The regulation of non-invasive medical devices in Australia: a case study of breast cancer imaging devices marketed direct-to-consumer

Thomas Vreugdenburg
BHealthSciences(Hons)

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy
August 2014

Discipline of Public Health
School of Population Health
Faculty of Health Sciences
The University of Adelaide
# Table of contents

**Thesis summary** ............................................................................................................. V

**Declaration** ................................................................................................................ V

**Conference presentations resulting from this thesis** .................................................. VIII

**Peer-reviewed journal articles resulting from this thesis** ........................................ IX

**Acknowledgements** .................................................................................................. X

**List of tables** ............................................................................................................... XI

**List of figures** .............................................................................................................. XII

**List of terms** ................................................................................................................ XIII

**Chapter 1 - Introduction and literature review** ......................................................... 1

1.1 Introduction .................................................................................................................... 2

1.2 Health services research and the regulation of medical devices ................................. 2

1.2.1 Pathway to market: pre-market conformity assessment of medical devices in
Australia .......................................................................................................................... 5

1.2.2 Risk management approach to medical device regulation ...................................... 7

1.3 Medical devices advertised directly towards consumers ........................................... 12

1.3.1 Regulating dtca of medical devices in Australia ..................................................... 12

1.4 Challenges to the effective regulation of devices and their advertising material ...... 13

1.4.1 Debate around the benefit of dtca ........................................................................ 14

1.5 Case study: emerging breast cancer imaging devices ............................................. 17

1.5.1 Clinical relevance and burden of disease in Australia ............................................ 17

1.5.2 Australia’s national breast cancer screening program ........................................... 19

1.6 Emerging breast imaging devices .............................................................................. 22

1.6.1 Digital infrared thermal imaging (DITI) ................................................................. 22

1.6.2 Electrical impedance scanning (EIS) ..................................................................... 23

1.6.3 Electronic palpation imaging (EPI) ..................................................................... 25

1.6.4 The evidence base for DITI, EIS and EPI ............................................................... 26

1.7 Gaps in evidence base and research justification .................................................... 27

1.8 Research aims and questions ..................................................................................... 28

1.9 Thesis outline .............................................................................................................. 29
Chapter 2 - Policy issues surrounding DtCA of breast imaging devices in Australia...31

2.1 Preface to Chapter 2 ........................................................................................................32
2.2 Statement of authorship .................................................................................................33
2.3 Abstract ..........................................................................................................................34
2.4 Introduction ....................................................................................................................34
2.5 Importance of breast cancer screening and diagnostic devices ..................................35
2.6 Pre-market regulation of medical devices in Australia ................................................37
2.7 Post-market regulation of dtca in Australia ................................................................39
2.8 Conclusion and implications .........................................................................................41

Chapter 3 - Evaluating the evidence base: a systematic review of emerging breast
imaging devices ..................................................................................................................43

3.1 Preface to Chapter 3 ........................................................................................................44
3.2 Statement of authorship .................................................................................................45
3.3 Abstract ..........................................................................................................................46
3.4 Introduction ....................................................................................................................47
3.5 Methods ..........................................................................................................................48
   3.5.1 Search strategy .......................................................................................................48
   3.5.2 Study selection ......................................................................................................48
   3.5.3 Data extraction and quality appraisal .................................................................48
   3.5.4 Data synthesis ......................................................................................................49
3.6 Results ............................................................................................................................50
   3.6.1 Literature search results ......................................................................................50
   3.6.2 Risk of bias within studies ...................................................................................51
   3.6.3 Publication bias ....................................................................................................52
   3.6.4 Investigation of heterogeneity ..............................................................................52
   3.6.5 Synthesis of results ..............................................................................................57
3.7 Discussion .......................................................................................................................59
3.8 Conclusions ...................................................................................................................61
   3.8.1 Acknowledgements ..............................................................................................62

Chapter 4 - Content analysis of online DtCA of emerging breast imaging devices.......63

