaluation on which the regulatory and reimbursement approval was based (16,18,27,28).

*"they* [apps] *do work differently and even…so I've got a really old iPhone and everything will look different when a new iPhone comes out potentially and just the way the different buttons on Android verses iPhone"*

Application developer, 1

Table 1: Summary of findings from the preceding studies and the stakeholder interviews

| Regulation of MMAs (18) | Reimbursement of MMAs internationally (Evaluation framework systematic review) (13) | Pathways and impediments to MMA reimbursement (Stakeholder interviews) |
|---|---|---|
| Effectiveness<br>- Accuracy (i.e. consistency)[1]<br>- Analytical (reliability)[2] validity<br>- Precision (i.e. repeatability)[3]<br>- Configuration<br>- Communication and display<br><br>Safety<br>- The risk of misinformation (MMA credibility)<br>- Information security (cybersecurity)<br><br>Technical characteristics<br>- Operating system<br>- Operating platform<br><br>Post-market<br>- Software changes (updates)<br>- Post-market 'real-world' data on MMA effectiveness (process and health outcomes)<br>- Post-market data monitoring | Description and technical characteristics<br>- Connectivity<br>- Operating system<br>- Operating platform<br>- Software changes (updates)<br><br>Effectiveness<br>- Consider comparator<br>- Effects of software changes (updates)<br><br>Safety<br>- The risk of misinformation (MMA credibility)<br><br>Ethics<br>- Equity<br>- Access<br>- Privacy<br>- Confidentiality<br>- Information security (cybersecurity) | Pathways<br>- Trust in HTA processes (MSAC)<br>- Rationale for use<br>- Evidence-based policy<br><br>Impediments<br>- Responsibility (i.e. indemnity issue, data ownership)<br>- Technological evolution<br>- Digital health literacy |

**Explanatory Notes**
[1]**Accuracy:** Closeness of the quantity's true value to its measured quantity.
[2]**Analytical validity:** The MMAs ability to reliably and accurately produce the intentional output from the input data
[3]**Precision:** Under unchanged conditions the degree to which the recurrent measurements generate the same result (i.e. reproducibility, repeatability)
**HTA:** Health technology assessment
**MMA:** Mobile medical application
**MSAC**: Medical services advisory committee

## Development of MMA evaluation module

The complete evaluation module for MMAs is detailed in Table 2. The module is evidence-based and all of the domains are mandatory, with the exception of the social domain. Items that could fall under the jurisdiction of a regulatory authority were integrated into the module due to Moshi et al.(18) identifying that Australian and other international regulators do not properly assess MMAs. In Australia, regulatory approval is the first step to being eligible for reimbursement. Regulatory and reimbursement evaluations are independent of each other and typically focus on different aspects of the technology. However, if the criteria used by the regulatory authority to evaluate the MMAs do not cover all relevant concepts and/or items, than these must be addressed in the HTA.

Table 2: A module which can be used to adapt HTA and/or reimbursement evaluation frameworks to assess MMAs

| HTA domain | HTA domain status | MMA technology specific considerations | |
|---|---|---|---|
| | | Challenge posed by MMA | MMA specific modifications and adaptation(s) |
| Description and technical characteristics | Mandatory | Operating system(s) for MMA | - Operating systems of the MMA (i.e. Android, iOS, etc.) |
| | | Operating platform(s) for MMA | - Operating platforms of the MMA (i.e. smartphone, tablet, smartwatch) |
| Current use of the technology | | Rationale for use | - The intended purpose of the MMA (i.e. diagnose, treat, inform clinical management, clinical management)<br>- The healthcare condition or situation that the MMA addresses<br>- MMA input (i.e. image, physiological status, symptoms, etc.)<br>- MMA algorithm (i.e. equations, analysis engine model logic, algorithm, etc.)<br>- MMA output (i.e. inform, treat, diagnose) |
| | | Potential software changes (i.e. updates) | - Post-market software changes, that do not require the re-evaluation of an MMA and are corrective, preventive, adaptive, and/or perfective (see *Effectiveness* for more information)<br>- Post-market software changes that do require a re-evaluation of the effectiveness and safety of an MMA and which enable or disable new MMA functions (see *Effectiveness* for more information) |
| Effectiveness | | Accuracy (i.e. reliability) | - Closeness of the output to the true value to the MMA's output<br>- Accuracy measures the effect of software errors on the MMA output<br>- Total accuracy = ±(0.1% of input + *x* [relevant unit of measure (i.e. heart rate, blood sugar)]) |
| | | Configuration | - The MMA's ability to withstand user configuration in an unintended way (i.e. results of *fuzzing* or *fuzz testing*)<br>- Limitations of the MMA (i.e. assumptions, data quality, algorithms) |
| | | Communication and display | - The design of the MMA user interface (i.e. level of complexity, type of platform, how information is displayed, etc.)<br>- The appropriateness of the MMA interface as a means of information display (i.e. language translation, units displayed, clarity, etc.)<br>- The MMA's ability to communicate the relevant information (i.e. data quality, network availability, correct installation, etc.) |
| | | Cybersecurity and connectivity | - Formalised and safe methods have been implemented to convert, transmit, and/or store MMA data (i.e. results of *fuzzing* or *fuzz testing*)<br>- Users can safely implement information security updates<br>- System supports ensure protection of MMA system information<br>- MMA software adheres to robust programming principles (i.e. paranoia, stupidity, dangerous implements, can't happen)<br>- Balances the availability of timely information and against privacy and security (i.e. results of *fuzzing* or *fuzz testing*)<br>- How MMA integrates with other software (i.e. results of *fuzzing* or *fuzz testing*)<br>- The need for MMA security software to be updated so it can be used alongside other systems, applications or in operating environments (i.e. results of *fuzzing* or *fuzz testing*) |
| | | Potential software changes (i.e. updates) | - Adaptive software changes (i.e. maintains software with dynamic environment)<br>- Perfective software changes (i.e. recoding to improve performance)<br>- Corrective software changes (i.e. corrects problems) |

| | | | |
|---|---|---|---|
| | | | - Preventive software changes (i.e. corrects latent faults before they cause operational problems) |
| | | Precision (i.e. repeatability) | - Under unchanged conditions the degree to which the recurrent measurements input into the MMA generates the same output (e.g. reproducibility, repeatability)<br>- Values (in relevant unit) that are close together indicate that there is a high degree of software precision |
| | | Analytical validity | - MMAs ability to reliably and accurately produce the intentional output from the input data<br>- The algorithm used by the MMA is a recognised standard (the current standard of care or described in the literature (i.e. insulin dosing))<br>- MMA accuracy is relative to reference standard (i.e. *International normalisation ratio (INR)*)<br>- MMA comparable to another software or device that has an association between the software output and a health outcome |
| Safety | | The risk of misinformation | - How the MMA output (i.e. information) affects clinical decision-making regarding management of a patient's condition |
| Cost[1] Effectiveness | | Technological evolution | - Considerations of applicability of the system, platform, licensing, attachable hardware, and versions of the MMA to those used in the health system<br>- Unit costs including MMA costs and in-app purchases |
| Organisational aspects | | Digital health literacy | - The training/education (i.e. digital literacy) which may be needed for user(s) (i.e. medical practitioners, patients, care givers) to effectively utilise the MMA. Examples include:<br>• Continual professional development (CPD) courses for medical practitioner(s) could have to undergo to effectively learn how to utilise and recommend MMAs in clinical practice<br>• Education that patient(s) have to undergo to effectively learn how to utilise MMAs |
| | | Responsibility | - Accreditation that may be needed for professionals (i.e. medical practitioners, allied health workers, technicians) to prescribe and/or use the MMA |
| | | Connectivity | - The MMA interaction with current health informatics systems (i.e. hospitals and surgeries). Examples of health informatics systems include, but are not limited to, *PROCURA* and *Enterprise patient administration system (EPAS)* |
| | | Technological evolution | - How adopting the MMA could alter the current utilisation of services (i.e. workload, work force, compliance, etc.)<br>- How adopting the MMA will change treatment location (i.e. homebased, rural, remote, hospital, clinic, etc.) |
| Ethical aspects | | Patient privacy and confidentiality | - The presence of a privacy policy<br>- The contents of a privacy policy |
| | | Equity concerns | - Considerations include: user disability (how could users' with blindness use the MMA), language (users' who have English as a second language), age, literacy, socio-economic status, etc. |
| | | Access concerns | Considerations include: the cost of platform, in-app purchases, cost of MMA, geographical location, internet availability etc. |
| | | Technological evolution | Any possible conflicts of interest (i.e. developer or owner affiliation, sources funding, third party sponsorship, etc.) |
| Legal aspects | | Responsibility | - Litigation risks to the relevant person(s) associated with the use or recommendation of the MMA for healthcare practitioners (i.e. GPs, allied health workers, etc.)<br>- How insurance(s) (i.e. professional indemnity, life, health, income) for all stakeholders (i.e. patients, medical |

| | | | |
|---|---|---|---|
| | | | professionals, developers) could be affected through use or recommendation of the MMA<br>- How possible professional registrations could be affected through the use or recommendation of the MMA (e.g. for medical practitioners with AHPRA)<br>- Clarify which party owns the data related to the MMA (i.e. patient, third party, medical practitioners)<br>- Clarity around which party (i.e. manufacturer, medical practitioner who prescribed it) is responsible for the medical advice provided by the MMA<br>- Clarity around which party (i.e. manufacturer, medical practitioner, app developer) is responsible for monitoring and reviewing the patient data entered into the MMA |
| Post-market monitoring | | Reappraisal | - Post-market data that requires a full review of the effectiveness and safety of an MMA. These are performance data that alter the effectiveness measures of the MMA (i.e. inferior or superior to the original measures stated in the original HTA) and/or which change the harms posed by the MMA (i.e. inferior or superior to the original measures stated in the original HTA)<br>- How the manufacturer plans to monitor the MMA's performance data (i.e. data includes user feedback, complaints, and adverse events, etc.)<br>- How the data collection implemented has the least user burdensome approach to collect the MMA's performance data<br>- How the post-market data could be used to enable or disable new MMA functionalities (i.e. addition or removal of functionalities stated in the original submission, etc.)<br>- How post-market data could affect the MMA's cost-effectiveness, safety, effectiveness<br>- How post-market data could affect the ethical, legal, and/or organisational concerns associated with the MMA |
| Social aspects | Optional | None | - How the use of the MMA may affect the patients' care giver(s), including relationships with medical professionals<br>- How the use of the MMA may affect the users' relationships (i.e. family dynamics, friends, and other relevant social relations)<br>- How the MMA may benefit patient autonomy |

**Explanatory Notes**

[1] Using a fee for service model

**APHRA:** Australian Practitioner Regulation Agency

**GP:** General practitioner

**HTA:** Health technology assessment

**MMA:** Mobile medical applications

### Description and technical characteristics

Items were added to the module to identify and review the compatibility of the operating system (OS) and operating platform for the MMA.

### Current use of the technology

Numerous items relating to the current use of the technology were included in the module. The first were items related to the intended purpose(s) of the technology, in terms of whether the MMA is aimed at informing, diagnosing, and/or treating a medical condition (13,18). Items to review the MMA input, algorithm, and output were also included in the module (18).

### Effectiveness

Multiple technology specific items were added in the module to ensure the proper appraisal of an MMA's clinical effectiveness (Table 1). Previous research had found to that the *technical evolution* and dynamic nature of an MMA should be considered (13,18). To address this as well as the concerns raised in the stakeholder interviews, items were included to evaluate software changes (updates), information security (cybersecurity), communication and display, and connectivity (13,18). Items addressing regulatory concerns including analytical validity (reliability) of the software, software accuracy (consistency), software precision (repeatability), and software configuration. Furthermore, prior research found that a comparator should be considered for MMA evaluations, such as a clinical evaluation without the assistance of an app(or usual care).

### Safety

Only one item was added to address safety concerns. This item was focused on evaluating the risk of misinformation in the app and how this could affect healthcare decision-making.

### Cost-effectiveness

Module considerations relating to cost-effectiveness were minimal, and were made within a fee-for-service healthcare paradigm. These items include, a consideration of the applicability of the operating systems and platforms of the MMA being evaluated as well as the various versions of the MMA. The outright cost of the MMA and/or any possible in-app purchases were considered as unit costs. Change to subsequent care as a consequence of the MMA would be costed as part of the normal HTA process, along with incremental changes in health outcomes due to use of the app.

### Organisational aspects

To address data fidelity, organisational concerns were included into the module (Table 1). Organisational aspects that were incorporated included: if any training or education was needed for users (i.e. practitioners or patients); if any professional accreditation is needed for medical practitioners; if adopting the MMA will alter the current utilisation of services (i.e. work load, work force, compliance, etc.); if adopting the MMA will change treatment location (i.e. homebased, rural, remote, hospital, clinic, etc.); as well as an assessment of whether the MMA could interact with health informatics systems (i.e. Procura, Electronic Protocols Application Software (EPAS)) used in hospital, surgeries, and allied health clinics.

### Ethical aspects

The ethical aspects added to the module included equity (i.e. disability, language availability, age, literacy, socio-economic status, etc.), patient confidentiality, and patient privacy, as these were raised in Moshi, Tooher & Merlin(13), Moshi et al.(18), and in the stakeholder interviews. Privacy is a major concern due to cybersecurity risks and that some companies that manage or produce MMAs do sell consumer data without consumers' knowledge (13,18,29). Additional ethical considerations include access to the technology (i.e. cost of platform, in-app purchases, cost of app, geographic location, internet availability, etc.) and any potential conflicts of interest related to the app developer, app owner, third party sponsors, and funding sources.

### Legal aspects

Legal aspect were included in response to concerns raised in the stakeholder interviews. The domain specifically evaluated *responsibility*. To address this concern, items were added to review how MMA use and/or recommendations could affect personal insurance (i.e. professional indemnity, life, health, income, etc.), professional registrations (i.e. for healthcare practitioners), and risk of litigation. Furthermore, additional items were included to provide clarity around which party (i.e. manufacture, app developer, medical practitioner, etc.) owns: the data produced by the MMA; the medical advice produced by the app; as well as monitoring and reviewing the patient data. Legal concerns partially overlap with the *Ethical domain* above, in that it addresses some privacy concerns through seeking clarification around ownership (i.e. patients, medical practices, companies, etc.) of data produced by MMAs.

### Social aspects

Moshi, Tooher & Merlin(13) and Moshi et al.(18) found that currently an evaluation of social issues are not considered an integral part of an evaluation of MMAs. Therefore, items included in the module allowed related social issues to be considered, such as whether the MMA can affect a care giver, the patient's autonomy, and the patient's relationship with their healthcare practitioners.

### Reappraisal

This newly added HTA domain has been created to address MMA specific challenges. The domain is aimed at evaluating post-market data as part of a HTA. Items were added to allow the post-market surveillance of MMAs, in terms of data monitoring (13,18). Including post-market data collection and utilisation (i.e. how the data could be used to modify the MMA) were also included (13,18).

## Testing the HTA evaluation module

The MSAC technical guidelines were selected to test the HTA evaluation module, as these guidelines are used by the Australian Federal Department of Health to determine if both therapeutic and investigative medical services should be reimbursed through the national universal health system (27,28). These guidelines one of several different guidelines used in Australia to assess health interventions for reimbursement purposes.

A range of adaptions were introduced to the MSAC guidelines from the MMA evaluation module (Table 2). Sections A through F of the original MSAC guidelines were modified to assess technology specific and pre-market (regulatory) evaluative concerns. Two new sections --G and H-- were added to incorporate additional technology specific items as well as any additional HTA information deemed relevant (27). All proposed adaptations made to the MSAC guidelines to ensure the proper assessment of MMAs are summarised in Table 3, with specific details given in Table 1 of the Supplementary material B. The complete adapted MSAC framework created using the evaluation module is available in Supplemently material B and is titled *Framework for health technology assessment (HTA) of mobile medical applications (MMA) for reimbursement purposes*.

Table 3: Module adaption of the MSAC technical guidelines

| Section letter(s) | Technical guidelines for preparing assessment reports for the MSAC | MMA evaluation framework for HTA and reimbursement purposes | |
|---|---|---|---|
| | Technical guidelines section title(s) | MMA evaluation framework section title(s) | MMA specific modifications and adaption(s) |
| A | Details of the proposed medical services (therapeutic or investigative) and its intended use on the *Medical Benefits Schedule (MBS)* | Description and technical characteristics of the MMA used in the clinical service | - Details of the MMA<br>- Details of the MMA's intended purpose<br>- Details of the operation system (OS)<br>- Details of the operation platform |
| B | Clinical evaluation for the proposed MMA (therapeutic or investigative) | Evaluation of a clinical service involving a MMMA | - Therapeutic MMAs [1]<br>- Investigative MMAs [2]<br>- Accuracy (i.e. consistency) [3]<br>- Analytical (reliability) validity [4]<br>- Connectivity<br>- Configuration<br>- Communication and display<br>- Cybersecurity<br>- Potential software changes (i.e. updates)<br>- Post-market monitoring<br>- Precision (i.e. repeatability) [5]<br>- The risk of misinformation (MMA credibility) |
| C | Translational issues | Translational concerns for the economic modelling | Considerations of applicability of system, platform, licensing, attachable hardware, and versions of the MMA to the Australian context |
| D | Economic evaluation for the main indication | Economic evaluation of a clinical service involving a MMA | Unit costs including MMA costs and in-app purchases |
| E | Estimated utilisation and financial implications | Projected financial consequences of MMA utilisation | No changes made |
| F | Option to present additional relevant information | Evaluation of broader concerns with MMA use | - Ethical considerations for MMAs (i.e. privacy, confidentiality, licensing, subscriptions, equity, access, etc.)<br>- Legal considerations (responsibility) for MMA (i.e. medicolegal liability, data ownership, etc.)<br>- Additional organisational considerations (i.e. training in digital health literacy) |
| G | N/A | MMA post-market evaluation | - How to evaluate MMA software changes (i.e. updates and determine the re-assessment trigger)<br>- How and when to evaluate post-market performance data (real world data and incorporate into the re-assessment) |
| H | N/A | Optional considerations for MMAs | - Social considerations for MMAs<br>- Other information considered relevant to specific MMA clinical evaluation |

**Explanatory Notes**

[1] Only applies to therapeutic MMAs

[2] Only applies to investigative MMAs

[3] **Accuracy:** Closeness of the quantity's true value to its measured quantity.

[4] **Analytical validity**: The MMAs ability to reliably and accurately produce the intentional output from the input data

[5] **Precision**: Under unchanged conditions the degree to which the recurrent measurements generate the same result (i.e. reproducibility, repeatability)

**MMA:** Mobile medical application

## Discussion

This research aims to address the technology specific concerns of MMAs. The module that was developed was informed by HTA theory described in Busse et al.(30), a systematic review of MMA evaluation frameworks, guidance documents from the IMDRF's working group on medical software, specifically *SaMD: Clinical evaluation(16)*, together with insights gained from in-depth discussion with stakeholders.

Many of the stakeholders' concerns about MMA use in clinical practice pivots on the *trustworthiness* of the apps, the evidence-base underpinning them, and the regulatory and evaluative processes that support their use. Building stakeholder *trust* in the system for evaluating apps will strongly encourage integration of MMAs into the healthcare system and services. The module that has been developed attempts to address concerns about MMAs and increase *trust* in MMAs through a thorough evaluation of issues that are of particular concern for these types of digital health technologies. Doing so should allow MMAs to be accepted as part of standard clinical care alongside other more familiar medical and health technologies.

However, there are broader policy issues outside the scope of HTA regarding the use of MMAs that need to be considered. These policy issues could possibly impact the nature of individual clinical consultations and the *trust* that clinicians and patients have in the interventions being used. Some of the concerns, in particular about the jurisdictional responsibility for apps, as distinct from the responsibilities of health practitioners, will need to be considered in a wider context than can be captured through an HTA (31). For example, in Australia uncertainties around data ownership and IP may fall under the jurisdiction of the Australian government department responsible for proprietary knowledge and ideas applied to inventions, trademarks and inventions (*IP Australia(32))* rather than with the Federal Department of Health.

Similarly, clinical liability matters may be best dealt with by authorities such as the *Australian Health Practitioner Regulation Agency (APHRA)(33)* and professional indemnity insurers. In particular, there needs to be clarity as to whether professional indemnity insurance can adequately deal with the use of apps in clinical consultations, or any other forms of malpractice that could occur through the professional use of the technology.

Furthermore, in Australia concerns around patient privacy and the ownership of patient health data has been an significant contemporary national issue with the release of the Federal Government's *My Health Record* in 2018 (11,34). The concerns were mainly around citizens' personal medical information being sold to third parties, unauthorised healthcare practitioners reviewing data that is not relevant them (e.g. celebrities' health records), and/or cybersecurity risks (34,35). In response, the Department of Health announced that they would strengthen the privacy provisions related to *My Health Record* (11,34,35). The

impending alterations to the privacy provision added to the *My Health Record Act (2012)(12)* may be able to act as precedent for other eHealth technologies such as MMAs and their related concerns around data ownership.

## Limitations

The limitations of the analysis and synthesis conducted to develop the MMA evaluation module is that for some sections the *SaMD: Clinical evaluation(16)* regulatory document was used as the gold standard for measuring specific indicators. Regulation and reimbursement have different aims, and thus the borrowing of concepts from a regulatory guidance documents may not be relevant for HTA processes developed in countries where there is a mature MMA regulation system (36,37). However, our review of regulatory processes in English-speaking countries found that only the US is close to having a mature regulatory system for MMAs (14,38-41).

The limitations to the utilisation of interviews as a mechanism to identify possible pathways and impediments to MMA reimbursement is that the participants could have produced biased answers (25,42,43). The epistemology of pragmatism assumes that the participants will answer the questions truthfully (44-46). The questions prepared and asked by the facilitator were open-ended and single barrelled to avoid leading the participant(s) (25,42,43). Only a limited number participants were recruited which could have affected result, however the study design attempted to address this by assessing the information power (see Supplementary material A) (19).

The module was only tested by modifying the Australian MSAC HTA process. Further research needs to be conducted into how successfully it could be adapted to other HTA processes internationally.

## Conclusion and Policy Implications

In conclusion, various steps need to be taken to facilitate the evaluation of MMAs. We have chosen to create a module that can be used to adapt existing HTA processes to address the unique technology-specific characteristics of MMAs. The module recommends making provisions for the analytical (reliability) validity, cybersecurity concerns, software updates, incorporation of post-market performance data, assessment of compatibility issues (e.g. platform and operating systems), as well as MMA-specific ethical and legal considerations.

Use of the MMA evaluation module in an HTA would enable policy-makers to decide if an app should be reimbursed or not, particularly when used in the context of a clinical consultation. Thus the module could be used to inform policy decisions.

Other implications are that broader policy changes are needed to ensure that the MMAs are evaluated properly and that the technology can be completely integrated into the health system. These policies need to improve stakeholders trust in MMAs, including through gaining clarity on professional liability for health practitioners who use or recommend MMAs during clinical consultations as well as who owns the heath data the apps produce and/or the IP (e.g. for the app or the code, or app content). Other considerations are around how policies should be adjusted to address the rapid lifecycle of MMAs, as well as cybersecurity concerns and the privacy and confidentiality of patient health data.

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### 7.2.4 Supplementary material

# Supplementary material A

## S.1: Clarification of Methods used in the in-depth interviews with stakeholders

### Epistemology

Pragmatism was the epistemology used, it views that all research is focused on answering the research question. It is frequently used in health systems research as it allows for abduction in research and aims at producing knowledge which is socially beneficial, and can be applied.(1-6) Pragmatism finds the truth through assuming that all knowledge is empirical and that there is one truth which differs due interpretations or perspectives.(1-3) This epistemology applies to the study as the research falls within health systems research, as well as there being a clear research question to be addressed that is part of a larger research project, i.e., to create an MMA evaluation module to adapt HTA frameworks.