4.1 Preface to Chapter 4 ........................................................................................................64
4.2 Statement of authorship .................................................................................................65
4.3 Abstract ......................................................................................... 67
4.4 Introduction................................................................................... 68
4.5 Methods.......................................................................................... 69
  4.5.1 Search strategy .......................................................................... 69
  4.5.2 Codebook development .............................................................. 69
  4.5.3 Coder training ........................................................................... 69
  4.5.4 Data analysis ............................................................................. 70
4.6 Results ........................................................................................... 70
  4.6.1 Device performance ................................................................... 71
  4.6.2 Application of device ................................................................. 71
  4.6.3 Device safety ............................................................................ 72
  4.6.4 Target population ...................................................................... 73
  4.6.5 Comparison with conventional breast imaging technology ....... 73
  4.6.6 Change over time ...................................................................... 74
4.7 Discussion ....................................................................................... 75
  4.7.1 Acknowledgements ................................................................... 77
  4.7.2 Competing interests .................................................................. 77

Chapter 5 - Exploring options to reform the regulation of medical devices and medical
device advertising ................................................................................. 79
5.1 Introduction .................................................................................... 80
  5.1.1 The TGA reform process ............................................................ 81
  5.1.2 Research aims and objectives ..................................................... 83
5.2 Methods ......................................................................................... 85
  5.2.1 Design ...................................................................................... 85
  5.2.2 Stakeholder selection and recruitment ........................................ 85
  5.2.3 Interview schedule .................................................................... 86
  5.2.4 Data analysis ............................................................................ 87
  5.2.5 Ethical requirements .................................................................. 87
5.3 Results ........................................................................................... 88
  5.3.1 Stakeholder demographics ........................................................ 88
  5.3.2 Section 1: The TGA’s proposals to reform the pre-market assessment of
          medical devices ........................................................................... 89
5.3.3 Section 2: The TGA’s options to reform the advertising arrangements for medical devices in Australia ................................................................. 96

5.3.4 Section 3: Recommended criteria for the pre-market assessment of medical devices, and medical device advertising ........................................ 100

5.4 Discussion .................................................................................................................. 105

5.4.1 Limitations ................................................................................................................. 107

5.4.2 Conclusions and policy considerations ........................................................................ 108

Chapter 6 - Discussion and conclusions ........................................................................... 109

6.1 Introduction ...................................................................................................................... 110

6.2 Key findings and implications ......................................................................................... 110

6.2.1 What is the available evidence of safety, effectiveness and diagnostic accuracy of digital infrared thermal imaging (DITI), electrical impedance scanning (EIS) and electronic palpation imaging (EPI) for breast cancer screening and diagnosis? ................................................................................. 110

6.2.2 What is the nature and frequency of advertising claims made on Australian websites for DITI, EIS and EPI? To what extent are claims made on websites for these devices supported by evidence? ................................................................. 112

6.2.3 What are the strengths and weaknesses of the TGA’s proposed reforms to the pre-market assessment of medical devices and their advertising material in Australia? Which characteristics of medical devices and their advertising should be assessed by an independent regulator? ......................................................... 114

6.3 Thesis limitations and recommendations for future research .................................... 116

6.4 Conclusion ...................................................................................................................... 118

Appendix A – Peer reviewed publications arising from this thesis .................................. 119

Appendix B – Supplementary material for the systematic review publication ............... 123

Appendix C – Supplementary material for the content analysis ................................... 133

Appendix D – Supplementary material for the stakeholder engagement ....................... 139

Appendix E – TGA submission: premarket assessment of devices ................................. 153

Appendix F – TGA submission: regulation of therapeutic goods advertising ................. 167

Reference list ...................................................................................................................... 181
Thesis summary

Background

The premarket assessment of medical devices by an independent regulator is necessary to ensure that devices are safe and effective before they are made available to consumers in Australia. This responsibility is further necessitated by the practice of direct-to-consumer advertising (DtCA), whereby devices can be promoted to, and accessed by consumers without the involvement of a registered healthcare practitioner. An increase in the number of complaints against medical device advertising in Australia has raised questions around the effectiveness of the current regulations at ensuring that devices and their advertising material are adequately supported by evidence.

Aims

The aim of this thesis is to explore the relationship between scientific evidence and DtCA in the policy context of medical device regulation in Australia. This aim is investigated using a case study of three emerging breast cancer imaging devices: digital infrared thermal imaging (DITI), electronic impedance scanning (EIS) and electronic palpation imaging (EPI). In this thesis, the evidence supporting the safety and effectiveness of these devices is evaluated, the nature and frequency of claims presented in online advertisements for these devices are assessed and compared against the available evidence, and stakeholders are engaged in a discussion around options to reform the regulation of medical devices and medical device advertising.

Methods

A mixed methods approach was undertaken, involving three interrelated studies. The first study presents a systematic review of the available evidence for the safety and effectiveness of DITI, EIS and EPI. Following the systematic review, a quantitative content analysis was used to investigate the evidentiary basis of advertising claims made on websites that promote DITI, EIS and EPI in Australia. Finally, the results of the first two studies were used to inform stakeholder engagement around options to reform the regulation of medical devices and medical device advertising. Thematic analysis was used to synthesise stakeholder preferences in relation to a series of reform options proposed by Australia’s principal therapeutic goods regulator, the Therapeutic Goods Administration (TGA).
Results

Study 1

As no direct effectiveness data were identified, the surrogate outcome measure of diagnostic accuracy became the primary focus of the systematic review. Significant heterogeneity was present among all three device classes, limiting the potential for meta-analyses. There was insufficient evidence to support the use of DITI, EIS or EPI for breast cancer screening, and the reported estimates of the sensitivity and specificity in symptomatic populations varied greatly for DITI (Sens 0.25-0.97, Spec 0.12-0.85) and EIS (Sens 0.26-0.98, Spec 0.08-0.81), while only two poor quality studies were identified for EPI.

Study 2

Thirty-nine Australian websites promoting DITI, EIS or EPI were identified. Despite a lack of primary evidence identified in the prior systematic review, the devices were advertised for diagnosis (n = 22 websites), screening (n = 20), prevention (n = 13) and risk factor identification for breast cancer (n = 13). Similarly, advertising claims of diagnostic accuracy (Sens 0.78-0.99, Spec 0.44-0.91) did not reflect the evidence base. Direct comparisons with conventional imaging were highly prominent (n = 31), and one third of websites explicitly promoted their device as a suitable alternative to conventional imaging (n = 12).

Study 3

Sixteen stakeholders representing breast cancer research, patient advocacy and screening provided input into reforms to premarket medical device regulation and advertising proposed by the TGA. Participants highlighted important benefits and limitations of the proposed options. Differences between the TGA’s options for reform and stakeholder views indicated a need to update the current model for regulation that allows consumer choice and supports innovation, but within a more tightly regulated, safety-oriented framework.

Conclusion

Online advertising claims made for DITI, EIS and EPI extend the indications and efficacy of these devices beyond the available research evidence. This disconnect suggests the regulatory framework tasked with ensuring the safety and efficacy of these devices and their promotion is in need of reform. Extending the current regulations for advertising pre-approval to include medical devices, assessing diagnostic imaging devices for efficacy prior to market, and monitoring the use of a device in practice compared to its approved use on the Australian Register of Therapeutic Goods (ARTG) will help close the gap between DtCA and the evidence for emerging breast imaging devices.
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.

I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

The author acknowledges that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I also give permission for the digital version of my thesis to be made available on the web, via the University’s digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Signed: ..............................

Date: ..............................
Conference presentations resulting from this thesis


Acknowledgements

A number of people helped guide me through this PhD candidature, offering motivation, guidance, support, and time. To these people I am sincerely grateful, and would like to offer thanks.

First and foremost, my supervisors: Janet Hiller, for generously offering her time, intellect and genuine passion for public health, proving in the process that there are in fact more than 24 hours in a day. Cameron Willis, for providing a truly endless source of motivation and support, and offering guidance and input into every aspect of my role of as a PhD candidate. Caroline Laurence, who joined the panel partway through my candidature, and lent her level-headed pragmatism to anchor the content analysis and stakeholder engagement studies. Linda Mundy, for contributing her vast knowledge of systematic review methodology, and for playing the role of informal editor with so much enthusiasm that I still have nightmares about incorrectly using the letter ‘z’.