### Information power

The aim of the interviews was not to develop theory in the area but instead to identify barriers and facilitators to MMA integration into the Australian health system funding model. Since this is a developing area, there are a limited number of stakeholders with experience throughout the world. Rather than seeking data saturation,(7,8) we sought high information power to meet the aims of the study.(9)

### Background information on information power

Information power is a qualitative research concept used to estimate the number of participants needed to ensure that the aim of the study can be achieved. There is an inverse relationship between information power and the number of participants needed in order to achieve the aim of the study. For example the higher the information power, the smaller the number of participants necessary.

According to Malteured, Siersma,& Guassora(9) information power can be determined by five dimensions. These dimensions are: the aim of the study; the specificity of the participants used in the study; how established the theory used in the study was used; the quality of the dialogue between the facilitator(s) and the participant(s); and finally, the strategy utilised to analyse the interview.

### Information power in the in-depth interviews with stakeholders

Information power used in the in-depth interviews with stakeholders to identify pathways and impediments to MMA reimbursement was high as the study design and method used the aforementioned dimensions. Firstly, the study aim was narrow. Secondly, the study design enabled the use of dense sample specificity

of the participants as they were purposefully recruited from a limited pool of 'expert' stakeholders who had experience with MMAs and health systems funding. As mentioned earlier, the theory used during the analysis was pragmatism. This is an established epistemology which has been used within the communicative and dynamic technology in health system research.(1,4-6) There was a strong dialogue between the facilitator (MM) and the participants. Though the facilitator (MM) can appear shy, she had detailed knowledge of MMAs, as well as the Australian reimbursement and regulation structures. As these were semi-structured interviews, she was able to probe and adapt the interview schedule when required to attain the empirical data. Finally, the analysis strategy chosen was a case study. The case study was aimed at an in-depth exploration and analysis of selected patterns between MMAs and their relationships with the relevant selected stakeholders, and there was not an investigative cross-case appraisal of various discourse details and/or narratives.

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# Supplementary material B

# A Framework for the Health Technology Assessment (HTA) of Mobile Medical Applications (MMA) for Reimbursement Purposes in Australia

# Table of Contents

## List of abbreviations

**APHRA:** Australian Practitioner Regulation Agency

**ARTG:** Australian Register of Therapeutic Goods

**FDA:** U.S. Food and Drug Administration

**GP:** General practitioner

**HTA:** Health technology assessment

**MBS**: Medicare Benefits Schedule

**MMA:** Mobile medical application

**MSAC**: Medical Services Advisory Committee

**PICO**: Population, Intervention, Comparator, Outcomes

**TGA**: Therapeutic Goods Administration

## Glossary

**Accuracy:** Closeness of the quantity's true value to the observed quantity that was measured.(1)

**Algorithm:** A model, or set rules, or logic that the MMA is based on (e.g. inferences engine, equations, model based logic; affected by reference data, knowledge base, criteria, rules).

**Analytical validity:** The MMA's ability to reliably and accurately produce the intentional output from the input data.(1)

**Clinical utility**: the benefits and risks which result from the use of the MMA.(2)

**Clinical validity:** the ability of an MMA to identify a particular condition.(2)

**False negative(FN):** MMA's has incorrectly identified that the patient does not have the condition.(3)

**False positive (FP):** MMA's has incorrectly identified that the patient does have the condition (3)

**Fuzzing or fuzz testing**: an effective automated method to identify software errors or 'bugs' in an MMA.(4)

**Input:** Digitised content fed to the MMA (e.g. laboratory results, image, medical device data, physiological status, symptoms).(1,5)

**Investigative MMA:** A MMA's output that is intended to diagnose and/or drive clinical management by differentiating or monitoring patients or their physiological conditions (e.g. screening apps, diagnostic apps, risk predicting apps).(1)

**Linearity of associated transfer function:** "Behaviour of output across the range of input data that is allowed"(1) by the MMA.

**Output:** A product of the MMA that has the ability to affect the users health (e.g. inform, treat, diagnose).(1,5)

**Positive predictive value (PPV):** The likelihood that the patient has the condition given the MMA result is positive.(1,3)

**Precision:** Under unchanged conditions the degree to which the recurrent measurements generate the same result (e.g. reproducibility, repeatability).(1)

**Reference standard:** a standard that is used and widely accepted to determine the benchmark for a performance or presence/absence of a medical condition.

**Robust:** An MMAs ability to deal with errors during software performance.(6)

**Sensitivity:** MMA's ability to correctly identify a patient with the condition.(1,7)

**Specificity:** A MMA's ability to correctly identify a patient as not having the condition.(1,7)

**Therapeutic MMA:** A MMA's output that is intended to treat a healthcare condition or situation.(1)
**Validate (software validation):** The MMA achieves its intended purpose.(8)

**Verify (software verification):** The MMA achieves its intended purpose without hindrances in the form of software errors.(8)

# Introduction

This framework has been developed to provide some clarity on how to conduct a health technology assessment (HTA) on mobile medical applications (MMA) in the Australian healthcare context. MMAs are a subset or mobile health (mHealth) applications (app) that have a therapeutic of diagnostic purpose.(1,2)

These guidelines address concepts which would generally be reviewed during the assessment of an MMA for regulatory purposes. As the Australian *Therapeutic Goods Administration (TGA)* does not review the MMA configuration, post-market monitoring, software changes, cybersecurity, and/ or communication and display, in their regulatory processes, these concepts were included in this HTA framework to ensure that they are addressed.

The framework is aimed at policymakers and health technology evaluators. However, it can be utilised by any interested party and adapted accordingly.

## Context of framework

This evidenced-based framework was developed to be used within the Australian healthcare context. Moreover, the studies that were conducted to assist in the development of research were conducted within the Australian healthcare context. The framework that has been adapted is based on the available guidance to evaluate health technologies by the Medical Services Advisory Committee (MSAC).(9, 10)

## Structure of framework

A: Description and technical characteristics of the MMA used in the clinical service

B: MMA clinical evaluation

C: Translational concerns of the economic modelling

D: Economic evaluation of a clinical service involving a MMA

E: Projected financial consequences of MMA utilisation

F: Evaluation of broader concerns with MMA use

G: MMA post-market evaluation

H: Other considerations for MMA (Optional)

## Instructions

All MMAs – and attachable hardware – are to undergo a pre-market assessment (*Section A, C, D*, *E* and *F)*. For MMAs that have a therapeutic intended purpose, complete *sub-section B.1*. For, MMAs that have an intended purpose that is diagnostic, complete *sub-section B.2*. In the situation where an MMA – and attachable hardware – have both a therapeutic and investigative intended purpose both *sub-section B.1* and *B.2* should be completed. *Sub-sections B.3* through *B.7* should be addressed for all therapeutic or investigative MMAs – and attachable hardware. *Section H* is optional, and provides an area for the evaluation of relevant considerations that may have not been assessed in other sections of the framework (i.e. social considerations).The pre-market assessment is illustrated in Figure 1.

*Section G* addresses post-market concerns and consists of two sub-sections. Each sub-section can assist in determining what software changes (i.e. updates) and/ or post-market performance data would be required if the MMA was to be re-assessed (see Figure 2).

Figure 5: Order of the pre-market HTA evaluation of MMAs

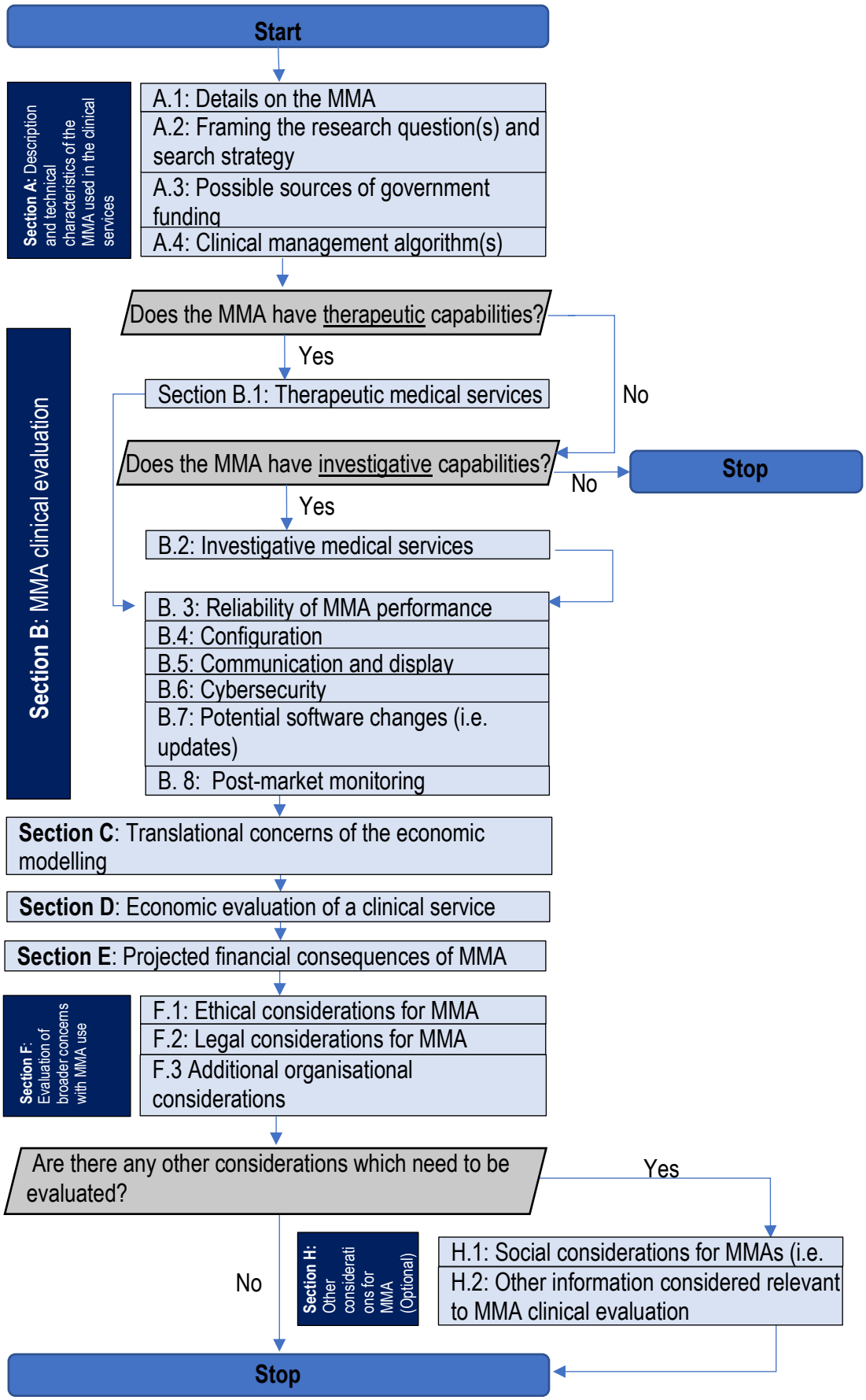
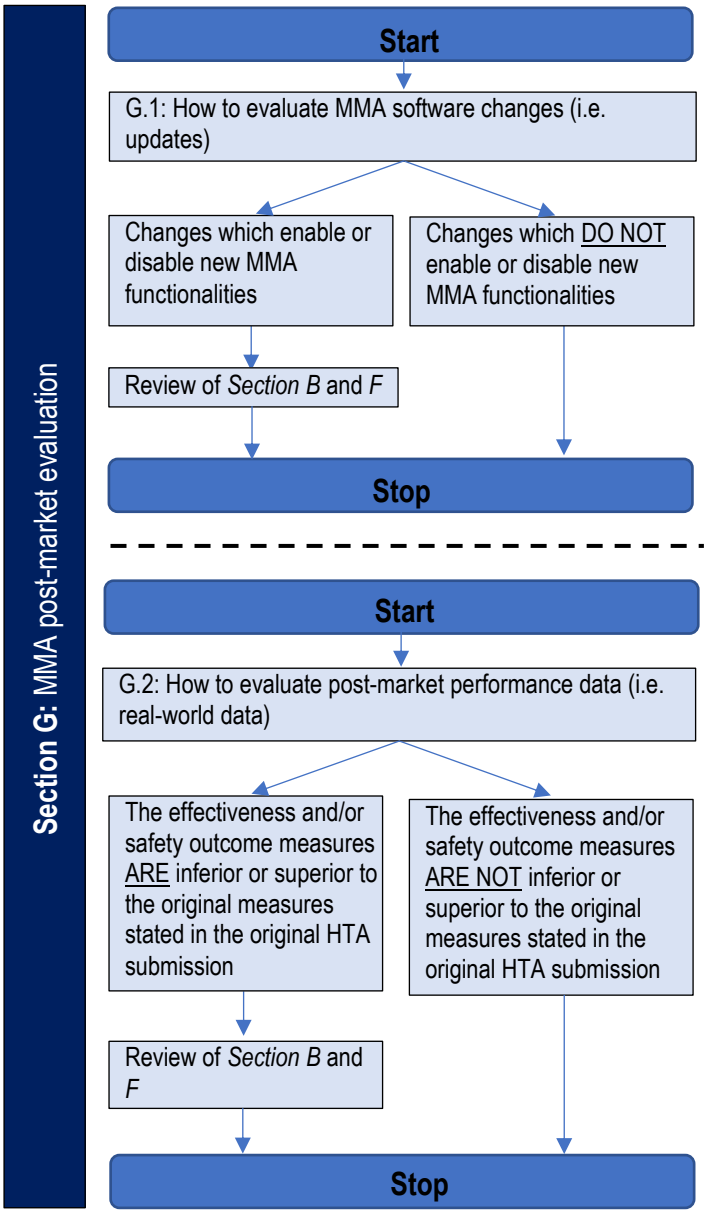


Figure 6: Order of the post-market HTA evaluation of MMAs



## Section A: Description and technical characteristics of the MMA used in the clinical service

| Framework item(s) | Example(s) |
|---|---|
| A.1: Details of the MMA | |
| 1. Detail the question(s) relating to the MMA and its capabilities. | • What is the effectiveness of a skin cancer screening app for Australian residents of working age (18 to 67 years of age) |
| 2. Provide information on the MMA's registration – or application submitted - with the *TGA* (or other relevant regulatory body). | • ARTG entry number 26548 or FDA 510k database entry number K842857. |
| 3. Detail the intended purpose of the MMA in which reimbursement is being sought. | • The intended purpose of the MMA is to detect basal cell carcinoma or squamous cell carcinoma [*insert details on the algorithm and other specifications*] in Australian residents of working age (18 to 67 years of age). |
| 4. Detail the key mechanisms of the MMA. | • The intended medical purpose of the MMA is to… (i.e. diagnose, treat, inform clinical management, drive clinical management).<br>• The healthcare condition or situation that the MMA addresses.<br>• The MMA input, algorithm, and output.<br>• The operating system(s) that reimbursement for the MMA is being sought for.<br>• The operating platform(s) that reimbursement for the MMA is being sought for. |

| A.2: Framing the research question(s) and search strategy | |
|---|---|
| 1. Provide a summary of the PICO criteria that was used to address the question(s). | • Population (P): Australian residents of working age (18 to 67 years of age).<br><br>• Intervention (I): Assessment of skin lesion using a software application [*insert details on the algorithm and other specification*] on a mobile platform.<br><br>• Comparator (C): Skin biopsy, skin exam (conducted by physician) without use of software application.<br><br>• Outcome (O): Diagnostic measure(s) (sensitivity, specificity, false positive, etc.), or health outcome measures (e.g. remission, recurrence, cure rate, metastasis, mortality). |
| 2. Describe the intended population(s). | • Australian residents of working age (18 to 67 years of age). |
| 3. Described any comparator(s). | • The main comparators (e.g. comparator described in 1. above).<br><br>• Relevant additional comparators.<br><br>• Investigative MMAs:<br>a. The reference standard [a].<br><br>b. In situations where there is no reference standard state this and provide information on app concordance, with other diagnostic tests. |

| | |
|---|---|
| 4. Describe the intended outcome(s). | • The main outcome(s) (e.g. comparator described in 1. above).<br>• Relevant additional outcome(s) (i.e. surrogate outcome(s)). |
| 5. Detail the included language(s). | • Limited to the English language. |
| 6. Detail the time period. | • Limited to 01 January 2008 to 31 December 2017. |
| 7. Provide rationale (justification the reasons for selection) for choice of PICO. | |
| 8. Describe the differences between the intervention and the main comparator (i.e. indication, likelihood, contraindications, and adverse events). | • Difference in contraindications, adverse events, mode of delivery, associated technologies, setting of use. |
| A.3: Possible sources of government funding | |
| 1. Detail the intended MBS listing (i.e. medical service item which receives government funding) for the MMA. | • *MBS* item: Malignant skin lesion items;<br>• *MBS* descriptor code: 31356, 31358, 31359, 31361, 31363, 31365, 31367 and 31369 |
| 2. Detail any other possible pathways for the MMA to receive public funding that has been sought, or that has or is being pursued. | • Through the Australian Department of Veteran Affairs (DVA). |
| A.4: Clinical management algorithm(s) | |
| 1. Detail the clinical management algorithms | • Describe the clinical management algorithm(s) that demonstrates the context in which the MMA is intended to be used.<br>• Describe the clinical management algorithm(s) that demonstrates |

| | |
|---|---|
| | current management without the use of an MMA.<br><br>• Summarise any changes between the two algorithms described in A.4 i. and ii. ie changes in clinical algorithms could be patterns in resource allocation, etc. |

**Explanatory note**

[a] Applies to investigative medical devices only

[b] In the absence of studies, *Nil Return* should be listed

[c] Only relevant to MMAs when the intended purpose is for continuous use and/or monitoring

ARTG: Australian Register of Therapeutic Goods

FDA: U.S. Food and Drug Administration

MBS: Medicare Benefits Schedule

MMA: Mobile medical application

PICO: Population, Intervention, Comparator, Outcomes

TGA: Therapeutic Goods Administration

## Section B: MMA clinical evaluation

*Instructions: For therapeutic interventions complete section B.1, for investigative interventions complete section B.2, and for both therapeutic and investigative interventions complete section B.3-B.5*

| Framework item(s) | Example(s) |
|---|---|
| Section B.1: Therapeutic medical services | |
| B.1.1: Literature identification | |
| 1. Describe the search strategies used to identify the potentially relevant literature. | • Should aim to be systematic and include all available resources.<br>• Should include published and grey literature, as well as registers of clinical trials.<br>• Should include the date(s) in which the searches were conducted. |
| 2. List all relevant studies [b] that have been included using the pre-determined criteria from section A. | • All direct randomised trials should be included.<br>• List all randomised trials considered for inclusion in indirect comparison.<br>• List all non-randomised studies. |
| B.1.2: Identification of bias | |
| 1. Describe the characteristics of the included literature (i.e. study designs, data sources). | |
| 2. Provide an evaluation of the quality (internal validity) of the literature included in the assessment. | • Describe the measures taken by investigators to minimise bias (i.e. randomisation, follow-up period, blinding) in the included literature.<br>• The use of a reputable quality assessment tool is recommended (i.e. Cochrane Risk of Bias tool; *Grading of Recommendations Assessment, Development and Evaluation (GRADE)*). |
| B.1.3: Effectiveness | |
| 1. Provide outcome measures and analysis | |

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|---|---|
| | • Such as, primary outcomes (including quality-of-life instruments), or surrogate outcomes. |
| B.1.4: Safety | |
| 1. Provide extended assessment of comparative harms. | • The assessment should include an appraisal of how the MMA output (i.e. information) affects clinical decision making regarding management of a patient's condition.<br><br>• If relevant the assessment should include an appraisal of possible physical harms from the app and associated hardware. |

*Instructions: ONLY complete this section for **investigative medical services**, SKIP this section if the medical service is therapeutic*

| Framework item(s) | Example(s) |
|---|---|
| Section B. 2: Investigative medical services | |
| B.2.1: Literature identification | |
| 1. Describe the search strategies used to identify the potentially relevant literature. | • Should aim to be systematic and include all available resources.<br>• Should include search of published and grey literature, as well as registers of clinical trials. |
| 2. Provide an overview of the linked evidence approach. Describe the basis for the linked evidence steps such as whether there is a reason to utilise the method and steps taken to conduct the analysis. | • Information on the basis for utilising a linked evidence approach.<br>• A detailed summary of the treatment options that result from the use of the investigative MMA.<br>• Sufficient evidence available on the health outcomes of the aforementioned treatment options and if they have been trialled in a comparable population. |
| 3. Report and list all of the MMA diagnostic accuracy studies [b]. | • Possible examples include: MMA test conditions, demographics, recruiting strategy, follow-up, etc. |
| 4. Report and list all included change in management studies b. | • The main outcome(s) (e.g. change in planned treatment). |
| B.2.2: Identification of bias | |
| 1. Provide an evaluation of the quality (internal validity) of the literature included in the assessment. | • Assess risk of bias at each step of the linked evidence approach.<br>• Use of a reputable quality assessment tool is recommended (i.e. QUADAS-2 for diagnostic accuracy studies; *Grading of Recommendations Assessment, Development and Evaluation (GRADE)*). |
| B.2.3: Effectiveness | |
| B.2.3.1: Diagnostic accuracy | |
| 1. Provide details on the diagnostic performance of the MMA. | • Diagnostic measure(s) such as sensitivity, specificity, false positive (FP), false negative (FN), etc. |

| | |
|---|---|
| | • Mention, reference standard, and indicate whether direct comparison studies, indirect comparison studies, meta-analysis, concordance, etc. |
| 2. Provide details on the clinical validity of the MMA. | • Measure of the clinical validity (i.e. positive predictive values (PPV)) of the MMA.<br>• Clarify if the information provided relates to the predisposition or of any prognostic value of the MMA. |
| 3. Provide a systematic overview of the MMA accuracy studies results. | • Primary analysis for each MMA accuracy study.<br>a. The analysis for each primary measure in the form of tables or forest plots.<br>b. Statistically combine (meta-analyse) multiple MMA accuracy studies that used the same accuracy measures. |
| B.2.3.2: Change in management | |
| 1. Provide details on the clinical utility (i.e. net change in clinical management, clinical importance of false positive and false negatives) of the MMA. | • Research on the impact of the changes in clinical management that result from investigative MMAs.<br>• Clinical importance and impact of false positives (FP) and false negative (FN) finding from the MMA.<br>• Health outcomes of the subsequent therapeutic treatment and how it links to the investigative MMA. |
| B.2.3.3: Repeat testing and monitoring | |
| 1. Impact of repeat testing/ use of MMA as part of a monitoring strategy (i.e. evidence supporting repeat use) [c]. | • Evidence that supports the repeated use of the investigative MMA for monitoring purposes using the criteria below:<br>a. Reiteration of clinical validity<br>b. Responsiveness |

| | |
|---|---|
| | c. Detectability of long term change<br>d. Practicality |
| B.2.4: Safety | |
| 1. Provide extended assessment of comparative harms. | • The assessment should include an appraisal of how the MMA output (i.e. information) affects clinical decisions regarding management of a patient's condition.<br><br>• If relevant the assessment should include and appraisal of possible physical harms. |

*Instructions: Complete sections B.3 to B.8 for BOTH **therapeutic** and **investigative** medical services*

| Framework item(s) | Example(s) |
|---|---|
| Section B. 3: Reliability of MMA performance | |
| 1. Assess the analytical validity of the MMA software. | • The algorithm used by the MMA is a recognised standard (the current standard of care or described in the literature (i.e. insulin dosing)).<br>• MMA accuracy is relative to reference material (i.e. *International normalisation ratio (INR)*).<br>• MMA comparability to another software or device that has an association between the software output and a health outcome. |
| 2. Provide an assessment of the reliability of the MMA to generate the intended technical output from the information input. | • Total accuracy = ±(0.1% of input + x [relevant unit of measure]).<br>• Accuracy measures the offset and gain of the effects of software errors. |
| 3. Provide the precision (i.e. reproducibility, repeatability) of the MMA to generate the intended technical output from the information input. | • Values (in the relevant unit) that are close together indicate that there is a high degree of software precision. |
| Section B.4: Configuration [d] | |
| 1. Describe the limitations of the MMA | • The limitations could be in the, algorithms, clinical models, assumptions, and quality of the data. |
| 2. Assess whether the MMA is robust enough to withstand user configuration in an unintended way. | • The results of *fuzzing* or *fuzz testing*. |
| Section B.5: Communication and display [d] | |
| 1. Assess the design of the MMA user interface. | Provide finding from user testing:<br>• The complexity of the user interface designs (i.e. complicated screens). |

| | |
|---|---|
| | • Appropriateness of the user interface design for the intended platform (i.e. smartphone, smartwatch, tablet).<br><br>• How dynamic the MMA data are (i.e. displaying appropriate information for an appropriate length of time). |
| 2. Assess whether the MMA has the appropriate means of information display. | Provide finding from user testing:<br><br>• Has the information been displayed in the MMA in a way that the target audience can understand it.<br><br>• Item(s) to be considered are, the units displayed, language translation, etc. |
| 3. Assess whether the MMAs can communicate relevant information. | Provide finding from user testing:<br><br>• Can users utilise the MMA within the current facilities (in terms of available network, data quality input, competence, and hardware).<br><br>• The correct installation and configuration of the MMA to enable the appropriate integration into clinical workflows. |
| Section B.6: Cybersecurity [d] | |
| 1. Consider whether formalised and safe methods have been implemented to convert, transmit, and/or store MMA data. | • The results of *fuzzing* or *fuzz testing*, etc. |
| 2. Consider whether control measures to address data integrity are appropriate, in the circumstance where common information is accessed by multiple applications and users. | Provide findings from user testing:<br><br>• Can users safely implement information security updates?<br><br>• Do system supports ensure protection of system information for the MMA? |
| 3. Consider whether MMA design includes robust and resilient measures to address potential adverse system interactions. | Provide findings from user testing:<br><br>• MMA software adherence to robust programming principles.<br><br>a. Paranoia,<br>b. Stupidity, |

| | |
|---|---|
| | c. Dangerous implements,<br>d. Can't happen. |
| 4. Consider whether the MMA balances the availability of timely information against privacy. | • The results of fuzzing or fuzz testing, etc. |
| 5. Consider whether there are instructions for the user to safely manage MMA information security. | |
| 6. Consider whether the MMA integrates with other software. | |
| 7. Consider whether there needs to be updated security software for use of the MMA with other systems, applications or operating environments. | |
| Section B.7: Potential software changes (i.e. updates) | |
| 1. Assess potential changes to the software (updates). | Determine likely:<br>• Adaptive software changes (i.e. maintains software within dynamic environment).<br>• Perfective software changes could be (i.e. recoding to improve performance).<br>• Corrective software changes (i.e. corrects problems).<br>• Preventive software changes(i.e. corrects latent faults before they cause operational problems).<br>• Determine when software updates should trigger re-assessment (see Section G) |
| Section B. 8: Post-market monitoring [d] | |
| 1. Review of how the manufacturer plans to monitor the MMA's performance data. | • Performance data includes user feedback, complaints, and adverse events.<br>• Include timetable for re-assessment subsequent to collection of post-market data. |

| | |
|---|---|
| 2. Provide details on how the post-market data collection is to be implemented using the least user burdensome approach. | |

**Explanatory notes**

[a] Applies to investigative medical devices only

[b] In the absence of studies, *Nil Return* should be listed

[c] Only relevant to MMAs that's intended purpose is for continuous use and/or monitoring

[d] Regulatory domain-may be assessed by authority providing market access to the MMA.

MMA: Mobile medical application

## Section C: Translation concerns of the economic modelling

| Framework item(s) | Example(s) |
|---|---|
| 1. Identify issues which need to be reviewed. | • Applicability concerns - How the environment in which the intended population use of the MMA differs from the study circumstances in which the MMA was used (e.g. operating platform, operating system, version of the app, licensing, attachable hardware, versions of app, etc.).<br><br>• Population characteristics - Any evidence which indicates a variety of risks for adverse clinical outcomes in the intended population.<br><br>• Circumstances of use - Identify and assess direct randomised trials that demonstrate evidence of: the MMA being used alongside a method of delivery and/ or co-administered therapies which have not received approval from the TGA (or other relevant jurisdictional regulatory bodies the); the MMA being used in an environment that does not meet the standards to be listed on the MBS (or other public funding bodies); and of the MMA being used in different situations than the intended listing on the prostheses and devices list or as part of a medical service on the MBS (other public funding bodies).<br><br>• Extrapolation issues - Define any key items that need to be extrapolated. |

| | |
|---|---|
| | • Transformation issues - Define any concerns with the outcomes measured in the key studies that indicates that they need to be transformed for the economic model. |
| 2. Provide a focused analytical plan for each issue(s) identified above in C.1. | • A focused analytical plan should include information on the:<br>a. Data that will be used,<br>b. Source of the information,<br>c. Details on the method used by each pre-modelling study provided. |
| 3. Provide a presentation of results of pre-modelling studies planned above in C.2. | |
| 4. Describe the relationship between the economic evaluation and each pre-modelling study created in C.3. | • Explain how the pre-modelling studies will be used in the economic evaluation. |

**Explanatory notes**
MBS: Medicare Benefits Schedule
MMA: Mobile medical application
TGA: Therapeutic Goods Administration

## Section D: Economic evaluation of a clinical service involving a MMA

| Framework item(s) | Example(s) |
|---|---|
| 1. Provide an overview of the economic evaluation. | • How the base case economic evaluation was generated (i.e. trial-based, stepped, modelled).<br>• Type(s) of economic evaluation. |
| 2. Provide a description of the population and circumstance of use of the MMA utilised in the economic evaluation. | • Justify characteristics of the patients as well as the demographics of the population used.<br>• Justify the circumstances in which the MMA and its main comparator, are used.<br>• Appraise the consistency across the population demographics and patient characteristics. |
| 3. Describe the structure and rationale of the economic evaluation. | • A literature review of relevant information.<br>• The software utilised.<br>• Justify economic evaluation structure. |
| 4. Describe the variables in the economic evaluation. | • For each variable used in the evaluation, provide the following:<br>a. Name and definition,<br>b. Source,<br>c. Quantity in units.<br>• Direct health care resource items and costs (eg outright cost of an app, in-app purchases) in which an alteration will be associated with |

| | |
|---|---|
| | the substitution of MMA for the main comparator.<br><br>• Estimates of any direct healthcare costs and health outcomes.<br><br>• Describe the insufficiencies in the evidence and the repercussions this will have on the economic evaluation. |
| 5. Provide the results of the economic evaluation | |
| 6. Provide sensitivity analyses. | • Provide a univariate sensitivity analysis for each variable using extreme values.<br><br>• Using the sensitive variables identified in the univariate analyses provide a multivariate sensitivity analysis. |

**Explanatory notes**
MBS: Medicare Benefits Schedule
MMA: Mobile medical application

## Section E: Projected financial consequences of MMA utilisation

| Framework item(s) | Example(s) |
|---|---|
| 1. Justify how the data was selected and why the particular data sources were used. | |
| 2. Estimate the cost and use of the MMA. | • Approximate the amount of patients the MMA will target.<br>• Estimate the number of eligible patients the MMA is likely to be used by.<br>• Estimate the amount of times the MMA will be downloaded per year for five years.<br>• Estimate the cost for each MMA downloaded per year for five years.<br>• Aggregate the MMA cost calculations per year for five years. |
| 3. Provide an estimation of how the MMA would cause changes to the cost and use of other medical services on the MBS (or other public funding schemes). | • MBS items affected by the proposed service,<br>• Aggregate costs of affected service. |
| 4. Provide estimations of uncertainty and ways to reduce it. | • Calculate and assess the possible sources of uncertainty.<br>• Identify the type(s) of uncertainly.<br>• Estimate the degree of uncertainty affecting the MMA utilisation and any financial estimates. |

| | |
|---|---|
| | • Explore the nature of the uncertainty and how it impacts the overall estimates.<br><br>• Estimates the uncertainty level and consider ways to reduce it. |

**Explanatory notes**
MBS: Medicare Benefits Schedule
MMA: Mobile medical application

## Section F: Evaluation of broader concerns with MMA use

| Framework item(s) | Example(s) |
|---|---|
| F.1: Ethical considerations for MMA | |
| 1. Assess if the MMA has a privacy policy. | • The presence of a comprehensive privacy policy. |
| 2. Appraise the contents of the MMA's privacy policy | • Such as, if the data collected by the MMA can be sold without users' consent, etc. |
| 3. Describe access issues related to MMAs | • Such as the cost of platform, app, in-app purchase, internet availability (cellular or Wi-Fi), etc. |
| 4. Appraise any equity issues related to the MMA | • Such as user disability (how could users' with blindness use the MMA), language (users' who have English as a second language), age, literacy, socio-economic status, etc. |
| 5. Assess possible conflicts of interest | • Such as, developer or owner affiliation, sources of funding, third party sponsorship, etc. |
| F.2: Legal considerations for MMA | |
| 1. Review litigation risks to the relevant person(s) associated with the use of the MMA. | • Possible litigation risks that medical professional(s) such as GPs or allied health worker(s) could be subject to due to the use of, or recommendation to use, MMAs in clinical practice. |
| 2. Review how insurance(s) (i.e. professional indemnity, life, health, income) for all stakeholders (i.e. patients, medical professionals, developers) could be affected through use of the MMA. | • Review of insurance (i.e. professional indemnity, life, health, income) policies have clauses that are relevant to the use and/or recommendation to use MMAs. |
| 3. Review possible professional registration issues associated with the use of the MMA (i.e. for medical practitioners). | • Review how professional registration(s) boards/ organisations (i.e. *Australian* |

| | |
|---|---|
| | *Practitioner Regulation Agency (AHPRA)*) view the use of MMAs. |
| 4. Assess which party owns the data related to the MMA (i.e. patient, third party, medical practitioners). | |
| 5. Assess which party (i.e. manufacturer, medical practitioner who prescribed it) is responsible for the medical advice provided by the MMA. | |
| 6. Assess which party (i.e. manufacturer, medical practitioner, app developer) is responsible for monitoring and reviewing the patient data entered into the MMA. | |
| F.3 Additional organisational considerations | |
| 1. Assess if training/education (i.e. digital literacy) is need for user(s) (i.e. medical practitioners, patients, care givers) to effectively utilise the MMA. | • Need for continual professional development (CPD) courses for medical practitioner(s) to effectively learn how to utilise and recommend MMAs in clinical practice.<br>• Education that patient(s) have to undergo to effectively learn how to utilise MMAs. |
| 2. Describe how the MMA will interact with current health informatics systems (i.e. hospitals and surgeries) used in Australia. | • How MMAs send and receive information from health information software such as *PROCURA, Enterprise patient administration system (EPAS)*, etc. |
| 3. Describe if adopting the MMA will change treatment location | • Such as, rural, remote, hospital, clinic, etc. |
| 4. Describe if additional accreditation will be needed for professionals (i.e. medical practitioners, allied health workers, technicians) to prescribe and/or use the MMA. | |

| | |
|---|---|
| 5. Describe if adopting the MMA will alter the current utilisation of services. | • How the post-market MMA data is integrated into clinical workflows with appropriate use of safety (i.e. misinformation and cybersecurity) features.<br><br>• Such as, workload, work force, compliance, etc. |

**Explanatory notes**
APHRA: Australian Practitioner Regulation Agency
GP: General practitioner
MMA: Mobile medical application

## Section G: MMA post-market evaluation

| Framework item(s) | Example(s) |
|---|---|
| G.1: How to evaluate MMA software changes (i.e. updates) | |
| MMA updates that do not require a review of Section A to F. | |
| i. Software changes that are corrective. | • The software changes correct existing problems within the MMA. |
| ii. Software changes that are preventive. | • The software changes correct latent faults before they cause operational problems. |
| iii. Software changes that are adaptive. | • The changes maintain the MMA software within a dynamic technological environment. |
| iv. Software changes are perfective. | • The software changes are recoding to improve MMA performance. |
| MMA updates that do require a review of *Section B* and *F* | |
| v. Software changes that enable or disable new MMA functionalities. | |
| G.2: How to evaluate post-market performance data (i.e. real-world data) | |
| MMA post-market performance data that requires a full review of *Section B* and *F.* | |
| i. Post-market performance data that alters the effectiveness of the MMA. | • The effectiveness outcome measures (i.e. analytical validity) are inferior or superior to the original measures stated in the original HTA (i.e. MSAC) submission. |
| ii. Post-market performance data that alters harms posed by the MMA. | • The safety outcome measures (i.e. harm, misinformation) are inferior or superior to the original measures stated in the original HTA (i.e. MSAC) submission. |

**Explanatory notes**
HTA: Health technology assessment
MMA: Mobile medical application
MSAC: Medical services advisor committee

## Section H: Other considerations for MMA (Optional)

| Framework item(s) | Example(s) |
|---|---|
| H.1: Social considerations for MMAs | |
| 1. Assess how the MMA may benefit patient autonomy. | |
| 2. Asses how the MMA may affect the patients' care giver(s). | |
| 3. Assess how the MMA may affect the users' relationships. | • How the MMA could affect the users' family dynamics.<br>• How the MMA could affect the users' friends and other relevant social relations.<br>• How the use of the MMA may affect the patients' relationships with their medical professionals. |
| H.2: Other information considered relevant to MMA clinical evaluation | |
| 1. Assess other information which was unable to be reported elsewhere. | |

**Explanatory notes**
MMA: Mobile medical application

## Index

Where the technology specific characteristic of an MMA was evaluated in this framework is summarised in *Table 1* below.

Table1: MMA technology specific performance that needs to be evaluated in an HTA

| Item(s) | Where the item(s) is addressed in the framework | |
|---|---|---|
| | Section[1] | Page number [1] |
| Analytical validity (reliability) | B. 3 | 21 |
| Accuracy (i.e. reliability) | B. 3 | 21 |
| Communication and display | B. 5 | 21 |
| Configuration | B. 4 | 21 |
| Connectivity | B. 5 | 21 |
| | B. 6 | 22 |
| | F.3 | 32 |
| Consideration of a comparator (e.g. comparative effectiveness, safety) | A.2 | 12 |
| Digital health literacy | F. 3 | 32 |
| Equity | F. 1 | 31 |
| Access | F.1 | 31 |
| Information security (cybersecurity) | B. 6 | 22 |
| Operating platform(s) for MMA | A. 1 | 12 |
| Operating system (s) for MMA | A. 1 | 12 |
| Patient confidentiality | B. 6 | 22 |
| | F. 1 | 31 |
| Patient privacy | B. 6 | 22 |
| | F. 1 | 31 |
| Precision (i.e. repeatability) | B. 3 | 21 |
| Post-market 'real-world' data monitoring | B. 8 | 23 |
| | G. 2 | 34 |
| Responsibility | F. 2 | 31 |
| | F. 3 | 32 |
| Software changes (updates) | B. 7 | 23 |
| | G. 1 | 34 |
| Technological evolution | B. 6 | 22 |
| | B. 7 | 23 |
| | B. 8 | 23 |
| | F.1 | 31 |
| | G. 1 | 34 |
| | G. 2 | 34 |
| The risk of misinformation | B. 1. 4 | 17 |
| | B. 2. 4 | 20 |

**Explanatory notes**

[1] Section in the framework where the item(s) is addressed

MMA: Mobile medical application

# Reference List


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9. Medical Services Advisory Committee (2016) *Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee – Medical Service Type: Therapeutic.* Australian Government.

10. Medical Services Advisory Committee. Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee – Service Type: Investigative Australian Government; 2016

## 7.3 Applicability of the MMA HTA evaluation module to other jurisdictions

### 7.3.1 Introduction

Currently, there are no criteria that can be used to conduct an HTA on an MMA to determine whether it should be publicly funded. MMAs pose different risks than traditional medical devices and software. A few of these risks relate to the software having a fast lifecycle, being downloadable through off-the-shelf non-specialised platforms, and potentially having cybersecurity vulnerabilities.(22, 23, 36, 149) The MMA evaluation module developed by Moshi, Tooher & Merlin(149) --detailed in *Section 7.2*-- outlines an approach that can be used to modify current HTA frameworks so that they can be used to evaluate apps for reimbursement and decision-making. The focus was on the Australian healthcare context. However, as the aforementioned module was only tested to be used within the Australian healthcare context, it is currently unclear if it can be applied to other healthcare jurisdictions in other developed countries.

### 7.3.2 Aim

The aim of this analysis was to determine if the MMA evaluation module (described in *Section 7.2*) could be used in other developed countries' jurisdictions to adapt their HTA frameworks to enable the evaluation of apps for reimbursement and decision-making purposes.

### 7.3.3 Methods

Existing HTA frameworks and their methodologies for reviewing medical services for decision-making purposes were compared and contrasted to the MMA HTA evaluation module to determine whether the module included evaluative criteria that were not already present in the jurisdictions' current HTA processes.

To be included, the jurisdictions had to have an HTA agency with reimbursement policies, methodological documentation, and/or guidance documents available in English. The documentation needed to be available on the official HTA agency or network website (Table 7.1) and/or through snowballing of sources. The full list and of guidelines and/or documents reviewed are available in Table D.1 in *Appendix D*.

Table 7.1: Sources of literature

| Jurisdiction | Health Technology Assessment (HTA) Agencies | Websites | Time Period |
|---|---|---|---|
| Canada | Canadian Agency for Drugs and Technologies in Health (CADTH) | https://www.cadth.ca/ | 1st January 2008 to 31st August 2018 |
| European Economic Area (EEA) | European Network for Health Technology Assessment (EUnetHTA) | https://www.eunethta.eu/methodology-guidelines/ | 1st January 2008 to 31st August 2018 |
| United States of America (US) | Agency for Healthcare Research and Quality (AHRQ) | https://www.ahrq.gov/research/ | 1st January 2008 to 31st August 2018 |

The HTA methodologies were evaluated against a data extraction form to determine what the HTA bodies did and did not assess. The data extraction form was created by MM and was based on the domains included in the MMA HTA evaluation module for (Table 7.2).

### 7.3.4 Results

The USA, Canada, and EEA were selected as comparable jurisdictions as they have consolidated and comprehensive HTA guidelines available in English. In total, 25 guidelines and documents (Table D.1 in *Appendix D*) from the American Agency for Healthcare Research and Quality (AHRQ), Canadian Agency for Drugs and Technologies in Health (CADTH), and the European Network for Health Technology Assessment (EUnetHTA) all met the inclusion criteria.(163-179) None of the jurisdictional HTA bodies assessed all of the MMA technical characteristics evaluated in the HTA MMA module.(163, 167, 169, 171-179) Table 7.2 (also the data extraction table) summarises the findings of this review.

#### *Description and technical characteristics*

None of the jurisdictional HTA bodies assessed the operating system (e.g. Android, iOS, etc.) or platforms (e.g. smartphone, tablet, smartwatch) that MMAs can be run on.(163, 167, 169, 171-179)

Table 7.2: Detailed comparison between MMA module and HTA methodologies employed by the respective jurisdictional bodies

| Content addressed in framework categorised by HTA domain | Health technology assessment (HTA) bodies | | |
|---|---|---|---|
| | Agency for Healthcare Research and Quality (AHRQ) | Canadian Agency for Drugs and Technologies in Health (CADTH) | European Network for Health Technology Assessment (EUnetHTA) |
| Description and technical characteristics | | | |
| 1. Operating systems the MMA can be run on (i.e. Android, iOS, etc.) | ✗ | ✗ | ✗ |
| 2. Operating platforms the MMA can be run on (i.e. smartphone, tablet, smartwatch) | ✗ | ✗ | ✗ |
| Current use of the technology | | | |
| 1. The intended purpose of the MMA (i.e. diagnose, treat, inform clinical management drive clinical management) | ✓ | ✓ | ✓ |
| 2. The healthcare condition or situation that the MMA addressed | ✓ | ✓ | ✓ |
| 3. MMA input (i.e. image, physiological status, symptoms, etc.), MMA algorithm (i.e. equations, analysis engine model logic, algorithm, etc.), MMA output (i.e. inform, treat, diagnose) | ✗ | ✗ | ✗ |
| Evaluate MMA software changes (i.e. updates) | | | |
| 1. Post-market software changes, that require the re-evaluation of the MMA (i.e. changes that are corrective, preventive, adaptive, and/or perfective) | ✗ | ✗ | ✗ |
| 2. Post-market software changes that require the re-evaluation of the effectiveness and safety of an MMA (i.e. changes that enable or disable new MMA functions) | ✗ | ✗ | ✗ |
| Effectiveness | | | |
| MMA performance | | | |
| 1. Accuracy (i.e. reliability) - Closeness of the actual output to the true value of the MMA's output | ✗ | ✗ | ✗ |
| 2. Analytical validity - MMAs ability to reliably and accurately produce the intentional output from the input data | ✗ | ✗ | ✗ |
| 3. Precision (i.e. repeatability) - Under unchanged conditions the degree to which the recurrent measurements input into the MMA generates the same output (e.g. reproducibility, repeatability) | ✗ | ✗ | ✗ |
| Configuration | | | |
| 1. The MMA's ability to withstand user configuration in an unintended way (i.e. results of fuzzing or fuzz testing) | ✗ | ✗ | ✗ |
| 2. Limitations of the MMA (i.e. assumptions, data quality, algorithms) | ✗ | ✗ | ✗ |
| Communication and display | | | |
| 1. The design of the MMA user interface (i.e. level complexity, clarity) | ✗ | ✗ | ✗ |
| 2. The appropriateness of the MMA interface as a means of information display (i.e. language translation, units displayed) | ✗ | ✗ | ✗ |
| 3. The MMA's ability to communicate the relevant information (i.e. data quality, network availability) | ✗ | ✗ | ✗ |
| Cybersecurity | | | |
| 1. Formalised and safe methods implemented to convert, transmit, and/or store MMA data (i.e. results of fuzzing or fuzz testing) | ✗ | ✗ | ✗ |
| 2. Users can safely implement information security updates | ✗ | ✗ | ✗ |
| 3. System supports ensure protection of MMA system information | ✗ | ✗ | ✗ |

| | | | |
|---|---|---|---|
| 4. MMA software adheres to robust programming principles (i.e. paranoia, stupidity, dangerous implements, can't happen) | ✗ | ✗ | ✗ |
| 5. Balances the availability of timely information against privacy and security (i.e. results of fuzzing or fuzz testing) | ✗ | ✗ | ✗ |
| 6. Describes how MMA integrates with other software (i.e. results of fuzzing or fuzz testing) | ✗ | ✗ | ✗ |
| 7. The need for MMA security software to be updated so it can be used alongside other systems, applications or in operating environments (i.e. results of fuzzing or fuzz testing) | ✗ | ✗ | ✗ |
| Assess the potential for changes to the software (updates). | | | |
| 1. Adaptive software changes (i.e. maintains software within dynamic environment) | ✗ | ✗ | ✗ |
| 2. Perfective software changes (i.e. recoding to improve performance) | ✗ | ✗ | ✗ |
| 3. Corrective software changes (i.e. corrects problems) | ✗ | ✗ | ✗ |
| 4. Preventive software changes (i.e. corrects latent faults before they cause operational problems) | ✗ | ✗ | ✗ |
| Safety | | | |
| 1. How the MMA output (i.e. information) affects clinical decision-making regarding management of a patient's condition | ✗ | ✗ | ✗ |
| Cost- effectiveness[1] | | | |
| 1. Considerations of applicability of the system, platform, licensing, attachable hardware, and versions of the MMA in the evidence base to the target population | ✗ | ✗ | ✗ |
| 2. Unit costs including the MMA, attachments and in-app purchases | ✗ | ✗ | ✗ |
| Organisational aspects | | | |
| 1. Assess if training/education (i.e. digital literacy) is need for user(s) (i.e. medical practitioners, patients, care givers) to effectively utilise the MMA | ✓ | ✓ | ✓ |
| 2. Describe how the MMA will interact with current health informatics systems (i.e. hospitals and surgeries) | ✗ | • | ✗ |
| 3. Describe if adopting the MMA will change treatment location | ✗ | ✗ | ✗ |
| 4. Describe if additional accreditation will be needed for professionals to prescribe and/or use the MMA | • | • | • |
| 5. Describe if adopting the MMA will alter the current utilisation of services | ✗ | ✓ | ✓ |
| Ethical aspects | | | |
| 1. Assess if the MMA has a privacy policy | ✗ | ✓ | ✗ |
| 2. Appraise the content of the MMA's privacy policy | ✗ | ✗ | ✗ |
| 3. Describe access issues related to MMAs | ✗ | ✓ | ✗ |
| 4. Appraise any equity issues related to the MMA | ✗ | ✓ | ✓ |
| 5. Assess possible conflicts of interest | ✓ | • | • |
| Legal aspects | | | |
| 1. Review litigation risks to the relevant person(s) associated with the use or recommendation of the MMA | ✗ | ✓ | ✗ |
| 2. Review how insurance(s) for all stakeholders would be affected through use or recommendation of the MMA | ✗ | ✗ | ✗ |
| 3. Review possible professional registrations to the relevant person(s) associated with the use or recommendation of the MMA | ✗ | ✗ | ✗ |
| 4. Assess which party owns the data related to the MMA | ✗ | ✗ | ✗ |
| 5. Assess which party is responsible for the medical advice provided by the MMA | ✗ | ✗ | ✗ |
| 6. Assess which stakeholder is responsible for monitoring and reviewing the patient data entered into the MMA | ✗ | ✗ | ✗ |
| Social aspects | | | |

| | | | |
|---|---|---|---|
| 1. How the use of the MMA may affect the patients' care giver(s) | ✗ | ✓ | ✓ |
| 2. How the use of the MMA may affect the users' relationships (i.e. family dynamics, friends, and other relevant social relationships) | ✗ | ✓ | ✓ |
| Reappraisal | | | |
| Post-market monitoring | | | |
| How the manufacturer plans to monitor the MMA's performance data | ✗ | ✗ | ✗ |
| How the data collection implemented is the least user burdensome approach to collect the MMA's performance data | ✗ | ✗ | ✗ |
| How the post-market data could be used to enable or disable new MMA functionalities | ✗ | ✗ | ✗ |
| Post-market data that requires a full review of the effectiveness and safety of an MMA i.e. performance data that alters the effectiveness measures of the MMA and/or which changes the harms posed by the MMA | ✗ | ✗ | • |