Tracy Merlin, Jacqueline Street, Liz Buckley, Dagmara Riitano, David Johnson, Danika Hall, Shona Crabb, and Tom Sullivan, for assisting on various projects presented in this thesis, with only free beer, lunch or reciprocity as an incentive.

Adam Elshaug, for providing valuable input into the direction of this thesis during the early stages of conception.

I highly recommend that every commencing PhD candidate find a resident philosopher, like Drew Carter, to bounce ideas off and help guide them through inevitable crises.

Alun Cameron and Wendy Babidge from ASERNIP-s, for understanding the pressures associated with completing a PhD thesis, and for allowing me to work at a reduced capacity while finishing the write up.

My fellow inmates: Tori, Phi, David, Vicki, Icha, Kerri, and Andrew, for helping discuss and empathise with the big and small issues of life as a postgraduate student.

My friends and family, who remained genuinely interested in my thesis topic at every barbeque over the course of my candidature.

And my loving partner, Sharon, who survived 18 months at long-distance, and an equal amount of time dealing with the phrase “not-this-weekend-I'm-still-working-on-my-thesis”.

List of tables

Table 1.1 NHMRC hierarchy of evidence according to research question ........................................ 4

Table 1.2 Examples of medical devices under different risk categories ........................................ 7

Table 1.3 Australian conformity assessment requirements for different classes of medical devices, adapted from the Australian regulatory guidelines for medical devices ...................... 9

Table 3.1 Characteristics of studies included in the systematic review ........................................ 53

Table 4.1 Reliability score for each main code category ................................................................. 70

Table 4.2 Advertising content on direct-to-consumer websites for breast cancer imaging devices, by code category and device classification ......................................................... 71

Table 4.3 Examples of advertising claims and supporting evidence reported on direct-to-consumer websites for breast cancer imaging devices ......................................................... 74

Table 5.1 Participant demographics ............................................................................................... 88

Table 5.2 Stakeholder perspectives on the proposals for reform to the pre-market assessment of medical devices ........................................................................................................... 89

Table 5.3 Stakeholder perspectives on options to reform advertising regulations for medical devices ............................................................................................................................... 96

Table 5.4 Illustrative quotes demonstrating themes identified from participants regarding the pre-market approval of devices ......................................................................................... 101

Table 5.5 Illustrative quotes of themes identified from participants views regarding the assessment of advertising material for medical devices......................................................... 103

eTable 1 Systematic review search strategy .................................................................................... 124

eTable 2 Inclusion and exclusion criteria based on pico criteria .................................................... 124

eTable 3 NHMRC hierarchy of evidence according to research question ........................................ 125

eTable 4 Diagnostic accuracy results of included studies ............................................................... 126

eTable 5 Investigation of heterogeneity in subgroup likelihood ratios ......................................... 129

eTable 6 Explanation of the QUADAS quality appraisal tool, as adapted for the systematic review ............................................................................................................................................................................. 130
List of figures

Figure 1.1  Algorithm to determine the risk classification of an active medical device........8
Figure 1.2  Pathway of supply for medical devices in Australia.................................10
Figure 1.3  Technology adoption curve with possible patterns of diffusion .................11
Figure 1.4  Age standardised incidence of breast cancer by age at diagnosis, females, 1982-2009........................................................................................................18
Figure 1.5  Clinical pathway for screening and diagnosis of breast cancer in Australia ....20
Figure 1.6  Examples of thermography imaging results..............................................23
Figure 1.7  Examples of electrical impedance imaging results....................................24
Figure 1.8  Examples of elastography imaging results ..............................................25
Figure 3.1  PRISMA flow diagram of study inclusion...................................................50
Figure 3.2  Forest plot of estimated sensitivity and specificity reported in ultrasound elastography studies that employed the elasticity score method...........................57
Figure 3.3  Forest plot of estimated sensitivity and specificity reported in digital infrared thermal imaging studies, all methods.........................................................58
Figure 3.4  Forest plot of estimated sensitivity and specificity reported in electrical impedance scanning studies that employed the 5 point “level of suspicion” method..............................................................................................58
Figure 3.5  Forest plot of estimated sensitivity and specificity reported in electrical impedance scanning .................................................................58
Figure 5.1  Approximate timeline of the major reviews contributing to the TGA’s blueprint for reform package .................................................................................81
eFigure 1  Percentage of all studies fulfilling individual QUADAS criteria ..............131
eFigure 2  Individual study estimates of sensitivity and specificity for use using artificial neural networks............................................................131
eFigure 3  Individual study estimates of sensitivity and specificity for use using length ratio ...................................................................................131
eFigure 4  Individual study estimates of sensitivity and specificity for use using strain ratio. .....................................................................................132
<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCC</td>
<td>Australian Competition and Consumer Commission</td>
</tr>
<tr>
<td>AIMD</td>
<td>Active Implantable Medical Device</td>
</tr>
<tr>
<td>ARTG</td>
<td>Australian Register of Therapeutic Goods</td>
</tr>
<tr>
<td>ASMI</td>
<td>Australian Self Medication Industry</td>
</tr>
<tr>
<td>ANZHSN</td>
<td>Australia and New Zealand Horizon Scanning Network</td>
</tr>
<tr>
<td>AusPAR</td>
<td>Australian Public Assessment Report</td>
</tr>
<tr>
<td>CAM</td>
<td>Complementary and Alternative Medicine</td>
</tr>
<tr>
<td>CBE</td>
<td>Clinical Breast Examination</td>
</tr>
<tr>
<td>CHC</td>
<td>Complementary Healthcare Council of Australia</td>
</tr>
<tr>
<td>CINAHL</td>
<td>Cumulative Index to Nursing and Allied Health Literature</td>
</tr>
<tr>
<td>CRD</td>
<td>Centre for Reviews and Dissemination</td>
</tr>
<tr>
<td>CRP</td>
<td>Complaints Resolution Panel</td>
</tr>
<tr>
<td>Cth</td>
<td>Commonwealth</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability Adjusted Life Year</td>
</tr>
<tr>
<td>DITI</td>
<td>Digital Infrared Thermal Imaging</td>
</tr>
<tr>
<td>DM</td>
<td>Digital Mammography</td>
</tr>
<tr>
<td>DtCA</td>
<td>Direct-to-Consumer Advertising</td>
</tr>
<tr>
<td>EBM</td>
<td>Evidence Based Medicine</td>
</tr>
<tr>
<td>EIS</td>
<td>Electrical Impedance Scanning</td>
</tr>
<tr>
<td>EPI</td>
<td>Electronic Palpation Imaging</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GHTF</td>
<td>Global Harmonization Task Force</td>
</tr>
<tr>
<td>GMDN</td>
<td>Global Medical Device Nomenclature</td>
</tr>
<tr>
<td>HTA</td>
<td>Health Technology Assessment</td>
</tr>
<tr>
<td>LOS</td>
<td>Level of Suspicion</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>OTC</td>
<td>Over-The-Counter</td>
</tr>
<tr>
<td>PRL</td>
<td>Proportional Reduction in Loss</td>
</tr>
<tr>
<td>QD</td>
<td>Qualitative Description</td>
</tr>
<tr>
<td>QUADAS</td>
<td>Quality Assessment of Diagnostic Accuracy Studies</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>USE</td>
<td>Ultrasound Elastography</td>
</tr>
<tr>
<td>YLD</td>
<td>Years Lost to Disability</td>
</tr>
<tr>
<td>YLL</td>
<td>Years of Lost Life</td>
</tr>
</tbody>
</table>
CHAPTER 1

Introduction and literature review
1.1 Introduction

Regulators and clinicians act as gatekeepers to the safe and effective use of medical devices by serving two distinct roles. Regulators aim to ensure that devices are safe and effective prior to entry onto the market, and that the advertising material for these devices is balanced and accurate. Clinicians act as providers of services that use medical devices, and serve the function of determining which devices are most appropriate and beneficial for patients. In direct-to-consumer advertising (DtCA) the role of the clinician in this process can be circumvented, as products are promoted to, and accessed directly by, consumers. In this case, the role of the regulator is paramount to ensure that consumers are accessing safe and effective care that is supported by evidence.