**Explanatory notes:**
Item(s) addressed: ✓
Item(s) partially addressed: •
Item(s) not addressed: ✗
[1] Using a fee for service model
HTA: Health technology assessment
MMA: Mobile medical applications

### Current use of the technology

All of the HTA agencies reviewed the key concepts regarding the use of apps as part of the medical service. These concepts included the intended purpose of the medical service under evaluation, as well as the healthcare conditions or situation the services aims to address.(165, 167, 169, 170, 172-175, 178) Unlike AHRQ and CADTH, EUnetHTA did not review the MMA algorithm (software) of the medical services under review. (165, 167, 169-175, 177) None of the HTA agencies reviewed the MMA input, algorithm, or output.(163, 167, 169, 171-179)

### Effectiveness

The additional assessment methodologies recommended for appraising the effectiveness of apps by the MMA HTA module, were not addressed by AHRQ, CADTH, and EUnetHTA. Specifically, none of these jurisdictions reviewed software performance measures (e.g. accuracy, precision, or analytical validity) of MMAs during HTA evaluations.(163, 167, 169, 171-179) Similarly, an MMA's configuration, cybersecurity, and interface were not assessed. (163, 167, 169, 171-179)

### Safety

All of the included HTA agencies and network(s) utilised various, but, similar methods to review the safety of a medical service. These methods included, but were not limited to, assessing the diagnostic accuracy of medical device. However, none of the methods included any techniques that evaluated the harm of misinformation produced by any of the medical services, and how this information impacts on clinical decision making.(163, 167, 169, 171-179)

### Cost- effectiveness

None of the included HTA agencies made any concessions for MMAs (i.e. in-app purchases, applicability of operation system or platform, etc.) in their respective cost-effectiveness evaluations.(163, 167, 169, 171-179) However, the respective agencies all have different requirements for economic assessments, and this needs to be taken into consideration.

Unlike CADTH and EUnetHTA, AHRQ did not include an economic evaluation in their assessment of medical services.(165, 167, 169, 170, 172) The AHRQ does consider "*Potential for significant economic impact: To reduce unnecessary or excessive cost"*(167), however the methodological documents do not expand on how to evaluate or define a significant economic impact in the American healthcare context. CADTH and EUnetHTA review the type of, and rationale for, an economic evaluation, as well as the circumstance in which the medical service is used.(170, 172) Sensitivity analyses are also required by CADTH and EUnetHTA.(165, 167)

All of the jurisdictions incorporated an estimation of cost and use of the medical services.(165, 167, 169, 170, 172-177) However, CADTH did not estimate how the adoption of the medical service under review could affect the use and cost of other medical services or additional financial implications. AHRQ, CADTH, and EUnetHTA, did not evaluate the justification for the data source selection nor the steps taken to identify, estimate, or reduce uncertainty within a financial context. (165, 167, 169, 170, 172-177)

Finally, none of the included jurisdictional HTA bodies thoroughly assess translational issues to the same extent that the HTA MMA module does.(26) AHRQ did not evaluate any translational issues; whereas, CADTH and EUnetHTA do identify whether any translational issues have been identified (e.g. population characteristics and circumstances of use).(169-177)

### Organisational aspects

AHRQ, CADTH, and EUnetHTA all evaluated if additional training and accreditation is needed to properly deliver a medical service.(165, 169, 172) However, only CADTH and EUnetHTA considered whether if implementation of a medical service may affect the utilisation of other services.(169, 170, 172) Whereas, CADTH partially appraised how a medical service interacts with the current health informatics systems as it reviews implementation issues such as operations constraints.(169) None of the HTA agencies evaluated if the adoption of a medical service may result in a change in treatment location.

### Ethical aspects

MMAs present a number of ethical concerns. All of the agencies reviewed conflicts of interest (COI) to some extent. AHRQ evaluated the COI related to the studies included in the evaluation as well as those

related to the authors of the submission and/ or the person conducting the HTA evaluation on the selected medical service.(167) CADTH reviewed the COI related to the submission authors and/ or the HTA evaluator, and EUnetHTA appraised COI related to the included studies.(169, 172) Regarding privacy and confidentiality, only CADTH reviewed the privacy policy of medical services as well as any access issues that may arise from implementation or use of a selected medical service.(169) None of the agencies reviewed the contents of the privacy policies. However, both CADTH and EUnetHTA evaluated any equity concerns that may arise from use or adoption of a particular medical service.(169, 170, 172)

### Legal aspects

Unlike CADTH, neither EUnetHTA nor AHRQ reviewed any liability or other legal concerns related to the medical service under review.(169) Legal concerns are a major concern in MMA evaluation due to the lack of clarity around professional liability and responsibility as well as the ambiguity surrounding data ownership and data monitoring.

### Social aspects

This domain is deemed non-compulsory and should be included in the optional section of the HTA guidelines. AHRQ, CADTH and EUnetHTA all had an optional section to review medical service capabilities.(165, 169, 172) The social implications of how an MMA may affect the patient or their carer (e.g. relationships, training, home care) domain were appraised by CADTH and EUnetHTA.(169, 172)

### Reappraisal

The evaluation of post-market changes to medical services was only partially assessed by EUnetHTA. Their evaluation includes the re-assessment of a medical service using post-market 'real world data' and post-market RCT data to review the technologies' relative effectiveness and safety after they have been implemented.(174, 175) Finally, the potential for software alterations --through updates—and their impact on a, MMAs effectiveness was not considered.(163, 167, 169, 171-179)

### 7.3.5 Discussion

The MMA evaluation module could feasibly be used by international HTA agencies to assess whether apps should be reimbursed as part of a medical service. Where the international HTA agencies differed was with respect to addressing the cost-effectiveness of a medical service. AHRQ did not have comprehensive cost-effectiveness guidelines. Whereas, CADTH and EUnetHTA had comparable guidance on the evaluation of economic aspects. However, the assessment guidelines used by CADTH and EUnetHTA examine different concepts to the ones used in Australia by MSAC.(170, 172) AHRQ, CADTH, and EUnetHTA have comparable HTA methodologies to Australia for assessing clinical effectiveness of medical services to Australia's MSAC guidelines.

The difference in approaches to assessing the cost-effectiveness of medical services has provided challenges to the transferability of the MMA evaluation module to comparable jurisdictions. The module was created within the parameters of the Australian healthcare context and the fee-for-service funding model. Thus, to ensure that the MMA evaluation module can be used to adapt jurisdictional HTA bodies' methodologies for assessing apps for reimbursement and decision-making purposes, it would need to be recognised that the recommended cost-effectiveness domains may not be relevant or achievable.

For AHRQ to use the MMA evaluation module, the cost-effectiveness domain would need to be removed as the agency does not appraise it.(180) Whereas, CADTH and EUnetHTA would only have to make minimal adaptations to the MMA evaluation module to be able to employ it.(165, 167, 169-177)

Other changes to the MMA evaluation module that would be needed to make it transferable to other jurisdictions are limited to the organisational, ethical, and legal domains. These adaptions would involve the removal of items within each domain that are already addressed, in order to prevent unnecessary repetition and re-evaluation of the same concept.

Minimal content would need to be modified within the organisational domain. One of the concepts which could be removed from the module, if adopted, is the consideration of whether extra training is needed to be able to effectively utilise the app with a medical service. There is currently already provision for this. Finally, the need to assess utilisation of services would be unnecessary for CADTH and EUnetHTA, but required for AHRQ as it does not address this.

Concerning the ethics, legal, and social domains, the majority of the module content would need to be added to the respective agencies HTA processes.

Regarding the ethics domain, the assessment of possible conflicts of interest would need to be removed from the module by AHRQ, while EUnetHTA would need to remove the assessment of equity issues.(165, 167, 169, 170, 172) CADTH assesses the majority of the relevant ethical concepts in their methodology.(169, 170) Thus, the only items which would be kept from the MMA module are the assessment of the content of MMA privacy policies, as well as a possible thorough review of any possible conflict of interests related to the app.(170)

Only a minimal modification would need to be made to the legal domain of the module for it to be transferable to similar jurisdictions. CADTH is the only one of the three jurisdictional agencies that assesses legal concerns. The concept which would need to be removed is the one that reviews possible litigation risks associated with the use and recommendation of MMAs from the module.

The assessment of the social domain is non-compulsory, so there is no pre-determined guideline of what concepts needs to be evaluated.(165, 167, 169, 172) However, common concepts from this domain evaluated by both CADTH and EUnetHTA include how a medical service may affect the patients' carer (e.g. relationship, training, home care).(169, 172)

With some changes to the MMA evaluation module, the remaining evaluation criteria could be used by the respective jurisdictional HTA agencies to adapt their methodological guidelines to enable the proper evaluation of apps for reimbursement and decision-making purposes. Furthermore, the relevant HTA bodies could use this MMA evaluation module while they research into developing their own approach within their own healthcare context.

This module is the first of its kind to enable an HTA evaluation of MMAs. The closest comparison is the *Evidence Standards Framework for Digital Health Technologies (March 2019*) by the *National Institute for Health and Care Excellence's (NICE)* in the United Kingdom (UK).(181) This framework provides standards of evidence that ought to be available and/or developed for a digital health technology. The evidence should include information on the effectiveness of the intended use of the software, as well as associated economic impact relative to any financial risk.(181) This is done to demonstrate the health technology value to the healthcare system in the UK. This standards of evidence may not be applicable to MMAs globally as the *Framework* is aimed at evaluating digital technologies specifically commissioned for use with the UK health system and not for digital health software available direct to use through global app stores.(181)

### Limitations

There were two major limitations to this study. Since the HTA methodology documents from the included jurisdictions were compared and contrasted to the MMA evaluation module and all the documents were only evaluated by myself, hence, there is a risk that my conclusions may not be generalisable. The second limitation is that one source of information (publicly available methodological documentation) was used. There may well be methodological guidance documents used by these HTA agencies that are not in the public domain.

## 7.3.6 Conclusion

In conclusion, based on publicly available information, in its current form the MMA evaluation module is transferable to other comparable HTA agencies. Minimal modifications would need to be made to the module for it to be used by these agencies. Aside from the adaption and integration of the newly created reappraisal domain, most of the adaptations to the MMA evaluation module are small and many unique MMA items (e.g. post-market software, updates, cybersecurity) would remain. Those concepts being removed from the module are ones that are already evaluated in the current agencies' guidelines, to prevent the repetition of elements. The modifications made to the cost-effectiveness domain, are dependent on the healthcare context and the methodologies employed by respective jurisdictional agencies to facilitate the economic evaluation.

## 7.4 Postface

### 7.4.1 Chapter summary

This chapter addresses the third research question which was to determine what key policy changes and assessment criteria are needed to facilitate the development of a system that evaluates MMAs for reimbursement purposes in Australia. This was achieved through synthesising the findings from *Chapter 5 and 6* with the results of in-depth interviews with stakeholder groups.

The results demonstrated that there were policy holes in the regulatory and reimbursement criteria used to evaluate MMAs. Regarding regulatory policy, the TGA does not adequately evaluate MMAs with respect to the unique challenges the technology presents. Policy changes to current regulation should include an assessment of the potential harm from misinformation, as well as possible risks associated with connectivity compatibilities, and cybersecurity threats. For more information, see *Chapter 5*.

Similarly, there were a number of policy changes identified that could be used to facilitate reimbursement of MMAs as part of a medical service in Australia. The systematic literature review of MMA evaluation frameworks found that there was a greater need to evaluate the harms posed by MMAs (i.e. misinformation) as well as to undertake a more comprehensive consideration of the likely comparator for the technology. Other considerations included, but were not limited to, equity of access to MMAs (i.e. by way of age, literacy, user disability, etc.) as well as the importance of secure and proper management of confidential data. In addition, technology specific concerns would need to be considered. These considerations include, the possible effect of software updates on the effectiveness and safety of MMAs, as well as variation in app performance on different operating systems (OS), mobile platforms, and generations of the same platform. For more information, see *Chapter 6*.

Finally, the interview with stakeholders sought to explore possible pathways and impediments to MMA reimbursement in Australia, and highlighted the need for a few policy changes. These policy considerations could include: clarification around where the responsibility lies regarding various aspects of MMAs, such as data ownership and professional liability for using and prescribing apps; ensuring the digital health literacy of healthcare practitioners, patients, and any other MMA users (i.e. carers); and finally, providing evaluative measure which address the technological evolution of MMAs, such as the technology's rapid lifecycle (e.g. updates). Current Australian policies which provide a pathway for MMA reimbursement are generally trusted by stakeholders as the HTA process ensures that there is rationale behind why an MMA should be used as part of a medical service.

All the aforementioned policy concerns indicated that in order for MMAs to be reimbursed in Australia, the first step is to ensure that they are evaluated properly. To ensure that the harms MMAs pose are properly evaluated, a module was developed which could be used to modify the current HTA framework employed by MSAC. This adaption of the current MSAC approach ensures the technology specific harms are addressed and thoroughly appraised. The adapted process could be used to evaluate MMAs used as part of a medical service for a public funding decision. It is important to note that the module addressed both regulatory and reimbursement policy concerns. This is to ensure that the regulatory issues are reviewed, as current TGA processes do not properly evaluate them.

The MMA evaluation module could feasibly be adapted (in part) to be used by comparable HTA jurisdictional bodies (EEA, Canada, USA). Minimal modifications would need to be incorporated to the module processes. Most of these adaptations included the adoption of the newly added reappraisal domain, as well as the adjustment to review the unique MMA items (e.g. software, updates, cybersecurity) that were not already addressed in the jurisdictional HTAs' agencies original processes. The remaining modification to the HTA MMA module addressed the cost-effectiveness domain. The adaptation to this domain would depend on the individual economic evaluations conducted by the respective jurisdictional HTA agencies and their individual healthcare contexts.

### 7.4.2 Publications and presentation of chapter findings

#### Publication(s)

*Under-review*

- Moshi MR, Tooher R, Merlin T. Development of a health technology assessment module for evaluating mobile medical applications. *International Journal of Technology Assessment in Health Care*.

*Conference proceedings*

- Moshi M, Tooher R, Merlin T, editors. OP144 mHealth App Evaluation Framework For Reimbursement Decision Making. HTAi 2019 Annual Meeting; 2019; Cologne, Germany: Health Technology Assessment International

#### Presentation(s)

- September 2019, **Poster**, Moshi* MR, Tooher R, Merlin T. mHealth app evaluation framework for decision-making purposes, *13th Annual Florey Postgraduate Research Conference*, Adelaide, South Australia.
    - Award: Florey medical research foundation prize

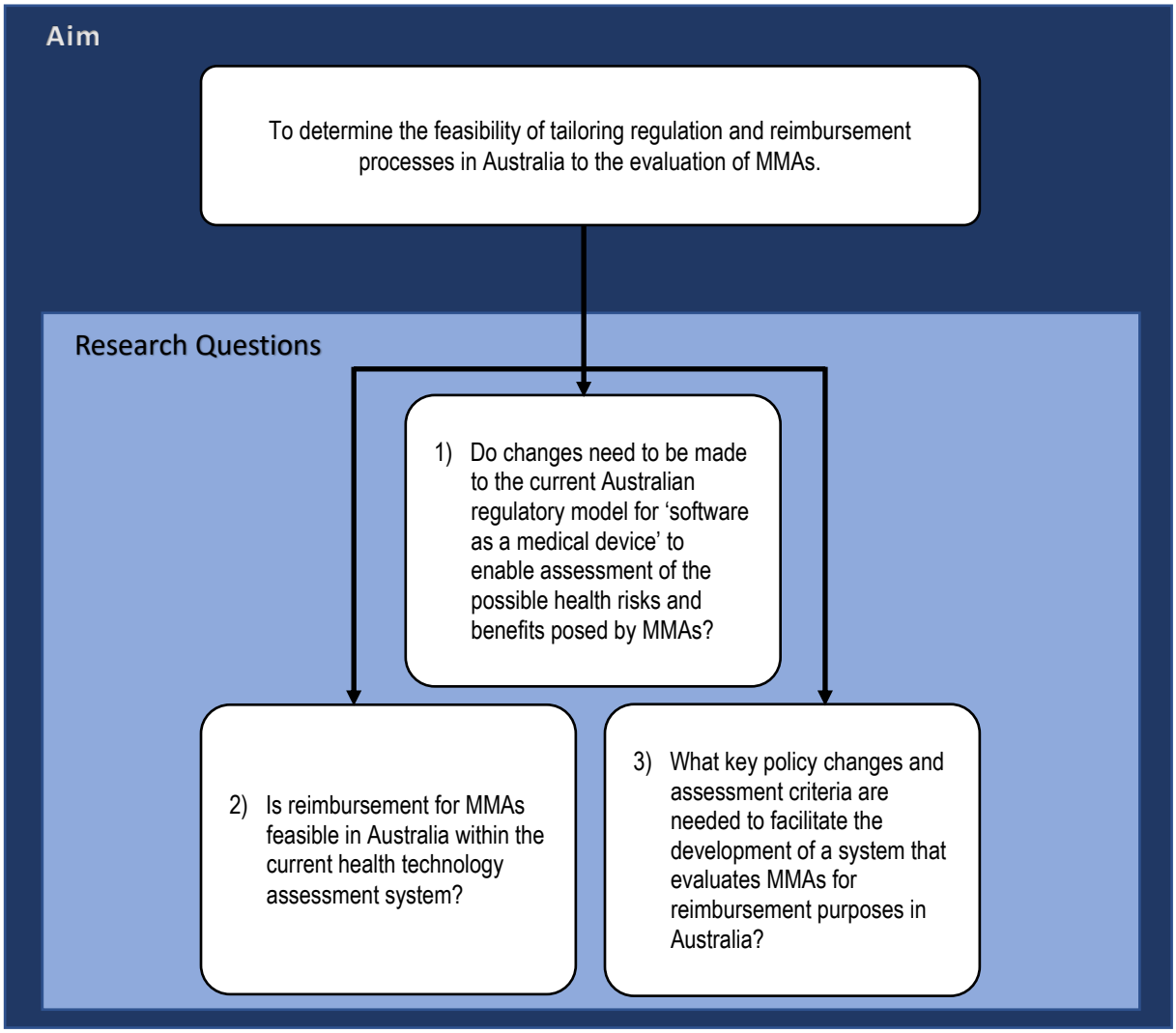
- June 2019, **Presentation**, Moshi* M, Tooher, R, & Merlin, T. mHealth app evaluation framework for reimbursement decision-making. *Health Technology Assessment International (HTAi) Annual Meeting,* Cologne, Germany.

# Chapter 8: Synthesis and recommendations

## 8.1 Introduction

The chapter draws together the findings from all of my research to address the overall aim of this thesis, which was to determine the feasibility of tailoring regulation and reimbursement processes in Australia to the evaluation of MMAs. How the thesis aim interacts with the three research questions addressed in *Chapter 5, 6, and 7*, is detailed below in Figure 8.1. Figure 3.1 in *Chapter 3* demonstrates how this section relates to the aim of this thesis to the respective research questions.

Figure 8.7: Structure of thesis aim and research questions



## 8.2 The feasibility of an MMA evaluation framework for HTA in Australia

In order to determine whether it is feasible to tailor regulation and reimbursement evaluation processes in Australia to MMA technologies, the findings from *Chapters 5, 6, and 7* and their respective studies were integrated and synthesised.

### 8.2.1 Evaluation of MMA regulation in Australia

In order to evaluate if regulation in Australia in its current form is capable of assessing the unique challenges posed by MMAs, a policy analysis and a comparative analysis of case studies was undertaken. The policies underpinning the Australian and international regulation of MMAs were compared and contrasted to the IMDRF's *SaMD: Clinical evaluation(22)* guidance document. This policy analysis focused on the approaches used by IMDRF member jurisdictions to regulate MMAs and determined whether these were consistent with the guidance they had also formulated to regulate software as a medical device (*SaMD: Clinical Evaluation(22)*). The case-studies from Australia and the United States examined to what extent the observable regulatory processes followed policy, and also investigated whether these SaMD policies had been enacted.