As the medical devices industry expands in both Australian and international markets, the regulatory burden associated with monitoring new technical innovations is likely to increase. Further complicating this issue is the potential for medical devices to diffuse in out-of-pocket, direct-to-consumer markets, presenting new challenges to regulatory agencies responsible for assessing the safety and efficacy of these products. Given the increasing number of devices and resource constraints, the extent to which medical devices are effectively regulated in practice is debatable.

Through a case study of three emerging breast imaging devices, this thesis will explore whether the current Australian regulatory framework for medical devices ensures that medical devices marketed direct-to-consumer are supported by evidence, as well as the extent to which advertising for these devices is accurate. In order to achieve these goals, an assessment of the performance and safety of these devices will be described, and compared with a quantitative analysis of the advertising content for these devices. The results of these studies are then synthesised to inform a stakeholder engagement around options to reform the current regulatory systems for the pre-market assessment of medical devices, and post-market regulation of their advertising material.

1.2 Health services research and the regulation of medical devices

Recent failures of high-profile implantable devices, namely metal-on-metal hip implants and poly implant prosthèse breast implants, have highlighted the importance of effective medical device regulation. However, implantable devices are only a subset of a broader industry encompassing multiple classes and subclasses of devices. According to
Australian law, as outlined by the *Therapeutic Goods Act* (1989) (Cth), the term “medical device” encompasses:⁵

“any instrument, apparatus, appliance, material or other article (whether used alone or in combination, and including the software necessary for its proper application) intended, by the person under whose name it is or is to be supplied, to be used for human beings for the purpose of one or more of the following:

(i) diagnosis, prevention, monitoring, treatment or alleviation of disease; (ii) diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disability; (iii) investigation, replacement or modification of the anatomy or of a physiological process; (iv) control of conception; and that does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but that may be assisted in its function by such means.”

The focus of investigation in this thesis is on imaging devices used for screening and diagnosing breast cancer. Throughout this thesis, the concept of ‘evidence’ will be discussed in many different contexts, including the pre-market assessment of medical devices and the regulation of advertising material. In each context, discussions around ‘evidence’ are related to the core principles of evidence based medicine (EBM), that is, the evidence of the safety, efficacy and effectiveness of a medical device demonstrated by high quality, transparent, objective and repeatable studies.⁶⁻⁸ Within this framework, the effectiveness of a device refers to the potential impact it may have on patient outcomes in clinical practice (for example, reduced mortality, change in patient management), the efficacy refers to the ability of the device to demonstrate a level of effect related to its intended function on a study population (for example, diagnostic accuracy), and the safety refers to the potential harms which may arise through the use of a device (for example, radiation exposure, tissue compression).

What constitutes acceptable evidence within the framework of EBM can be determined by referring to the National Health and Medical Research Council’s (NHMRC) levels of evidence.⁸ The levels of evidence provide a hierarchy that ranks the quality of individual study designs based on the type of research question being addressed, and indicate the amount of bias introduced by a particular study design. It is important to note, however, that the levels of evidence provide a summary of a body of evidence, and cannot be relied on entirely for critical appraisal of research evidence. The hierarchy is separated into five categories, including intervention, diagnostic accuracy, prognosis, aetiology, and
screening, as outlined in Table 1.1 As this thesis will investigate a case study of breast cancer imaging devices, acceptable evidence in this context is related specifically to the diagnostic accuracy and screening intervention arms of the hierarchy. The current pathway to market dictates the evidence requirements that devices must fulfil prior to market. Therefore, in order to gain an understanding of how evidence is used to regulate these devices in Australia, it is necessary to understand the pathway to market for these devices.