The Australian regulation of MMAs and/or any accompanying hardware is consistent with regulatory policies enacted internationally. However, it does not wholly comply with the IMDRF *SaMD: Clinical evaluation(22)* guidance document's recommendations.(141) Four of the five categories recommended in the IMDRF's *SaMD: Clinical Evaluation(22)* guidance document are addressed to some extent by the Australian MMA regulations. The fifth category that was not adopted by the TGA and other international jurisdictional regulatory agencies' in the evaluation of MMAs was safety (as defined in *SaMD: Clinical Evaluation(22)*).(141) International and national regulatory agencies do not evaluate MMA safety in terms of the cybersecurity risks, and do not classify the potential risk/harms of the software.(141) *SaMD: Clinical Evaluation(22)* recommends the utilisation of a risk-classification system that assesses the harm posed by software in terms of how the information provided affects clinical decision-making. The risk is calculated by comparing the severity of the condition the software is treating, diagnosing, or managing against the impact the software output has on clinical decision-making.(22, 141)

Internationally, the European Commission and the FDA have had to develop new medical device legislation to properly assess the challenges that SaMDs, like MMAs, present.(60, 89, 111-113) In April 2017 a new medical device policy was released by the European Commission which allows provision for regulatory processes to adapt to momentous developments in technology and science.(111) The adaptions include stricter evaluations and classifications of MMAs. For example all MMAs will have a

default risk-classification of IIa instead of the previous Class I.(182) These regulatory changes are to be implemented between 2020 and 2022.(111, 183) The FDA is currently exploring a software (including MMAs) pre-certification programme which is based on the guidance in the *SaMD: Clinical Evaluation.* This pilot investigates an approach which evaluates and pre-certifies the SaMD developers for their software designs, testing, and other matters.(60, 89, 112, 113) Similarly, in 2019 Health Canada put a draft guidance document for SaMD regulation out for public consultation.(184, 185) This draft guidance document details a risk-classification for SaMDs based on the one recommended by the IMDRF.(186) The aim of consultation is to discuss ways to better address the regulatory requirements for emerging technologies such as MMAs.(184, 185)

Currently, there is no publicly available information which details why these recommendations from the IMDRF's *SaMD: Clinical Evaluation guidance(22)* document have not been officially been adopted by the jurisdictional agencies which drafted them. However, since the recommendations were released in 2017, it appears that over time, the individual agencies are attempting to integrate aspects of the recommendations into their regulations. Nonetheless, the lack of adoption of the safety/risk classification system recommendation from the IMDRF guidance document by international regulatory agencies is concerning, particularly as these agencies *drafted* the IMDRF guidance document.

This analysis suggests that proper regulation of MMAs is currently an evolving process. Concerns about the impact of MMA information on clinical decision-making are known and understood but are not currently reflected in international regulatory policy. The risk of misinformation (through poor quality control of the information included in apps, as well as the deliberate harmful manipulation of this data (cybersecurity risks)) is, therefore, not being monitored or assessed in the international regulation of MMAs (see *Chapter 5*).(141) There does not appear to be comprehensive regulatory policies in place, domestically and globally, to *prevent* the harms posed by MMAs and their accompanying attachments; however current *post-market* measures are addressing any concerns that may arise. For example, the TGA issued a safety warning on MMAs, such as the one issued on the *Accu-Chek Connect Diabetes Management* app in September 2016 due to a programming error.(96) Similarly in June 2019, the FDA issued a safety warning on the *Medtronic MiniMed* insulin pump due to cybersecurity risks and patients were urged to cease use of the device and to change pumps. As with any other medical device Medtronic recalled the affected devices and replaced them with alternative insulin pumps.(187)

### 8.2.2 Evaluation of MMA reimbursement in Australia

Due to the fact that MMAs are such a dynamic technology which present different types of risks and benefits than traditional medical devices,(7, 22, 48, 60, 89, 112, 141, 149, 188) a universally accepted

Australian approach does not currently exist on how to provide the best evidence to decision-makers on the safety, effectiveness and cost-effectiveness of medical services that utilise MMAs. Thus, a systematic review of MMA evaluation frameworks was conducted to determine if any can be used to assess MMAs for reimbursement purposes.

### Assessment of other possible frameworks to evaluate MMAs for reimbursement purposes

All existing MMA evaluation frameworks (published prior to 31st October 2016) were assessed to determine if MMA reimbursement within the current Australian HTA system is feasible.(149)

In summary, none of the 45 MMA evaluation frameworks identified could be used, unaltered, to conduct an HTA of an app. These 45 frameworks did not address all six of the core domains that are needed to conduct a full HTA.(149) Although, notably, a framework by Walsworth(189) did assess the effectiveness, cost-effectiveness, and safety, of an MMA.(149) However, like the majority of the other frameworks, it did not evaluate the MMA parameters in enough detail – further information was needed on the comparator, as well as on the potential for harm.(149)

This review of MMA evaluation frameworks indicated that there are technologically specific considerations that need to be taken in to account when assessing apps. These include a more comprehensive evaluation of the ethical challenges associated with app use, as well as connectivity and compatibility issues.(149)

Ethical concerns were primarily related to privacy and confidentiality, and the role of cybersecurity.(36, 48, 60, 89, 113, 149, 190, 191) If the device is accessed by an unauthorised person (e.g. hacked) the users' sensitive medical information would be available to others without their consent and could be used for malicious purposes. There is the potential that cybersecurity breaches could be harmful for the patient – not only through the misappropriation of confidential information but also through changing information stored in the app. These type of breaches might alter how the MMA functions, which in turn could affect the output of the app that is used in clinical decision making.(22, 36, 48, 60, 89, 113, 149, 190, 191) Lastly, companies have been known to on-sell patient data without their consent, in breach of jurisdictional laws.(46, 149)

The connectivity and compatibility concerns identified through the systematic review of MMA evaluation frameworks relate to the dynamic nature of MMAs and how this affects the performance of an app. The fact that MMAs are available across a variety of operating platforms (i.e. smartphone, tablet, smartwatch), operating systems (i.e. Android versus iOS), and different versions of the same device (i.e. iPhone 8

versus iPhone X), is a known cause for changes in app performance. An MMA may pose different risks to a user on different platforms.(22, 36, 48, 60, 113, 149, 192) For example, on September 12th 2016 the TGA issued a safety warning for an error that only affected *Accu-Chek Connect Diabetes Management* app on Apple's iOS, but not for the same app that is available on Google's Android platform.(96) Another concern is that MMAs have a fast lifecycle, which results in multiple software updates. One incremental update may not alter the intended purpose of the MMA; however, a variety of incremental updates over time may dramatically change the focus of an app and its output.(22, 48, 60, 113, 149, 192) For a full summary of the study see Moshi, Tooher & Merlin(149) in *Chapter 6*.

As the review found that no existing MMA evaluation framework could be used to evaluate these technologies for reimbursement decisions, and so it may be more sensible to adapt existing HTA methods and processes to examine the specific characteristics of these technologies. Technology-specific elements relating to data ownership, privacy and data security, as well as information or algorithm credibility and stability, need to be incorporated into HTA processes when evaluating MMAs for a public funding decision both in Australia and elsewhere.

### 8.2.3 Possible impediments and pathways to MMA reimbursement

Stakeholder interviews were conducted to identify possible impediments and pathways to MMA reimbursement in Australia. The in-depth interviews involved healthcare practitioners (nutritionist(s), general practitioner(s) (GP), physiotherapist(s)), policymakers, and healthcare app developers.

The stakeholders who were interviewed expressed a fundamental underlying *trust* in MSAC and the HTA evaluation that informs which medical service can be reimbursed through the MBS. *Trust* was centred around how the HTA process requires a *rationale for use* and enables *evidence-based policy*. This suggests that healthcare practitioners would be more comfortable using MMAs in clinical consultations, and recommending the devices to their patients, if apps were reimbursed through *Medicare*. Specifically, that this comfort was not due to the financial benefits to the healthcare practitioners of having the review of app information subsidised, but was rather due to an awareness of the underlying rigour and completeness of an evaluation that a medical service must to undergo before it can be listed on the MBS. Particularly, there was understanding of how this process protects patient safety and ensures that the reimbursed devices are clinically effective.

Conversely, the stakeholders conveyed some concerns about MMAs and their integration into the current health system. These concerns were caused by the stakeholders' inability to *trust* the technology because they felt there was currently no evaluative method available to properly assess them. A major issue raised

was the post-market surveillance of MMAs. Interviewees were aware of the *technological evolution* of MMAs. They were concerned by the software's rapid lifecycle and the potential for multiple updates which could alter the various elements of how the health intervention could be delivered. A second major concern was that there were unclear lines of responsibility surrounding practitioner accountability and jurisdictional oversight of the advice provided on the basis of data collected through an app. Interviewees also wanted clarity around who owns the data produced by the MMA and how this could potentially infringe on patients' rights to confidentiality and privacy. Finally, *digital health literacy* of healthcare practitioners and patients was identified as a concern. The main concern of the healthcare practitioner was the fidelity of the data inputted into the MMA by the patient and how this could affect the app's safety and efficacy. Furthermore, practitioners raised concerns that patient self-management could be impaired by a lack of knowledge in how to interpret the MMA output.

The interviews with stakeholders provided insights into the possible pathways and impediments into MMA reimbursement. The current HTA pathway for medical services (used by MSAC in Australia) was considered the right pathway, although it was acknowledged that for MMAs this needed to change to accommodate a range of other methodological and policy issues associated with the ownership, curation and interpretation of digital information, as well as the responsibilities and consequences associated with using this information. For the complete study see Moshi, Tooher & Merlin(155) in *Chapter 7 (Section 2)*.

## 8.3 Policy changes required for MMA reimbursement adoption and development

If MMA reimbursement is going to be possible within the Australia healthcare system, various changes are needed within healthcare policy.(141, 149)

Firstly, regulatory policy would have to be adapted so it is capable of evaluating the challenges presented by MMAs.(141) To address the unique dynamic technological challenges presented by MMAs and other types of SaMDs, the TGA should adopt the IMDRF SaMD risk-classification system.(141) Moreover, the TGA should work on creating a method which is capable of evaluating the cybersecurity threats posed to MMAs due to the connectivity of their operating platforms, the app's software and/ or accompanying hardware.(141) Where there is a risk of physical harm, the current TGA risk-classification (*Appendix A.2*) should continue to be applied, e.g. for the hardware accompanying MMAs.(141) Since regulation is the first step to a medical service being eligible for *Medicare* reimbursement, a regulatory evaluative process that is capable of properly assessing the risk and benefits associated with MMAs, opens a reimbursement pathway for apps.(14, 19, 141, 193, 194)

Secondly, a variety of policy implications arose from the review of MMA evaluation frameworks. There is a need to develop an MMA evaluation framework that is specific for policy purposes, and specifically for HTA.(149) The framework should be capable of assessing HTA matters in the required depth of detail, as well as the technology specific challenges that MMAs represent.(149) The HTA concerns that would need to be addressed in processes to evaluate MMAs include the formal consideration of a comparator (to assess comparative safety, comparative effectiveness and comparative cost-effectiveness), assess all harms (including misinformation and the possible consequences to clinical decision making and patient health outcomes), and proper assessments of the cost-effectiveness of a medical service utilising an MMA.(149) The technology specific issues that should be considered, both in the methodological approach used by the HTA evaluator, as well as by decision makers, include the fast lifecycle of MMAs, varying platforms, multiple operating systems, ethical concerns, and cybersecurity risks.(149) It is important to mention that, traditionally, the mandate to evaluate the harms of a software would fall under the authority of the TGA.(149)

It is important to note that there are wider policy issues regarding ethical concerns related to the health data that MMAs produce. These issues could not be addressed in this thesis alone, however are still a major concern when undertaking an HTA on apps. The health data produced by eHealth technologies is changing the power dynamic in health research, in terms of data ownership, consent, privacy and confidentiality.(195, 196) For example, it is rather simple for corporations to gather a private individual's health data and conduct their own unsupervised research on the collected data. Whereas, for researchers to generate the same data would require approval from human research ethics committees (HREC) - a rather difficult procedure - and significant oversight of the welfare of the study participants. This change in "the gatekeeper" of data collection and research could result in a decrease in patient rights. Regulatory oversight over how private corporations conduct their big data research is often lacking; a role that was traditionally overseen by HRECs within academic research infrastructure. This could be a concern as patients generally provide consent to access goods and services - not overtly to be the subject of research. (195-197) Thus, the consent of these individuals may not be fully informed and could be partly coerced by making availability of a good/service contingent on participant agreement to offer their data. As the research done by corporations is technically not for enlightenment, but rather for audit purposes and quality assurance, it therefore does not fall under the purview of HRECs. This means that there is currently no clarification – as occurs under the HREC process - on who owns the data that is collected. Considerably more research and clarification needs to be provided regarding the ethics of data collection and data ownership in MMAs.

Lastly, policies would have to facilitate an increased *trust* in apps by stakeholders. This could be achieved through ensuring apps are evaluated in a manner consistent with other health technologies i.e. *evidence-based policy* development, and by also addressing stakeholder distrust. Addressing distrust could be achieved by increasing *digital health literacy*, monitoring *technological evolution*, and clarifying jurisdictional and practitioner *responsibility* regarding MMAs and the data they produce. What is most challenging about attempting to increase stakeholder *trust* in MMAs in Australia is that the mandate to address *digital health literacy*, *technological evolution*, and *responsibility* may not fall within the jurisdictional mandate of the federal or state health departments. Clarification on who has this mandate is needed. For example, ensuring the *digital health literacy* of health practitioners may fall under the responsibility of *APHRA*(54) (oversee healthcare practitioner registration), whereas the mandate to provide clarity around data ownership and intellectual property issues would come from *IP Australia(53)*. Moreover, health practitioners' concerns over malpractice and professional liability concerns could fall under the mandate of multiple entities. These include *APHRA*(54) and individual providers of professional indemnity insurance.(198, 199)

Most of the policy concerns highlighted above could be addressed as part of the development of an MMA evaluation module. This module was created with the intent to modify existing HTA guidelines utilised by MSAC to inform reimbursement decision-making in Australia. The module could be used as a permanent or temporary answer to the evaluative challenges posed by MMAs until wider policy solutions are found that address the concerns highlighted earlier.

### 8.3.1 Creation of MMA evaluation module

The MMA HTA evaluation module was created to support an evaluation of MMAs for HTA purposes. The module was aimed at filling the holes in current domestic policy responsible for evaluating MMAs for reimbursement and regulatory purposes. For example, the module evaluates the technology specific challenges presented by MMAs, which current domestic regulatory and HTA guidelines do not address. Thus, the intention of this module was to inform evidenced-based decision-making with regards to MMAs in Australia, through modifying current domestic HTA processes. Therefore, the module was applied to the MSAC guidance on evaluating medical services and a modified HTA framework was produced that could be used in Australia to evaluate MMAs.

Though the module is aimed at adapting HTA evaluation frameworks for reimbursement and decision-making purposes, it appraises some MMA technology specific regulatory concepts. This is due to the module being designed within the Australian healthcare context, where regulatory assessment needs to

be conducted prior to an HTA evaluation, and the TGA does not currently evaluate some MMA technology specific challenges.

Since there is no consensus on what funding mechanism should be used for MMA reimbursement in Australia, and because the findings from stakeholder interviews indicated that the MSAC HTA process was trusted, it is assumed that the current fee-for-service model (through the MBS) would be used when adapting the MMA assessment framework to MMA-specific considerations.

The complete version of the MMA HTA evaluation module and the subsequently created MMA evaluation module are available in *Chapter 7 (Section 2)*.

## 8.4 Recommendations

### 8.4.1 Use the MMA assessment framework to evaluate these apps in Australia

There is a gap in regulatory and reimbursement policies and processes in Australia with regard to the evaluation of MMAs. To make the assessment of these technologies feasible, and of use to policy makers, an MMA evaluation module was created. The subsequent adaption of the MSAC HTA process using this module meant that a way forward for evaluating MMAs for reimbursement or HTA purposes in Australia has been produced.

The MMA evaluation framework is capable of assessing apps for reimbursement and decision-making purposes with or without the recommended regulatory changes to the Australian TGA's SaMD policy. This is because the MMA evaluation framework has components that address MMA capabilities that are generally regulatory concerns. If the regulatory concerns are subsequently addressed by the TGA (i.e. their policies are changed), then these parts of the MMA evaluation framework can be removed, to avoid duplication.

Contrastingly, the clinical evaluation elements integrated into the MMA evaluation framework –at the recommendation of the module-- should not be removed if the policy recommendations are achieved. The inclusion of these elements ensures that the original core HTA domains (e.g. description and technical characteristics, current use of the technology, effectiveness, safety, cost-effectiveness, organisational aspects) properly evaluate the new technology specific characteristics of MMAs.

With the adoption of the MMA evaluation framework, it would be feasible for MMAs to be assessed properly to inform decisions on whether they should be marketed as part of a medical service, and whether the use of the MMA information in clinical decision making should be subsidised.

### 8.4.2 Clarification of important policy issues

Furthermore, clarifications about which organisations are legally responsible for various aspects of MMAs and the challenges presented by the software when used within the Australian healthcare context, is needed. There needs to be explanations of:

- The clinical liability of healthcare practitioners who use or recommend MMAs, and how this affects insurances,
- Who owns the data produced by MMAs,
- Who owns the intellectual property associated with various aspects of the MMAs.

### 8.4.3 Investigate whether it is feasible to apply the MMA evaluation module to other jurisdictions

The findings from Chapter 7 (*Section 3)* indicated that, with minimal adaptions, the MMA HTA module could be transferred and applied to processes used by HTA agencies in comparable international jurisdictions (Canada, EEA, USA). More research has to be done within the respective healthcare contexts to determine the feasibility of using the MMA evaluation framework.

## 8.5 Significance of research

No other research has been identified globally that focuses on how to assess MMAs for governmental reimbursement within a healthcare system. With increasing levels of mobile platform use for health purposes, the outcomes from this thesis have considerable policy significance, as it has been determined that MMA reimbursement in Australia is feasible through existing processes (albeit modified). Pathways for the implementation of a framework that could be used to evaluate MMAs for reimbursement decision-making have been identified. Additionally, the findings identify that the current regulatory model for SaMD in Australia is unable to properly regulate MMAs to decrease the risks they pose to the population, and that a number of policy changes are needed to ensure that proper regulation occurs.

As MMAs are not yet reimbursed as part of clinical services both domestically and internationally, the development of this possible implementation pathway (the module) may facilitate the adoption of MMAs for this purpose. There are a number of potential benefits that could occur if MMAs were publicly reimbursed in Australia. Access and equity within the Australian healthcare system could be facilitated with MMAs being truly available to every resident. Furthermore, if the recommendations help limit the potential health risks posed to the population by MMAs it may enable both medical and non-medical

consumers to make informed choices regarding the use of MMAs that have been proven (reimbursed) to be safe and clinically effective. If MMAs are reimbursable it may result in GPs and/or other healthcare workers becoming comfortable in prescribing and/or using MMAs as they would be reimbursed for using/interpreting the apps and would know that the apps are affordable for patients. Lastly, reimbursement itself could stimulate the development of good quality, evidence-based (credible) MMAs.

The recommendations from this thesis – when communicated to policymakers – could put MMA reimbursement on the policy agenda.

## 8.6 Thesis limitations

There were various limitations to this thesis. All the limitations related to the individual research articles in *Chapters 5, 6, and 7* and are detailed in the respective chapters. This sub-section will only explore limitations related to the overall thesis.

### 8.6.1 Research as a whole

There are two main limitations to the research as a whole. The first is that although the research findings may be applicable to similar healthcare jurisdictions, they may not be realistic to implement. This is due to the research being focused on the distinctive Australian healthcare context. The second limitation was the fact that the created MMA evaluation framework has not been pilot-tested on a sample of MMAs submitted for funding as part of a medical service. This is an area where further research would be beneficial.

### 8.6.2 Timeliness of research

There was a limitation specifically related the timeliness of this research. MMAs are a dynamic technology that is evolving at an incredibly fast pace. This has resulted in a significant amount of changes in the technology, regulations, and evaluative methods during the study. This was mitigated with the use of clear cut-off dates for time sensitive sections as well as acknowledging where regulations and guidelines were under review. However, the use of cut-off dates could have resulted in the information in this thesis being slightly out of date.

# Chapter 9: Conclusion

## 9.1 Conclusion of thesis

In conclusion, it is feasible to tailor Australian regulation and reimbursement processes to evaluate MMAs. However, a range of modifications to current processes are needed which will require changes to existing policy.

Regulation of software as a medical device (SaMD) needs to be changed so that it is able to assess the risks posed by MMAs. The major change includes modifying MMA regulation to evaluate the main harm posed by apps - the medical information provided and how this is material is used to inform clinical decision-making. Another policy change is the need to create a method to address the cybersecurity threats posed to MMAs though their connectivity capabilities, in order to protect user information.

Similarly, policy changes need to be made to current HTA processes in Australia. The current processes are inadequate to properly evaluate MMAs. These changes include ensuring the mandatory assessment of the ethical domain during an HTA of an MMA, to address concerns about the secure use and handling of confidential data and equity issues. Other changes involve the 'rolling review', or appraisal and re-appraisal, of app software updates and how these changes can affect the overall conclusions of an MMA's safety and effectiveness.

This study found that other policy changes would ease the pathway to MMA reimbursement in Australia, by increasing stakeholders' confidence in the technology. These policy changes include: clarifying where the responsibly lies regarding the ownership and use of data produced by an MMA; and facilitating the digital health literacy of patients, healthcare practitioners, and other possible app users (i.e. carers).

To ensure that the technology specific harms posed by MMAs are properly evaluated by regulators and funders, a module was created that was used to modify the current HTA evaluation framework used by MSAC. The adapted process could be used to evaluate MMAs properly, by taking into account their mutable digital characteristics and indirect impacts on human health.

All of the policy changes needed to feasibly tailor Australia's regulatory and reimbursement processes to evaluate MMAs can be achieved through the adoption of the MMA evaluation module. The use of the module to adapt current HTA frameworks could safeguard the Australian population until broader recommended changes (highlighted below) could be made to regulatory, reimbursement, and wider health policy.

## 9.2 Recommendations

There are a variety recommended policy changes which need to be made to ensure it is feasible to tailor regulatory and reimbursement processes in Australia to the properly evaluate MMA technology.

### 9.2.1 Evaluation of MMAs

#### Regulatory evaluation

- The TGA should adopt the risk-classification approach recommended by the IMDRF, to assess the indirect harms posed by MMAs (i.e. through misinformation and its impact on clinical decision-making).

- Attachable hardware which accompanies an MMA should be regulated in accordance with the current TGA assessment and risk-classification for physical harm.

- Due to the potential for cybersecurity threats to MMAs, the TGA should consider creating a method for penetration testing and risk categorising the information security (cybersecurity) of MMAs on different platforms and devices, and where relevant the accompanying hardware.

#### Reimbursement evaluation

- Regulatory and reimbursement authorities should work collaboratively on developing evaluation processes that are complementary.

- A HTA evaluation of an MMA should include formal consideration of a comparator in terms of the standard of care the MMA is likely to replace or supplement.

- Appraisal of the possible harms to human health presented by MMAs - through misinformation (i.e. information credibility) and its impact on clinical decision-making - should be included in the HTA of the technology.

- Technology specific challenges need to be considered for MMAs. One concern includes how software updates, OS, operating platforms, and different generations of same the platform, could alter the app performance as well as its safety and effectiveness. Additionally, MMA post-market

surveillance and HTA re-assessment should also be considered, to determine whether the original assessment still holds despite the software updates that have been applied.

- HTA processes should consider the ethical issues around privacy and confidentiality of data (due to concerns around cybersecurity) and the curation of data.

- Organisational issues which would need to be included in an HTA of MMAs include reviewing: if training and/or education would be needed for users of MMAs (i.e. practitioners or patients); if professional accreditation is needed of medical practitioners to be able to recommend clinical care on the basis of data produced by an MMA; and the assessment of whether MMAs can interact with health informatics systems utilised by surgeries, hospitals, and clinics throughout Australia.

### MMA module for HTA and reimbursement purposes

- The MMA HTA evaluation module should be trialled by international jurisdictions to modify their HTA processes to incorporate the technology-specific characteristics of apps.

- The creation of an MMA HTA evaluation framework for Australia, through the adoption of this module, means that there is now a roadmap for assessing the challenges presented by apps and their unique characteristics. These challenges include evaluating their analytical (reliability) validity, impact of software updates, cybersecurity concerns, compatibility issues (e.g. platform and operating systems), inclusion of post-market performance data, as well as other app specific concerns.

- The module could be used as a permanent or temporary solution, until wider policy solutions are found that address the concerns highlighted above.

## 9.3 Further research

The findings from my thesis have highlighted a variety of areas for further research. The MMA HTA evaluation framework (*Chapter 7*, *Section 2*) created through the use of the module, has not been pilot-tested for use in Australia and would benefit from this. Additional research should be conducted into the development of a risk-classification pathway which could be used to assess the harms posed by MMAs (and other SaMDs) that produce information, as well as the accompanying hardware. Similarly, there is a need to apply cybersecurity methods to the appraisal and risk classification of MMAs (and other SaMDs)

and any applicable attachable accompanying hardware. Moreover, there is a need for research to be conducted which could provide an evidence-base for exploration and clarification of where the various aspects of legal responsibility (e.g. data ownership, IP ownership, professional liability, etc.) for MMAs lie. Finally, in the long term, research should explore what barriers there are to the robust regulation of MMAs to safeguard the Australian population from avoidable harm.

# Appendices

# Appendix A

Supporting information to thesis background

- Definitions
- Medical device regulation
- Overview of the *Medical Service Advisory Committee (MSAC)*
- Telemedicine reimbursement

## A.1 Definitions

### A.1.1 Definition of mobile health (mHealth)

A sub-set of eHealth, mHealth, is defined by the WHO as public health and medical practices which are supported by mobile devices.(42) Mobile devices include: devices that monitor health, mobile phones (including smartphones), personal digital assistants (PDA), and other wireless devices such as tablets.(42) mHealth utilises and builds upon the core functions of mobile devices, including: short messaging services (SMS); global positioning systems (GPS); general packet radio services (GPRS); Bluetooth; third generation mobile telecommunications (3G); fourth generation mobile telecommunications (4G); as well as other software applications (apps); and complex functionalities to support health interventions at a population level.(42, 49)

### A.1.2 Definitions telemedicine and electronic health (eHealth)

It is important that mHealth is not confused with telemedicine. The WHO considers mHealth and telemedicine as both individual subsets of the overarching category of eHealth.(42, 43) eHealth is the electronic transfer of healthcare and health resources.(44) Telemedicine is the best established and most popular of the eHealth services.(43) Telemedicine is defined as *"the delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities"(43).* There is controversy surrounding the difference between telehealth and telemedicine. Some consider telehealth to be communication between allied health practitioners and patients and telemedicine to be point to point communication between medical doctors and patients.(43) In accordance with the WHO, telehealth and telemedicine will be considered interchangeable and the term will include all patient communication with any medical practitioners.(43)

### A.1.3 Definition of *In vitro* diagnostic medical device (IVD)

A medical device is considered to be an IVD "*if it is a reagent, calibrator, control material, kit, specimen receptacle, software, instrument, apparatus, equipment or system, whether used alone or in combination with other diagnostic goods for in vitro use. It must be intended by the manufacturer to be used in vitro for the examination of specimens derived from the human body, solely or principally for the purpose of giving information about a physiological or pathological state, a congenital abnormality or to determine safety and compatibility with a potential recipient, or to monitor therapeutic measures*"(93)

## A.2 Medical device regulation

### A.2.1 Medical device regulation applied to Software

How software is regulated as an active medical devices or IVDs depends on its intended purpose and how it is supplied.(6, 7, 92-94) If a piece of stand-alone software meets the TGA's definition of a medical device, it is regulated as a medical device in its own right. Software that is supplied as part of a medical device but which can act on its own without the related device, is also regulated as a stand-alone medical device. Similarly, updates to software that are supplied separately are regulated as a standalone medical device. Software that is part of a medical device, and is supplied alongside it, is regulated as within the device and not separately. Likewise, software corrections to errors that were supplied with the device software are not regulated by the TGA.(6, 7, 92-94)

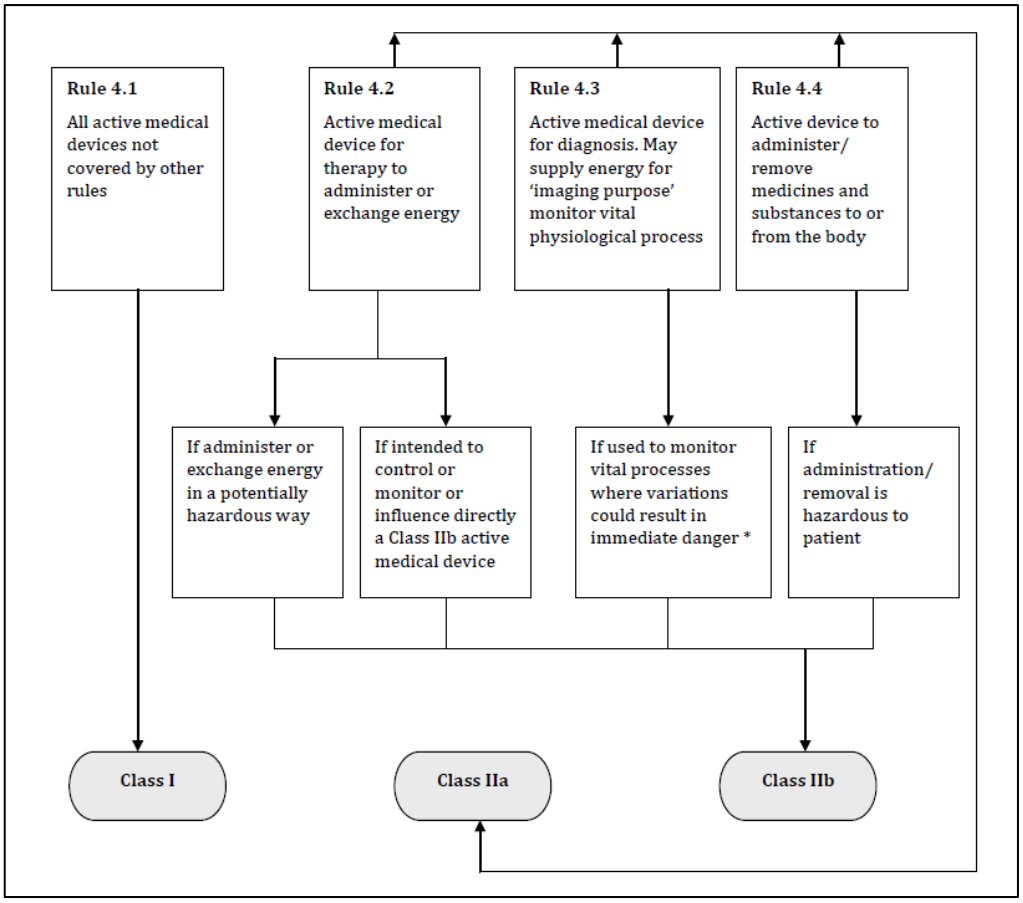
In the case where an IVD has software built into it, the software is regulated as part of the IVD.(6, 7, 92, 93) Similarly, software is regulated as an IVD when it is intended not to drive the IVD but to provide therapeutic or diagnostic information. An IVD which is supplied separately to the software and is intended to influence or operate it, is regulated as a separate and distinct IVD. Whereas, software corrections are generally regulated as a correction; however, if it changes the original functionality of the software, such as adding a new feature, the software will be regulated as a separate IVD. Furthermore, software used in combination with equipment used to manage patient data and information for both non-IVD medical devices and IVDs is not regulated by the TGA.(6, 7, 92, 93)

### A.2.2 Medical device risk-classification

#### Active medical devices

Both active medical device and IVD risk-classification applies to software and thus to MMAs. The risk-classification used for non-IVD medical devices is categorised as Classes I, IIa, IIb, III. The classification is scaled, so devices that are classified as Class I provide the lowest risk to public health and safety while Class III devices offer the highest risk. Software is classified using the categorisation for an active medical device (see Figure A.1).(6) Active medical devices which are classified within Class IIa or IIb are devices that are used for therapy (exchange or administer energy), diagnosis (supply energy for imaging, monitoring physiology process), and remove or administer medicines/substances. An active medical device such as standalone software/ MMAs that are not covered by the Class IIa or IIb classification are considered Class I.(6)

Figure A.1: Active medical device risk-classification




Source: Therapeutic Goods Administration (5)

### *In vitro* medical devices (IVDs)

IVD risk-classification is slightly different. IVDs are classified as Class 1, 2, 3, or 4. Class 1 posing the lowest risk to public health while devices in Class 4 offering the highest risk.(92, 94, 95) See Table 1 below for how IVDs are classified.

Table A.1: IVD risk-classification

| IVD Risk-classification | Level of risk |
|---|---|
| Class 1 | No public health risk or low personal risk |
| Class 2 | Low public health risk or moderate personal risk |
| Class 3 | Moderate public health risk or high personal risk |
| Class 4 | High public health risk |

Source: Therapeutic Goods Administration (82)

## A.3 Medical Services Advisory Committee (MSAC)

The MSAC is an independent common law committee within the Federal Department of Health. The committee makes a none-binding recommendations to the Federal Government Minister of Health on whether or not a medical service in Australia's should publicly funded through the MBS and the circumstances in which it can be.(19, 130) If MSAC are going to recommend a service for funding through the MBS the committee needs to ensure at the time of the recommendation that: the service in which the applicant is apply for public funding is registered on the ARTG; the service has met the HTA core domains of being comparatively clinically effective, comparatively cost effective, and comparatively safe; and that the services fits the criteria outlined in the *Health Insurance act 1973*[4].(19, 26)

There are two sub-committees within MSAC, the *Evaluation sub-committee (ESC)* and the *PICO*[5] *Advisory Committee (PASC)*. MSAC has an executive committee that manages actives between the sub-committees between formal meetings. This executive committee is made up the chairs of PASC and ESC as well as the deputy chair of MSAC.(26, 200)

[4] If needed MSAC can liaise with the Department of Health legal and policy services for advice.
[5] PICO: Population, Intervention, Comparator, Outcome

## A.4 Telemedicine reimbursement

The Federal Government has acknowledged the importance of the eHealth services,(3, 201) and as such, enables the reimbursement of telemedicine in Australia. The aim of the scheme is to remove barriers that may prevent people from accessing specialist medical services.(130)

### A.4.1 Telemedicine MBS items

There are currently 11 MBS items that enable specialist doctors, consultant physicians, and consultant psychologists to claim video consultations. Additionally, there are 23 MBS items for patient-end services.(202) These items are also available to nurse practitioners, medical practitioners, aboriginal health workers, and practice nurses who provide clinical support to patients during the video consultation with the specialist.(130, 202, 203)

### A.4.2 Telemedicine eligibility

There is no formal application process that determines telemedicine reimbursement eligibility in Australia. However, there are a number of requirements that need to be met to be considered eligible.(129, 203, 204) At the time of the video consultation there needs to be at least 15 km by road between the patient and practitioner (medical specialist, consultant psychiatrist consultant physician).(203, 204) Eligibility can also be affected by the geographic area. Generally, the patient needs to be situated outside of a major city (RA1)[6].(129, 203) Exceptions to geographic location apply where a patient is a resident of an eligible aged care facility, is present at an eligible Aboriginal Medical Services (AMS), or is present at an eligible *Aboriginal community controlled health services (ACCHS)*.(129, 202-204)

[6] The Australian Standard Geographic Classification-Remote Area (RA) scales remoteness numerically from 1-5. Department of Health DoctorConnect website can assist in determining telemedicine eligibility.(204)

# Appendix B

Supporting documentation used in the review of existing MMA regulatory policy

- Summary of correspondence with international medical device regulatory authorities
- Summary of *Freedom of Information (FOI) Act* requests and responses
- Data extraction form for submission and/ or clinical evaluation reports (CER) of MMAs

## B.1 Correspondence with international medical device regulatory authorities

Table B.1 summarises my correspondence with the respective Canadian and American medical device regulatory authorities.

Table B.1: Summary of correspondence with international medical device regulatory authorities

| Jurisdictional regulatory agency | E-mail details | | | |
|---|---|---|---|---|
| | Address | Title | Date sent | Date of response |
| Canadian Medical Devices Bureau (MDB) | MDB_Enquiries@hc-scgc.ca | Inquiry about active medical device risk classification | 8 May 2018 | 17 May 2018 |
| U.S Food and Drug Administration (FDA) | digitalhealth@fda.hhs.gov | Inquiry about present and future MMA regulation | 13 February 2018 | 22 February 2018 |
| U.S Food and Drug Administration (FDA) | digitalhealth@fda.hhs.gov | Inquiry about MMA and software regulation | 30 April 2018 | 30 April 2018 |

## B.2 *Freedom of Information (FOI) Act* requests and responses

Table B.2 summarises the two freedom of information (FOI) Act requests used to acquire the relevant information for the case studies in *Chapter 5*.

Table B.2: Summary of correspondence with *Freedom of Information (FOI) Act* requests and responses

| FOI request number | Date of request submission | Date documents were released |
|---|---|---|
| 059-1718 | 16 August 2017 | 15 December 2017 |
| 185-1718 | 23 January 2018 | 15 May 2018 |

**Explanatory Note**
**FOI:** Freedom of information request Act 1982

## B.3 Data extraction form for submission and/ or clinical evaluation reports (CER) of MMAs

# Data Extraction Form for Mobile Medical Applications (MMA) Submissions and/or Clinical Evaluation Report (CER) by the Therapeutic Goods Administration (TGA)

| | |
|---|---|
| **Clinical Evaluation Report (CER) Title and Date** | |
| **Author of CER** | |
| Was the CER performed by an independent reviewer | ☐Yes<br>☐ No<br>If no, please state the position of the CER reviewer _____ |
| **Name of MMA** | |
| **Intended Purpose of MMA** | |

This document is based on the *International Medical Devices Regulators Forum (IMDRF) Software as a Medical Device (SaMD): Clinical Evaluation* (N41)(22, 116) guidance document.

- This document expands details addressed in N41 that relate to the *IMDRF's SaMD: Possible framework for risk categorization and corresponding considerations (N12)(36)*.

- This document does not include detailed information on the IMDRF's *SaMD: Application of Quality Management Systems (N23)(205)*, as the TGA does not address quality management systems when conducting a clinical evaluation of an induvial medical device.

Glossary is available on page 14

| Description and current use of the technology | Yes<br>✓ | Unclear<br>? | No<br>✗ | N/A<br>/ | Comments |
|---|---|---|---|---|---|
| 1) Has the name of the MMA been stated in the CER? | | | | | |
| 2) Has the intended population(s) for the MMA been stated in the CER? | | | | | |
| 3) Does the CER consider the type(s) of MMA input(s) (e.g. digitized content such as: laboratory results, image, medical device data, physiological status, symptoms)? | | | | | |
| 4) Does the CER consider the MMA algorithm (e.g. logic such as: inferences engine, equations, model based logic; affected by reference data, knowledge base, criteria, rules)? | | | | | |
| 5) Does the CER consider the type(s) of MMA output(s) (e.g. inform, treat, diagnose)? | | | | | |
| 6) Does the CER consider the intended purpose(s) of the MMA?<br><br>*If yes, complete i-iii below, if no stop data extraction.* | | | | | |
| i. Does the MMA have therapeutic capabilities?<br><br>*If yes, complete both 7) Valid Clinical Association and 9) Analytical Validation and sub-sections in the effectiveness section, if no continue on to ii.* | | | | | |
| ii. Does the MMA have non-diagnostic (aid in diagnosis) capabilities?<br><br>*If yes, complete both 7) Valid Clinical Association and 9) Analytical Validation sub-sections in the effectiveness section, if no continue on to iii.* | | | | | |
| iii. Does the MMA have diagnostic capabilities?<br><br>*If yes, complete 7) Valid Clinical Association, 8) Clinical Validation and 9) Analytical Validation sub-sections in the effectiveness section; if no, stop data extraction.* | | | | | |
| Notes | | | | | |

**Explanatory note(s)**
**CER**= Clinical evaluation report
**MMA**= Mobile medical application

| Effectiveness | Yes ✓ | Unclear ? | No ✗ | N/A / | Comments |
|---|---|---|---|---|---|
| *7) Valid Clinical Association* | | | | | |
| a) Does the CER consider if literature searches for scientific validity evidence on the MMA have been conducted (e.g. peer reviewed articles, clinical guidance documents, conference proceedings, etc.)? | | | | | |
| b) Does the CER consider the manufacturers' experience data (e.g. consumer feedback, adverse events, real world data, etc.)? | | | | | |
| c) Have any purposefully conducted scientific validity studies (e.g. RCTs, cohort studies, etc.) that establish an association between the MMA output and the healthcare situation or condition, been considered in the CER? | | | | | |
| d) Does the CER consider the clinical equivalency of the MMA? | | | | | |
| e) Does the CER consider studies which evaluate the association between the MMA input and the output? | | | | | |
| f) Does the CER consider the association between the MMA's output and patient health outcomes?<br><br>*If yes, address i-ii below apply; if no continue on to question 8 and/or 9 depending on the intended purpose of the MMA (see question 6 for clarification).* | | | | | |
| i. Is the relationship between the MMA output and the patient heath outcome a well-known association? | | | | | |
| ii. Is the relationship between the MMA output and the patient heath outcome a novel association? | | | | | |
| *8) Clinical Validation* Note: this section is only to be completed for MMAs with diagnostic capabilities | | | | | |
| a) Does the CER consider whether the information sources used in the MMA are relevant to the intended purpose of the MMA? | | | | | |
| b) Does the CER consider whether the information provided is of sufficient quality to give an objective assessment of the MMAs clinical performance? | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| c) Does the CER consider whether the data sets are relevant to the MMA in question? | | | | | | |
| d) Does the CER consider whether the MMA is consistent across multiple datasets?<br>*If yes, complete i below; if no, continue on to part e).* | | | | | | |
| i. Has the reason for the difference in the datasets been determined? | | | | | | |
| e) Does the CER consider whether the MMA affects health related outcomes (patient focused)? | | | | | | |
| f) Does the CER consider whether the MMA affects surrogate health outcomes?<br><br>*If yes, complete i-vii below; if no, continue on to the 9) Analytical Validation section.* | | | | | | |
| i. Does the CER consider the calculation of the sensitivity of the MMA? | | | | | | |
| ii. Does the CER consider the calculation of the specificity of the MMA? | | | | | | |
| iii. Does the CER consider whether a receiver operating characteristic (ROC) curve has been developed for the MMA? | | | | | | |
| iv. Does the CER consider the calculation of the positive predictive value (PPV) of the MMA? | | | | | | |
| v. Does the CER consider the calculation of the negative predictive value (NPV) of the MMA? | | | | | | |
| vi. Does the CER consider the calculation of the likelihood ratio of the MMA? | | | | | | |
| vii. Does the CER consider whether there are pre-determined evidence based diagnostic thresholds (cut-off) for the MMA? | | | | | | |
| *9) Analytical Validation* | | | | | | |
| a) Does the CER verify and validate the analytical validate (accuracy) of the MMA? | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| *If yes, indicate from i-iv below apply (one or more which), if no continue on to the next question.* | | | | | | |
| | i. | Does the CER consider whether the algorithm used by the MMA is a recognised standard (the current standard of care or described in the literature (e.g. insulin dosing))? | | | | |
| | ii. | Does the CER consider whether the MMA accuracy is relative to a reference or gold standard? | | | | |
| | iii. | Does the CER consider whether the MMA accuracy is relative to reference material (e.g. International normalisation ratio (INR))? | | | | |
| | iv. | Does the CER consider whether the MMA is comparable to another software or device that has an association between the output and a health outcome? | | | | |
| b) | Has the calculation of the accuracy of the MMA's findings been considered in the CER? | | | | | |
| c) | Has the calculation of the precision of the MMA's findings been considered in the CER? | | | | | |
| d) | Has the calculation of the limit of detection for the MMA's findings been considered in the CER? | | | | | |
| e) | Has the calculation of the linearity of associated transfer function for the MMA been considered in the CER? | | | | | |
| f) | Has the calculation of the analytical sensitivity of the MMA's findings been considered in the CER? | | | | | |
| Notes | | | | | | |

**Explanatory note(s)**
**CER**= Clinical evaluation report
**MMA**= Mobile medical application

| Risk-Classification | Yes<br>✓ | Unclear<br>? | No<br>✗ | N/A<br>/ | Comments |
|---|---|---|---|---|---|
| 10) Does the CER consider the impact of the MMA's output on the clinical management of the patient?<br><br>*If yes, complete sections a and b below; if no, continue on to the question 11) Socio-technical and system environment considerations.* | | | | | |
| a) Does the CER consider whether the MMA output impacts healthcare decision making?<br><br>*If yes, complete sections i-iii below; if no, continue on to part b).* | | | | | |
| i) Does the CER consider whether the MMA is used to treat or diagnose?<br><br>For example:<br>• treat – provide therapy to a human body using other means;<br>• diagnose;<br>• detect;<br>• screen;<br>• prevent;<br>• mitigate;<br>• lead to an immediate or near term action | | | | | |
| ii) Does the CER consider whether the MMA is used to drive clinical management?<br><br>For example:<br>• aid in treatment - provide enhanced support to safe and effective use of medicinal products;<br>• aid in diagnosis - help predict risk of a disease or condition;<br>• aid to making a definitive diagnosis;<br>• triage early signs of a disease or condition;<br>• identify early signs of a disease or condition | | | | | |
| iii) Does the CER consider whether the MMA is used to inform clinical management?<br><br>For example:<br>• inform options for treatment;<br>• inform options for diagnosis; | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| • inform options for prevention | | | | | |
| b) Does the CER consider whether the MMA output impacts healthcare decision making?<br><br>*If yes, complete sections i-iii below, if no, continue on to the question 11) Socio-technical and system environment considerations .* | | | | | |
| i) Does the CER consider whether the MMA has a critical impact on healthcare decision making?<br><br>For example:<br>• **Disease Type/Patient Condition**<br>o Life-threatening<br>o Fragile<br><br>• **Intervention Type**<br>o Requires major therapeutic interventions<br>o Sometimes time critical<br>o Vital to: avoiding death; serious deterioration of health; mitigating public health situations or conditions<br><br>• **User Type**<br>o Specialised and trained users | | | | | |
| ii) Does the CER consider whether the MMA has a serious impact on healthcare decision making?<br><br>For example:<br>• **Disease Type/Patient Condition**<br>o Moderate in progression<br>o Often curable<br>o Not fragile<br>• **Intervention Type**<br>o Does not require major therapeutic interventions<br>o Not expected to be time critical<br>o Vital to avoiding unnecessary interventions<br>• **User Type**<br>o Either specialized and trained users or lay users | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| iii) Does the CER consider whether the MMA has a non-serious impact on healthcare decision making?<br><br>For example:<br>• **Disease Type/Patient Condition**<br>o Slow with predictable progression of disease state<br>o Minor chronic illness or disease states<br>o May not be curable<br>o Individuals who may not always be patients<br>o Can be managed effectively<br>• **Intervention Type**<br>N/A<br>• **User Type**<br>o Either specialized and trained users or lay users | | | | | | |
| Notes | | | | | | |

**Explanatory note(s)**
**CER**= Clinical evaluation report
**MMA**= Mobile medical application

| Technical Characteristics | Yes<br>✓ | Unclear<br>? | No<br>✗ | N/A<br>/ | Comment |
|---|---|---|---|---|---|
| *11) Socio-technical and system environment considerations* | | | | | |
| a) Does the CER address whether the manufacturers of the MMA have been transparent about the limitations of the MMA (e.g. the algorithms, clinical models, assumptions, and quality of the data)? | | | | | |
| b) Does the CER consider whether the real-world MMA is integrated into clinical workflows with appropriate use if safety features? | | | | | |
| c) Does the CER consider whether the MMA is robust enough to withstand user configuration in an unintended way? | | | | | |
| d) Does the CER consider the design of the MMA user interface?<br><br>*If yes, address i-iii below; if no, continue on to part e).* | | | | | |
| i. Does the CER consider whether the user interface has over complex designs (e.g. complicated screens)? | | | | | |
| ii. Does the CER consider whether the design of the user interface is appropriate for the intended platform (e.g. smartphone, smartwatch, tablet) | | | | | |
| iii. Does the CER consider whether the MMA data are dynamic (e.g. displaying appropriate information for an appropriate length of time)? | | | | | |
| e) Does the CER consider whether the MMA has the appropriate means of information display (so that the target audience can understand it (e.g. units displayed, language translation))? | | | | | |
| f) Does the CER consider whether the MMAs can communicate relevant information?<br><br>*If yes, address i-iii below apply; if no, continue on to part g)* | | | | | |
| i. Does the CER consider whether the user can use the MMA within the organisation (in terms of available network, data quality input, competence, and hardware)? | | | | | |
| ii. Does the CER consider whether there is correct installation and | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| configuration of the MMA to enable the appropriate integration into clinical workflows? | | | | | |
| g) Have possible MMA interdependencies (e.g. software, hardware) been considered in the CER? | | | | | |
| h) Has it been acknowledged in the CER that the MMA is not used as a specialised medical platform? | | | | | |
| i) Have potential changes to the software (updates) been considered in the CER?<br><br>*If yes, address i-iv below; if no, continue on to the next question part j)* | | | | | |
| i. Does the CER consider whether these software changes are adaptive (e.g. maintains software with dynamic environment)? | | | | | |
| ii. Does the CER consider whether these software changes are perfective* (e.g. recoding to improve performance)? | | | | | |
| iii. Does the CER consider whether these software changes are corrective (e.g. corrects problems)? | | | | | |
| iv. Does the CER consider whether these software changes are preventive (e.g. corrects latent faults before they cause operational problems)? | | | | | |
| j) Does the CER consider the operating platform(s) (e.g. hardware) of the MMA(s)?<br><br>*If yes, address i-vi below apply (one or more), if no continue on to the part k)* | | | | | |
| i. Does the CER note whether the MMA uses a tablet interface? | | | | | |
| ii. Does the CER note whether the MMA uses a smartphone interface? | | | | | |
| iii. Does the CER note whether the MMA uses a smartwatch interface? | | | | | |
| iv. Does the CER note whether the MMA uses a desk top computer interface? | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| v. | Does the CER note whether the MMA uses a smart glasses interface? | | | | | |
| *vi.* | Does the CER note whether the MMA uses another interface? | | | | | If yes please state_____ |
| k) | Has the operating system(s) that the MMA(s) are installed on been considered in the CER?<br><br>*If yes, address i-v below if; no, continue on to the Question 12* | | | | | |
| i. | Using iOS | | | | | |
| ii. | Using Android | | | | | |
| iii. | Using Blackberry | | | | | |
| iv. | Using Windows | | | | | |
| v. | Other | | | | | If yes please state_____ |
| *12) Information Security with respect to safety considerations* | | | | | | |
| a) | Does the CER consider whether a formalised and safe method has been implemented to convert, transmit, and/or store MMA data? | | | | | |
| b) | Does the CER consider whether control measures to address data integrity are appropriate, in the circumstance where common information is accessed by multiple applications and user? | | | | | |
| c) | Does the CER consider whether users can safely implement information security updates? | | | | | |
| d) | Does the CER consider whether there are system supports for access and control to ensure protection of system information for the MMA? | | | | | |
| e) | Does the CER consider whether MMA design includes robust and resilient measures to address potential adverse system interactions? | | | | | |
| f) | Does the CER consider whether there is a balance in the availability of timely | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | information against privacy and security? | | | | | |
| g) | Does the CER consider whether there are instructions for the user to safely manage MMA information security been? | | | | | |
| h) | Does the CER consider whether the MMA integrates with other software? | | | | | |
| i) | Does the CER consider whether there needs to be updated security software for use of the MMA with other systems, applications or operating environments? | | | | | |
| Notes | | | | | | |

**Explanatory note(s)**
**CER**= Clinical evaluation report
**MMA**= Mobile medical application

| Continuous learning using real world performance data | Yes ✓ | Unclear ? | No ✗ | N/A / | Comments |
|---|---|---|---|---|---|
| 13) Does the CER consider if the manufacturer monitors the MMA's real world performance data?<br><br>*If yes, address i-iii below; if no, stop data extraction* | | | | | |
| i. Does the CER consider if the manufacturer has aimed to implement the least burdensome approach to collect the MMA's performance data? | | | | | |
| ii. Does the CER consider whether the real world performance data collected by the MMA's manufacturer could be used to provide evidence that the clinical or analytical validity of the MMA is inferior or superior to the original measures stated in the TGA application? | | | | | |
| iii. Does the CER consider whether the real world performance data collected by the MMA's manufacturer could be used to allow for the enablement or disablement of a new MMA functionality? | | | | | |
| Notes | | | | | |

**Explanatory note(s)**
**CER**= Clinical evaluation report
**MMA**= Mobile medical application
TGA= Therapeutic Goods Administration

------ STOP, data extraction is complete ------

## Glossary

**Accuracy:** Closeness of the quantity's true value to its measured quantity.(1)

**Adaptive software changes:** Maintains the MMA software within a dynamic technological environment.(3)

**Algorithm:** A model, or set rules, or logic that the MMA is based on (e.g. inferences engine, equations, model based logic; affected by reference data, knowledge base, criteria, rules).

**Analytical sensitivity:** Degree to which the input data affects the algorithm's output.(1)

**Analytical validation:** The MMAs ability to reliably and accurately produce the intentional output from the input data.(1)

**Clinical equivalency:** Clinical association of MMA compared to a reference standard (e.g. predicate/ comparator device).(1)

**Valid clinical association:** A valid association between the MMA's output which and the targeted medical condition (e.g. measurable, clinical outcomes).(1,2)

**Corrective software changes:** Corrects existing errors or problems within the current MMA software.(3)

**Cut-off threshold:** A scale or indices for a MMA, it should be meaningful and determined prior to validation.(1)

**Diagnostic MMA:** A MMA's output that is intended diagnose and/or drive clinical management by differentiating patients or their physiological conditions (e.g. screening apps, diagnostic apps, risk predicating apps).(1)

**Input:** Digitised content fed to the MMA (e.g. laboratory results, image, medical device data, physiological status, symptoms).(1,2)

**Likelihood ratio:** The likelihood that a test result given by the MMA would be expected in a person with the condition compared to a person without it.(1)

**Limit of detection:** Ability to distinguish between random patterns that distract from information and information bearing patterns of a clinical condition.(1)

**Linearity of associated transfer function:** "Behaviour of output across the range of input data that is allowed"(1) by the MMA.

**Negative predictive value (NPV):** The likelihood that the patient does not have the condition given the MMA result is negative.(1)

**Non-diagnostic:** A MMA that has a generic functionality which can be used across several healthcare conditions or situations (e.g. calculator app, memory test app).(1)

**Novel association:** The MMA has a new input, algorithm, and/or output with a new target population, or a new intended target papulation, which are not well-known or established. (1,2)

**Output:** A product of the MMA that has the ability to affect the users health (e.g. inform, treat, diagnose).(1,2)

**Perfective software changes:** Recoding of MMA software to improve performance.(3)

**Positive predictive value (PPV):** The likelihood that the patient has the condition given the MMA result is positive.(1)

**Precision:** Under unchanged conditions the degree to which the recurrent measurements generate the same result (e.g. reproducibility, repeatability).(1)

**Preventive software changes:** Corrects latent faults in the MMA software before they can cause operational problems.(3)

**Receiver operating characteristic (ROC) curve**: A graphical plot that illustrates the trade-off between sensitivity and specificity.(1)

**Relevant studies:** One or multiple studies which evaluate the association between the input and the output.(1)

**Clinical Validation:** The MMA's output has a positive impact on the target population in the context of care context.(1,2)

**Sensitivity:** MMA's ability to correctly identify a patient's condition as positive.(1)

**Specificity:** A MMA's ability to correctly identify a patient's condition as negative.(1)

**Therapeutic MMA:** A MMA's output that is intended to treat a healthcare condition or situation.(1)

**Well-known association:** MMA output has well established association with health condition or physiological status in reference materials (e.g. peer-reviewed journals, clinical studies, clinical guidelines, etc.).(1,2)

## Reference List


1) International Medical Device Regulators Forum. Draft: Software as a Medical Device (SaMD): Clinical Evaluation. International Medical Device Regulators Forum; 2016.

2) International Medical Device Regulators Forum. Software as a Medical Device (SaMD): Clinical Evaluation. International Medical Device Regulators Forum.

3) International Medical Device Regulators Forum. "Software as a medical device":possible framework for risk categorization and corresponding considerations. International Medical Device Regulators Forum; 2014.

4) International Medical Device Regulators Forum. Software as a Medical Device (SaMD): Application of Quality Management System. International Medical Device Regulators Forum; 2015.

# Appendix C

Supporting documentation used in the review of existing MMA evaluation frameworks for use within HTA and reimbursement decision-making

- Search strategies
- Data extraction standardisation tool
- Structure of the data extraction table

## C.1 Search strategies

Table C.**1**: Search strategy *Embase*

| Mobile Medical Applications (MMA) | Mobile Platform |
|---|---|
| ('mobile applications'/exp OR 'mobile app*' OR 'telehealth'/exp OR telemedicine OR 'portable electronic app*' OR 'mHealth app*' OR 'portable software app*' OR 'mobile medical app*' OR 'mobile health app*' OR 'electronic health app*' OR 'eHealth app*') | AND ('mobile phones'/exp OR 'cell phone*' OR 'cellular phone*' OR 'cellular telephone*' OR 'mobile phone*' OR mobile OR 'mobile device*' OR 'mobile platform*' OR 'smartphone'/exp OR smartphone* OR 'smart phone*' OR android* OR ipad* OR iphone* OR 'apple watch*' OR 'smart watch*' OR tablet* OR iOS OR Blackberr* OR windows OR Microsoft OR google OR apple OR HTC) |

Table C.2: Search strategy *Cochrane Library*

| Mobile Medical Applications (MMA) | Mobile Platform |
|---|---|
| mobile applications OR mobile app* OR portable electronic app*OR mHealth app* OR portable software app*OR mobile medical app*OR mobile health app*OR telemedicine app* OR telehealth app* OR electronic health app* OR eHealth app*<br><br>MeSH: Mobile Applications, Telemedicine | cell phones OR cellular phone* OR cellular telephone* OR mobile phone* OR mobile OR mobile device* OR mobile platform* OR smartphone* OR smart phone* OR android* OR ipad* OR iphone* OR apple watch* OR smart watch* OR tablet* OR iOS OR Blackberr* OR window* OR Microsoft or google OR apple OR HTC<br><br>MeSH: Cell Phones |

Table C.3: Search strategy *CINAHL*

| Mobile Medical Applications (MMA) | Mobile Platform |
|---|---|
| ((MH "Mobile Applications") OR mobile app* OR portable electronic app* OR mHealth app* OR portable software app* OR mobile medical app* OR mobile health app* OR telemedicine app* OR telehealth app* OR electronic health app* OR eHealth app* (MH "Telemedicine") OR (MH "Telehealth")) | AND ((MH "Cellular Phone+") OR (MH "Smartphone+") OR cell phones OR cellular phone* OR cellular telephone* OR mobile phone* OR mobile OR mobile device* OR mobile platform* OR smartphone* OR smart phone* OR android* OR ipad* OR iphone* OR apple watch* OR smart watch* OR tablet* OR iOS OR Blackberr* OR window OR Microsoft or google OR apple OR HTC) |

Table C.4: Search strategy *PsycINFO*

| Mobile Medical Applications (MMA) | Mobile Platform |
|---|---|
| (exp Telemedicine/ OR mobile applications OR mobile app$.tw OR portable electronic app$.tw OR mHealth app$.tw OR portable software app$.tw OR mobile medical app$.tw OR mobile health app$.tw OR telemedicine app$.tw OR telehealth app$.tw OR electronic health app$.tw OR eHealth app$.tw) | AND (exp Cellular phones/ OR exp Mobile Devices/ OR cell phones.tw OR cellular phone$.tw OR cellular telephone$.tw OR mobile phone$.tw OR mobile.tw OR mobile device$.tw OR mobile platform$.tw OR smartphone$.tw OR smart phone$.tw OR android$.tw OR ipad$.tw OR iphone$.tw OR apple watch$.tw OR smart watch$.tw OR tablet$.tw OR iOS.tw OR Blackberr$.tw OR windows.tw OR Microsoft.tw or google.tw OR appl.tw OR HTC.tw) |

Table C.5: Search strategy *Business Source Complete*

| Mobile Medical Applications (MMA) | Evaluation | Other |
|---|---|---|
| ("mobile medical app" OR "mobile health app" OR "mobile health application" OR "mobile health app" OR “telemedicine app” OR “telemedicine application” OR “mHealth app” OR “mhealth application” OR “eHealth app” OR “eHealth application” OR “telehealth app” “telehealth application”) | AND (evaluat* OR criteri* OR apprais*) | AND medic*<br><br>(tool* OR framework*) |

## C.2 Data extraction standardisation tool

| | |
|---|---|
| **Name of framework/ criteria** | |
| **Intended purpose** | |
| **Type of applications assessed** | |

## Evaluation of core domains

### Domain 1: Current use of the technology

| Domain: Current use of the technology | | | | Question(s) Number |
|---|---|---|---|---|
| Does the framework have any item(s) that address how the current MMA assists the user(s) in managing their health concern (population/ clinical indications)? | ✓ | ? | ✗ | |
| Item(s) that address health concerns and current use of the technology could include:<br>• Item(s) about the medical condition the MMA is intended to aid;<br>• Item(s) which address the current use (e.g. rates, utilisation, trends) of the MMA;<br>• Item(s) about the MMA's intended purpose (e.g. diagnosis, management, treatment);<br>• Item(s) that ask about the MMAs intended population. | | | | |
| Comments | | | | |

Domain 2: Description and technical characteristics

| Domain: Description and technical Characteristics | | | | Question(s) Number |
|---|---|---|---|---|
| Does the framework have any item(s) that describe the technical characteristics of the MMA? | ✓ | ? | ✗ | |
| Item(s) that address the description and technical characteristics of the technology could include:<br>• Item(s) which consider the personalization capabilities of the MMA;<br>• Item(s) on what type of devices the MMA will be compatible with (e.g. mobile platform, operating system, version);<br>• Item(s) which address if experts were consulted or included during the development of the MMA;<br>• Item(s) that ask about the MMA's communicative capabilities (e.g. connectivity, communication with personal health records (PHR), electronic health records (EHR), healthcare provider-patient communications). | | | | |
| Comments | | | | |

Domain 3: Effectiveness

| Domain: Effectiveness | | | | Question(s) Number |
|---|---|---|---|---|
| Does the framework have any item(s) that address the clinical effectiveness a MMA? | ✓ | ? | ✗ | |

Item(s) that address clinical effectiveness could include:

- Item(s) that address if the MMA has been tested or trialed;
    a) Item(s) that address the design of the trial;
    b) Item(s) which address the number of subjects included in the trial;
    c) Item(s) which address the quality of the trial;
    d) Item(s) that address if trial results match the conclusion;
- Item(s) that address the therapeutic effectiveness of the MMA;
    a) Item(s) answerable by health related outcomes (e.g. mortality, DALYS);
    b) Effectiveness item(s) relating to surrogate outcomes (e.g. physiological, biochemical, behaviour change) and the corresponding underlying assumption used;
    c) Item(s) about a meta-analysis on the effectiveness;
    d) Item(s) that aimed at publication bias;
    e) Item(s) on about heterogeneity;
- Item(s) which address technical efficacy of the MMA;
- Item(s) that address diagnostic accuracy efficacy (e.g. specificity, sensitivity, likelihood ratio) of the MMA;
- Item(s) which ask about what intervention is the MMA's comparator for clinical effectiveness;
- Item(s) that address the MMA users' satisfaction.

Comments

## Domain 4: Safety

| Domain: Safety | | | | Question(s) Number |
|---|---|---|---|---|
| Does the framework have any items(s) that address the safety of the MMA? | ✓ | ? | ✗ | |
| Items(s) that address safety could include:<br>• Item(s) that address the harms (adverse events) caused by the MMA;<br>• Item(s) that ask why participant(s) may have left the trial when the MMA was tested;<br>• Item(s) that ask about the source of the information used in the MMA;<br>• Item(s) which concern how the MMA information sources were selected;<br>• Item(s) that address the psychological (fear, anxiety) effects of using the MMA;<br>• Item(s) which address how users of the MMA may feel stigmatised;<br>• Item(s) which ask about what intervention is the MMA's comparator for safety. | | | | |
| Comments | | | | |

Domain 5: Cost-effectiveness

| Domain: Cost, cost - effectiveness | | | | Question(s) Number |
|---|---|---|---|---|
| Does the framework have any item(s) that address whether the MMA is cost-effective? | ✓ | ? | ✗ | |

*Item(s) that address cost-effectiveness could include:

- Item(s) that address if an health economic evaluation of the MMA has been conducted;

  a) Item(s) which ask about what type of health economic evaluation was conducted and whether it has been justified;
     - Cost-consequence analysis (all health related cost(s) and outcome(s) are disaggregated and listed separately)[a] ;
     - Cost-minimisation analysis (multiple health outcomes are viewed as similar and the cost is the same as the least cost comparator);
     - Cost-effectiveness analysis (compares the relative difference of costs and effects of health interventions, and can be summarized in the form of the *incremental cost-effectiveness ratio (ICER)*)[a];
     - Cost-utility analysis (a form of cost-effectiveness analysis in which the measure of effectiveness is exclusively in *quality adjusted life years (QALYS)*)[a];
     - Cost-benefit analysis (places monetary value on health care resources as well as on health outcomes)[a];

  b) Item(s) that ask about the perspective (e.g. societal, insurance, social) that the economic analysis assumed;

  c) Item(s) which ask if the assumption used in the economic analysis can be justified (e.g. time horizon, discount rates), and if these had been tested in sensitivity analyses;

  d) Item(s) which address how the sources of literature for the economic analysis were collected (e.g. systematic review), and whether they were appropriate and had been tested in sensitivity analysis;
     - Item(s) that address if the sources of the cost are different to the ones used for outcomes (effectiveness/safety);

- Item(s) that address the transferability (e.g. prices, cost structure, remuneration) across settings/ jurisdictions.

Comments

**Explanatory note(s)**

*Economic analysis of a comparable MMAs may be included if the reasoning is provided,

[a] Includes questions about the economic model used and how it was justified.

Domain 6: Organisational aspects

| Domain: Organisational Aspects | | | | Question(s) Number |
|---|---|---|---|---|
| Does the framework have any Item(s) that address possible implications (e.g. professional or organisational) relating to the use or recommendation of MMAs? | ✓ | ? | ✗ | |

Item(s) that address organisational, and professional implications could include:

- Item(s) that address if training is need for users (e.g. medical practitioners, patients, care givers, allied health workers);
- Item(s) that address if additional accreditation will be needed for professionals (e.g. medical practitioners, allied health workers, technicians);
- Item(s) that address if adopting the MMA will alter the current utilisation of services (e.g. work load, work force, compliance);
- Item(s) that address if adopting the MMA will change treatment location (e.g. rural, remote, hospital, clinic);
- Item(s) which ask whether the uptake of the MMA affects the overall health system.

Comments

## Optional domains

### Domain 7: Legal aspects

| Domain: Legal Implications | ✓ | ? | ✗ | Question(s) Number |
|---|---|---|---|---|
| Does the framework have any item(s) that address legal implications related to the MMA? | | | | |
| Item(s) that address legal implications could include:<br>• Item(s) about possible litigation risks to the relevant person(s) associated with the use or recommendation of the MMA (e.g. for medical professional or allied health worker);<br>• Item(s) about how the users' insurance(s) (e.g. professional indemnity, life, health, income) would be affected through use or recommendation of the MMA. | | | | |
| Comments | | | | |

## Domain 8: Ethical aspects

| Domain: Ethical Considerations | | | | Question(s) Number |
|---|---|---|---|---|
| Does the framework have any item(s) that address ethical considerations related to MMA? | ✓ | ? | ✗ | |
| Item(s) that address ethical considerations could include:<br>• Item(s) that address if the MMA has a privacy policy;<br>• Item(s) that address the contents of the MMA's privacy policy (e.g. if the user data is owned by the company, if the data can be sold without user consent);<br>• Item(s) about whether the framework has questions that address patient confidentiality;<br>• Item(s) that address whether the MMA asks for the patients' consent prior to providing any clinical services;<br>• Item(s) that address MMA access (e.g. cost of device, cost of MMA, subscription cost, geographical location);<br>• Item(s) which consider equity in the use of MMA's (e.g. socioeconomic status, disability, language, age);<br>• Item(s) which address possible conflicts of interest (e.g. affiliation, funding, third party sponsorship). | | | | |
| Comments | | | | |

**Explanatory note(s)**

[a] Access in a health care context can be affected by influences demand and supply. Factors which influence demand include practices in self-care, attitudes, disease burden, as well as knowledge and skill. Influence on supply include cost, service appropriation, and geographical location.

[b] Equity in healthcare is can be unfair disparities.

Domain 9: Social aspect

| Domain: Social Considerations | | | | Question(s) Number |
|---|---|---|---|---|
| Does the framework have any item(s) that address social considerations related to MMA? | ✓ | ? | ✗ | |
| Item(s) that address social considerations could include:<br>• Item(s) about how the MMA may affect the care giver;<br>• Item(s) about how the MMA may affect the users' relationships (e.g. family dynamics). | | | | |
| Comments | | | | |

## C.3 Structure of the data extraction table

Table C.6: Data extraction table outline

| Author and Date of Publication | Name of Criterion/ Framework | Study Methodology | Outline of Framework | Intended MMA User (Population) | Applicability | HTA domains Addressed (Outcomes) | Notes |
|---|---|---|---|---|---|---|---|
| | | | | | | | |

# Appendix D

Supporting documentation used in-depth interviews used to determine possible pathways and impediments to MMA reimbursement in Australia.

- Ethics approval
- Recruitment email
- Participant information sheet
- Consent forms
- Interview schedules

Supporting documentation used to determine the applicability of the MMA HTA evaluation module to other jurisdictions

- Included documents

## D.1 Ethics approval

THE UNIVERSITY of ADELAIDE

RESEARCH SERVICES
OFFICE OF RESEARCH ETHICS, COMPLIANCE AND INTEGRITY
THE UNIVERSITY OF ADELAIDE

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FACSIMILE +61 8 8313 3700
EMAIL hrec@adelaide.edu.au

CRICOS Provider Number 00123M

4 April 2017

Dr Tooher
School of Public Health

Dear Dr Tooher

**ETHICS APPROVAL No:** **H-2017-039**

**PROJECT TITLE:** **Feasibility of a reimbursement pathway for mobile medical applications (MMA) in Australia**

The ethics application for the above project has been reviewed by the Low Risk Human Research Ethics Review Group (Faculty of Health and Medical Sciences) and is deemed to meet the requirements of the *National Statement on Ethical Conduct in Human Research (2007)* involving no more than low risk for research participants. You are authorised to commence your research on **04 Apr 2017**.

Ethics approval is granted for three years and is subject to satisfactory annual reporting. The form titled *Annual Report on Project Status* is to be used when reporting annual progress and project completion and can be downloaded at http://www.adelaide.edu.au/research-services/oreci/human/reporting/. Prior to expiry, ethics approval may be extended for a further period.

Participants in the study are to be given a copy of the Information Sheet and the signed Consent Form to retain. It is also a condition of approval that you **immediately report** anything which might warrant review of ethical approval including:

- serious or unexpected adverse effects on participants,
- previously unforeseen events which might affect continued ethical acceptability of the project,
- proposed changes to the protocol; and
- the project is discontinued before the expected date of completion.

Please refer to the following ethics approval document for any additional conditions that may apply to this project.

Yours sincerely,

**Sabine Schreiber**
**Secretary, Human Research Ethics Committee**
**Office of Research Ethics, Compliance and Integrity**

THE UNIVERSITY of ADELAIDE

RESEARCH SERVICES
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CRICOS Provider Number 00123M

**Applicant:** Dr R Tooher

**School:** School of Public Health

**Project Title:** Feasibility of a reimbursement pathway for mobile medical applications (MMA) in Australia

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**The University of Adelaide Human Research Ethics Committee**
**Low Risk Human Research Ethics Review Group (Faculty of Health and Medical Sciences)**

**ETHICS APPROVAL No:** H-2017-039 **App. No.: 0000022196**

**APPROVED for the period:** 04 Apr 2017 to 30 Apr 2020

Thank you for your response, dated 30.03.17, to the matters raised. It is also noted that this project involves PhD student Magdalena Ruth Moshi.

**Sabine Schreiber**
Secretary, Human Research Ethics Committee
Office of Research Ethics, Compliance and Integrity

## D.2 Recruitment e-mail

From: Magdalena R. Moshi (magdalena.moshi@adelaide.edu.au)
To: [Insert e-mail address]
CC: Rebecca Tooher (rebecca.tooher@adelaide.edu.au)

Subject: Recruitment for an in-depth interview on mHealth applications in Australia

Dear [Insert name]

I am a PhD candidate at The University of Adelaide, Australia and I am currently conducting research on the feasibility of reimbursing or publicly funding mobile health (mHealth) applications in Australia.

To achieve this I will need to talk to professionals such as medical practitioners, allied health workers, policy makers, and application developers who may be involved in recommending, using, regulating, or creating mHealth apps.

Your position on the [interest organization name] enables you to have valuable and unique insight into mHealth apps in Australia. Therefore, I am wondering if you would be willing to be interviewed about mHealth apps in Australia. The interview will take approximately 30-60 minutes ad can be concluded either face to face, by teleconferencing, videoconferencing, or by phone-whichever you prefer. Your identity will be concealed in any publications or presentations that could result from the research. For more information I have attached a participant information sheet.

If you would like to be interviewed please contact: myself; Dr Rebecca Tooher at rebecca.tooher@adelaide.edu.au or on (08) 8313 1316; or Professor Tracy Merlin at tracy.merlin@adelaide.edu.au or on (08) 8313 3575.

Similarly, if you know anyone who may be interested and willing to participate in the study please forward them this email and/or encourage them to get in contact with myself; Dr Rebecca Tooher, or Professor Tracy Merlin.

Furthermore, if you have any questions please feel free to contact myself, Dr Rebecca Tooher, or Professor Tracy Merlin.

Kind Regards,
Magdalena Moshi

**Magdalena R. Moshi**
Ph.D Candidate
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The University of Adelaide
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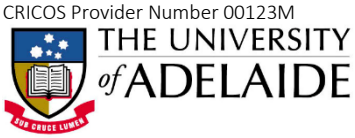
CRICOS Provider Number 00123M



## D.3 Participant information sheet

# PARTICIPANT INFORMATION SHEET

**PROJECT TITLE:** Feasibility of a Reimbursement Pathway for Mobile Medical Applications (MMA) in Australia

**HUMAN RESEARCH ETHICS COMMITTEE APPROVAL NUMBER: H-2017-039**

**PRINCIPAL INVESTIGATOR: Dr Rebecca Tooher**

**SENIOR INVESTIGATOR: Professor Tracy Merlin**

**STUDENT RESEARCHER: Ms Magdalena Moshi**

**STUDENT'S DEGREE: Doctor of Philosophy (Ph.D) in Medicine**

Dear Participant,

You are invited to participate in the research project described below.

**What is the project about?**
There is currently no public Medicare funding (reimbursement) in Australia available for mobile health/medical applications (apps) (MMAs) that are accessible on portable devices like smartphones. There is also no specific method to determine the likely eligibility of apps for reimbursement. Before MMA reimbursement can be implemented in Australia, a method or process for evaluating MMAs needs to be developed that is feasible and equally as rigorous as processes used to evaluate other health technologies.

This research aims to determine if reimbursement of MMAs is feasible in Australia and develop possible reimbursement implementation pathways.

**Who is undertaking the project?**
This project is being conducted by Magdalena R. Moshi who is a Ph.D candidate at the University of Adelaide under the supervision of Dr Rebecca Tooher and Professor Tracy Merlin.

**Why am I being invited to participate?**

You have been invited to participate in this study because you are a medical practitioner, allied health worker, policy maker, or application developer and are currently in the use of mobile health applications within Australia.

**What will I be asked to do?**
If you choose to participate you will be interviewed by the student researcher Magdalena Moshi via phone, teleconferencing, videoconferencing or in-person. There will be no additional follow-up requirements or remuneration for participation in the project..

**How much time will the project take?**
The interview will last between 30 and 60 minutes.

**Are there any risks associated with participating in this project?**
There may be the potential for reputational and/or professional risk through disclosure of information about clinical or regulatory practices. To ensure confidentiality and limit any risks associated with participating in this research project, a pseudonym will be used instead of your name, any identifying information will be omitted, and extra steps will be taken to maintain that you or your organisation cannot be identified from any data extracts used as quotation(s), or from any example(s) included in, written publications or presentations.

**What are the benefits of the research project?**
Your participation in the project is not expected to yield any immediate personal benefit. However, your input may contribute to determining whether public funding of MMA in Australia is feasible. Pathways identified for the implementation of frameworks that evaluate MMAs for reimbursement decisions may have a policy impact of some significance.

**Can I withdraw from the project?**
Your participation in this project is completely voluntary. If you agree to participate, you are free to withdraw your information any time before the submission of the thesis.

**What will happen to my information?**
The information you supply during the interview will be de-identified, stored securely, and published. The published information will omit any identifiable information and pseudonyms will be used in place of participants' names.

The digital copies of the voice recording, digital copies of consent forms, and accompanying transcripts will be stored within a secure area in the School of Public Health at the University of Adelaide. Only personnel affiliated with this particular research project will have access to the information you provide. Any storage drives, the voice recorder(s), and paper copies related to the research project will be kept in a locked drawer or compactus in a secure area within School of Public Health, The University of Adelaide.

The interview recording and transcripts will only be made available to the three researchers affiliated with this project. The results from the interviews will be published in publications such as journal articles, presentation(s), and the student researcher's

(MM) Ph.D thesis. In the publications or presentations pseudonyms will be used, and any identifying information will be omitted.

If you are interested in receiving a the copy of the final results please let the student researcher know and she will supply you with a copy.

At the completion of the project, it is not expected that the raw data will be reused for any future research.

**Who do I contact if I have questions about the project?**

*Principal Investigator*
Dr Rebecca Tooher
(08) 8313 1316
rebecca.tooher@adelaide.edu.au

*Senior Investigator*
Professor Tracy Merlin
(08) 8313 3575
tracy.merlin@adelaide.edu.au

*Student Researcher*
Magdalena Moshi
(08) 8313 6569
magdalena.moshi@adelaide.edu.au

**What if I have a complaint or any concerns?**

The study has been approved by the Human Research Ethics Committee at the University of Adelaide (approval number H-2016-xxx). If you have questions or problems associated with the practical aspects of your participation in the project, or wish to raise a concern or complaint about the project, then you should consult the Principal Investigator. If you wish to speak with an independent person regarding a concern or complaint, the University's policy on research involving human participants, or your rights as a participant, please contact the Human Research Ethics Committee's Secretariat on:

Phone: +61 8 8313 6028
Email: hrec@adelaide.edu.au
Post: Level 4, Rundle Mall Plaza, 50 Rundle Mall, ADELAIDE SA 5000
Any complaint or concern will be treated in confidence and fully investigated. You will be informed of the outcome.

**If I want to participate, what do I do?**

If you would like to participate in the research project please contact the student researcher Magdalena Moshi (08) 83136 569 or magdalena.moshi@adeliade.edu.au to book an appointment for an interview.

Yours sincerely,

**Dr Rebecca Tooher**
*Principal Investigator*

**Professor Tracy Merlin**
*Senior Investigator*

**Ms Magdalena Moshi**
*Student Researcher*

## D.4 Consent forms

### D.4.1 Consent form for interview conducted in person

**Human Research Ethics Committee (HREC)**

**CONSENT FORM**

1. I have read the attached Information Sheet and agree to take part in the following research project:

| | |
|---|---|
| **Title:** | Feasibility of a Reimbursement Pathway for Mobile Medical Applications (MMA) in Australia |
| **Ethics Approval Number:** | **H-2017-039** |

2. I have had the project, so far as it affects me, fully explained to my satisfaction by the research worker. My consent is given freely.

3. I have been given the opportunity to have a member of my family or a friend present while the project was explained to me.

4. Although I understand the purpose of the research project it has also been explained that involvement may not be of any benefit to me.

5. I have been informed that, while information gained during the study may be published, I will not be identified and my personal results will not be divulged.

6. I understand that I am free to withdraw from the project at any time.

7. I agree to the interview being audio/video recorded. Yes ☐ No ☐

8. I am aware that I should keep a copy of this Consent Form, when completed, and the attached Information Sheet.

**Participant to complete:**

Name: _____Signature: _____

Date: _____

**Researcher/Witness to complete:**

I have described the nature of the research to

_____

*(print name of participant)*

and in my opinion she/he understood the explanation.

Signature: _____Position:_____

Date: _____

## D.4.2 Consent form for interview conducted via teleconference

**Human Research Ethics Committee (HREC)**

**CONSENT FORM**

9. I have read the attached Information Sheet and agree to take part in the following research project:

| | |
|---|---|
| **Title:** | Feasibility of a Reimbursement Pathway for Mobile Medical Applications (MMA) in Australia |
| **Ethics Approval Number:** | **H-2017-039** |

10. I have had the project, so far as it affects me, fully explained to my satisfaction by the research worker. My consent is given freely.

11. I have been given the opportunity to have a member of my family or a friend present while the project was explained to me.

12. Although I understand the purpose of the research project it has also been explained that involvement may not be of any benefit to me.

13. I have been informed that, while information gained during the study may be published, I will not be identified and my personal results will not be divulged.

14. I understand that I am free to withdraw from the project at any time.

15. I agree to the interview being audio/video recorded. Yes ☐ No ☐

16. I am aware that I should keep a copy of this Consent Form, when completed, and the attached Information Sheet.

**Participant to complete:**

Name: _____Signature: _____

Date: _____

## D.5 Interview schedules

### D.5.1 Interviewers introduction for all interviews

*My name is Magdalena Moshi, I am currently a PhD candidate at the University of Adelaide and I will be conducting this interview today. It is estimated that the interview will take between 30-60 minutes. Thank you for volunteering to be a participant in this interview, your participation is greatly appreciated. The aim of this research project is to determine the feasibility of publicly funding (reimbursing) mobile health (mHealth) applications in Australia. To achieve this I will need to talk to professionals such as yourself (medical practitioners, allied health workers, policy makers, and application developers) who are involved in recommending, using, regulating, or creating mHealth apps to identifying anything that could potentially affect the evaluation, use and public funding of these technologies.*

*This interview will be recorded to assist in the transcription and analysis of the content at a later stage. The copy of the recording will be destroyed after it has been transcribed and your name will be changed to a pseudonym. The information you provide may be published, but any identifying information will be omitted and a pseudonym will be used in place of your name. The information you provide will assist the research project, but it will not directly benefit you as an individual. Your participation in the project is voluntary and you are free to withdraw at any time as well as refuse to answer any questions of your choosing.*

*You have been provided a copy of the participant information sheet as well as a copy of the University of Adelaide consent form. Please read both the consent from and participating information sheet so that you understand them. If you have any questions regarding either documents please feel free to ask.*

*Once you have read the sheets and are comfortable with the situation, please sign and date a copy of the consent form.*

*Before we start the interview, do you have any further questions?*

### D.5.2 Interview schedule for healthcare workers (medical practitioners and allied health workers)

Interviewer:_____
_____

Interviewee (Title, first name, surname):_____

Interviewee Profession:_____
_____

Date of Interview_____
_____

*I will start by asking you some basic questions,*

Age range (Please tick)
- ☐ 18-25
- ☐ 26-30
- ☐ 31-40
- ☐ 41-50
- ☐ 51-60
- ☐ 61-65
- ☐ above 66

Gender (Please tick)
- ☐ Female
- ☐ Male
- ☐ Other_____
- ☐ Choose not to specify

Can you tell me a little about your current role?
Probe: Public, private, community, government role?

Can you talk about your experience with MMAs?

*Now we will move on to more profession-specific questions,*

Do you currently recommend MMAs to your patients?
Probe: Why?/ Why not?/ How do you decide which ones to recommended?/ Does the type of medical condition affect how you how you recommend a MMA?

Do you currently use MMAs in clinical consultations?
Probe: Why?/ Why not?/ How do you decide which ones to use?/ Does the type of medical condition affect you choice?/ Would your use of MMAs be affected

by whether it was possible to claim the use in a clinical consultation through the *Medicare Benefits Scheme (MBS)*?/ If the MMA suggested a particular condition do you still recommend further testing?/ If the MMA suggested a particular type of management would you use other tools to confirm the advice?

Have you used MMAs (e.g. 'wearables') to monitor your patients?

Probe: Why?/ Why not?/ Would being able to claim on the MBS any remote monitoring and/or data analysis using the MMA affect your answer?

What is your current understanding of MMA reimbursement through private or public funding in Australia?

In the time you have been recommending or using MMAs in clinical practice have you checked the *Australian Register of Therapeutic Goods (ARTG)* to determine if the MMA is registered?

Probe: Why?/ Why not?/ If the MMA is registered on the ARTG, would this affect your recommendation to the patient?

To what extent do you trust MMA results?

Probe: Would this be affected by the quality of the apps? If MMAs were evaluated through the *Medical Services Advisory Committee (MSAC)* evaluation process would your opinion differ?

If MMAs were reimbursable would that change your willingness to recommend them?

Probe: Why is that?/ Would you say it is due to cost or that the MMA has been properly vetted?

In the past, how have your patients reacted to your recommendation of MMAs?

Probe: Why would you say they reacted in that manner? / Have you noticed a difference in the age of the patients and their reaction?/ Have you noticed a difference between the socioeconomic status and their reaction?/ Have your patients ever asked about the cost of the MMA?

Do you have any concerns about how using or recommending MMAs would affect your ability to practice in healthcare?

(*Clarify:* *Australian Health Practitioner Regulatory Agency (APHRA)* *registration, practicing* insurances)

Probe: Why?/ Why not?

*Lastly we will move one to more questions that related to MMA in a broader context,*

Can you describe your use of MMAs in your professional context?

What motivated you to get involved with using MMAs in your given profession?

Can you describe any resources you know that assist in using MMAs?
*(Clarify: training to use MMA for yourself or other user (i.e. patient))*

Can you describe any resources you know that assist in developing MMAs?

Can you describe any resources you know that would assist with integrating MMAs into the current system?

In your experience with MMAs how would you describe user experience with MMAs?
Probe: affected by age, socioeconomic status?

Does your current work place have an MMA strategy?
Probe: If yes, what is the current strategy, is it in place, would you say it is working?

What place do you think the MMAs should have in the Australian healthcare context?

What do you see as the benefit/downsides of MMAs for users (i.e. medical practitioners or consumers)?

### D.5.3 Interview schedule for applications developers

Interviewer:_____
_____

Interviewee (Title, first name, surname):_____

Interviewee Profession:_____
_____

Date of Interview_____
_____

*I will start by asking you some basic questions,*

Age range (Please tick)
- ☐ 18-25
- ☐ 26-30
- ☐ 31-40
- ☐ 41-50
- ☐ 51-60
- ☐ 61-65
- ☐ above 66

Gender (Please tick)
- ☐ Female
- ☐ Male
- ☐ Other_____
- ☐ Choose not to specify

Can you tell me a little about your current role?
Probe: Public, private, community, government role?

Can you talk about your experience with MMAs?

*Now we will move on to more profession-specific questions,*

What type of applications 'apps' do you develop?
Probe:Have you developed an app which meets the definition of a MMA?/ How does the development of MMAs differ from other types of apps?/ How does the evaluation of MMAs differ from other apps?

What is your current understanding of the *Therapeutic Goods Administrations (TGA)* regulation of MMAs?

Probe: Would you say there are areas in the TGA's regulation that of concern/ need improvement?

In your opinion, how well does the TGAs MMA regulation address the unique challenges presented by the technology?

Before developing an MMA are you concerned about adhering with the TGA's regulations?

Probe: Why?/Why not?

In your opinion as an App developer, what defines a good App?

Probe: Can you provide an example of what you define as a good apps?

How have you come to these findings?

Is there a criteria you use?

Probe: Why?/ Why not?/ How did you come across this criteria?

If public or private MMA reimbursement were available in Australia, how might this affect app development?

Probe: Why?/ Why not?/ How would this affect the overall development cycle of an apps or MMA?/ How would it affect cost?/ How would it affect software or hardware updates?/ How would it affect the quality of apps or MMAs?

If public or private MMA reimbursement were available in Australia, would you as a developer try to adhere to the guidelines for reimbursement?

Probe: Why/ Why not?/ Would your adherence to these guidelines be affected/ dependent on the financer/client of the MMA?

When developing an MMA, what kind of aspects do you focus on?

Probe: Do reserve any consideration for HTA domains?/ Such as safety (ability to do harm), effectiveness, cost-effectiveness?

How much time on average does it require to develop an MMA?

Probe: How much time goes into background research on content?/ How does this compare to other types of apps or MMAs?

How much focus in the MMA development process is on MMA testing/trialing?

Probe: What type of testing is done?/ what type of consumer base is used for the testing?

How does the development of an app differ between operating systems?

Probe: How do you address the challenges as developers?/ Would the evaluation and/or testing of an MMA need to differ depending on the type of operating system?

How does the functionality of an app differ between operating systems (e.g. iOS-Apples, Android-Google)?

Probe: How do you address the challenges as developers?/ Would the evaluation and/or testing of an MMA's functionality need to differ depending on the type of system?

How does the development of an app differ between devices?

Probe: How do you address this challenge?/ How would differences in devices affect the evaluation of MMAs?

Do MMAs function differently on different devices?

Probe: How do you address this challenge?/ How would these differences affect the evaluation of MMAs?

Apps have a fast turn over time for updates, how would this affect the evaluation of MMAs for reimbursement decisions?

Probe: Why would you include these specific aspects?

In your opinion, what would the ideal MMA evaluation system contain?

Probe: Why have you chosen these specific elements?

Can you describe any resources you know that assist in developing MMAs?

### D.5.4 Interview schedule for policymakers

Interviewer:_____
_____

Interviewee (Title, first name, surname):_____

Interviewee Profession:_____
_____

Date of Interview_____
_____

*I will start by asking you some basic questions,*

Age range (Please tick)
- ☐ 18-25
- ☐ 26-30
- ☐ 31-40
- ☐ 41-50
- ☐ 51-60
- ☐ 61-65
- ☐ above 66

Gender (Please tick)
- ☐ Female
- ☐ Male
- ☐ Other_____
- ☐ Choose not to specify

Can you tell me a little about your current role?
Probe: Public, private, community, government role?

Can you talk about your experience with MMAs?

*Now we will move on to more profession-specific questions,*

What do you see as the challenges of regulating MMAs?

Are you familiar with the TGA evaluation processes?
Probe: What about for MMAs?

Do you think this process works for MMAs?
Probe: what improvements could be made? Can you suggest an alternative method for evaluation? For improving developer compliance?

(*Clarify: Depending on familiarity with the TGA process – if participant is not familiar briefly describe process*)

How well do you think the TGA's "software as a medical device" works for MMAs?

How does this compare to the "MMA specific" approach used by the *Food and Drug Administration (FDA)* in the USA?

Currently, MMAs can be sold on global app stores without TGA approval (registration), can you think of any
methods that the Australian Government could implement to encourage global apps store to comply with TGA policies?

With the increased popularity of MMAs, are you aware of any consideration by the relevant authorities of a public funding (reimbursement) pathway?
Probe: Why?/ Why not? What aspects have been considered?

## D.6 Included documents in the study of the applicability of the MMA HTA evaluation module to other jurisdictions

Table D.1: Included documents

| Jurisdiction | Health Technology Assessment (HTA) Agencies | Document Title | Document Type | Time Period |
|---|---|---|---|---|
| European economic area (EEA) | European network for health technology assessment (EUnetHTA) | Comparators & comparisons: Criteria for the choice of the most appropriate comparator(s)- Summary of current policies and best practice recommendations (173) | Guideline | 2015 |
| | | Comparators & comparisons: Direct and indirect comparisons (173) | Guideline | 2015 |
| | | Endpoints used for relative effectiveness assessment: Composite endpoints (173) | Guideline | 2015 |
| | | Endpoints used for relative effectiveness assessment: Composite endpoints (177) | Guideline | 2015 |
| | | Endpoints used for relative effectiveness assessment: Health-related quality of life and utility measures (172) | Guideline | 2015 |
| | | Endpoints used in relative effectiveness assessment- Safety (175) | Guideline | 2015 |
| | | Endpoints used in relative effectiveness assessment: Surrogate endpoints (174) | Guideline | 2015 |
| | | Evidence submission templates to support production of core HTA information and rapid assessments: Adaptation notes (206) | Template | 2015 |
| | | HTA core model® (179) | Website | 2018 |
| | | Internal validity of non-randomised studies (NRS) on interventions (175) | Guideline | 2015 |
| | | Levels of evidence: Applicability of evidence for the context of a relative effectiveness assessment (174) | Guideline | 2015 |
| | | Meta-analysis of diagnostic test accuracy studies(171) | Guideline | 2014 |
| | | Methodology guidelines (178) | Website | 2018 |
| | | Methods for health economic evaluations - a guideline based on current practices in Europe (206) | Guideline | 2015 |
| | | Personalised medicine and co-dependent technologies, with a special focus on issues of study design (176) | Reflection paper | 2015 |
| | | Therapeutic medical devices (172) | Guideline | 2015 |
| Canada | Canadian agency for drugs and technologies in health (CADTH) | About the health technology assessment service(207) | Website | 2019 |
| | | Guidelines for authors of CADTH health technology Assessment reports(169) | Guideline | 2003 |
| | | Guidelines for the economic evaluation of health technologies: Canada(170) | Guideline | 2017 |
| United States of America (USA) | Agency for healthcare research and quality (AHRQ) | AHRQ Methods for Effective Health Care(164) | Website | 2008 |
| | | Methodology (166) | Website | 2013 |
| | | Methods guide for effectiveness and comparative effectiveness reviews(167) | Guideline | 2014 |
| | | Methods guide for medical test reviews(165) | Guideline | 2012 |

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