Table 1.1 NHMRC hierarchy of evidence according to research question

<table>
<thead>
<tr>
<th>Level</th>
<th>Intervention</th>
<th>Diagnostic accuracy</th>
<th>Prognosis</th>
<th>Aetiology</th>
<th>Screening intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
</tr>
<tr>
<td>II</td>
<td>A randomised controlled trial</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation.</td>
<td>A prospective cohort study</td>
<td>A prospective cohort study</td>
<td>A randomised controlled trial</td>
</tr>
<tr>
<td>III-1</td>
<td>A pseudorandomised controlled trial (i.e. alternate allocation or some other method)</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation.</td>
<td>All or none</td>
<td>All or none</td>
<td>A pseudorandomised controlled trial (i.e. alternate allocation or some other method)</td>
</tr>
</tbody>
</table>
| III-2 | A comparative study with concurrent controls:  
  - Non-randomised, experimental trial  
  - Cohort study  
  - Case-control study  
  - Interrupted time series with a control group | A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence | Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial | A retrospective cohort study | A comparative study with concurrent controls:  
  - Non-randomised, experimental trial  
  - Cohort study  
  - Case-control study |
| III-3 | A comparative study without concurrent controls:  
  - Historical control study  
  - Two or more single arm study  
  - Interrupted time series without a parallel control group | Diagnostic case-control study | A retrospective cohort study | A case-control study | A comparative study without concurrent controls:  
  - Historical control study  
  - Two or more single arm study |
| IV    | Case series with either post-test or pre-test/post-test outcomes | Study of diagnostic yield (no reference standard) | Case series, or cohort study of persons at different stages of disease | A cross-sectional study or case series | Case series |

Table Source: Merlin et al, 2009(8)
1.2.1 Pathway to market: pre-market conformity assessment of medical devices in Australia

Through the administration of the *Therapeutic Goods Act* (1989), \(^5\) the Therapeutic Goods Regulations (1990), \(^9\) and the Therapeutic Goods (Medical Devices) Regulations (2002), \(^10\) the Therapeutic Goods Administration (TGA) is responsible for regulating safety and quality standards applicable to medical devices. Administration of the Act and associated regulations requires the TGA to fulfil three key responsibilities as Australia’s principal therapeutic goods regulator:

1. The pre-market evaluation and approval of all therapeutic products that are intended for supply in Australia.
2. Licensing of pharmaceutical manufacturers and the certification of medical device manufacturer quality systems, for both Australian companies and overseas companies providing a product in Australia, to ensure that they are operating at Australian standards.
3. Post-market surveillance of therapeutic goods, such as monitoring adverse events and drug interactions, including a role in the regulation of therapeutic goods advertising.

The TGA’s main pre-market responsibility for medical devices is to determine which devices can be included on the Australian Register of Therapeutic Goods (ARTG); a requirement for the import to, export from, and supply of therapeutic goods within Australia. \(^11\) Medical devices must pass through a conformity assessment process in order to be included on the ARTG. This process involves an examination of the evidence supporting a device, the evidence of prior approvals from another regulatory agency such as the United States Food and Drug Administration (FDA), and an assessment of manufacturing procedures to ensure they comply with Australian standards. \(^12\)

Conformity assessment procedures required for the pre-market approval of medical devices in Australia were derived from high-quality principles outlined by the Global Harmonization Task Force (GHTF); an initiative comprised of international representatives from industry and medical device regulatory agencies, of which the TGA was an active member. \(^13\) Operating for over 20 years, the primary aim of the GHTF was to align international conformity assessment procedures for medical devices. Aligning regulatory procedures aimed to reduce the time and cost required to gain regulatory compliance for devices, and to allow earlier access to market for innovative devices and tests. \(^14\) Although the GHTF disbanded in 2011, its work in guiding principles for conformity assessment has
been continued by the International Medical Device Regulators Forum, and is reflected in the current pathway onto the Australian market for medical devices.\(^{(15)}\)

Although the majority of medical devices must pass conformity assessment before they can be included on the ARTG, there are four key exceptions to this requirement. Devices accessed through these arrangements are not officially approved for use by the TGA, and therefore are not assessed for safety or efficacy prior to supply. These exceptions include:\(^{(12)}\)

1. **Special access scheme**: assessed on a case-by-case basis, some devices can be accessed by patients who are likely to die within a short period of time, or who may die prematurely due to a lack of available treatment options available on the ARTG.
2. **Authorised prescribers**: clinicians can register to become authorised prescribers for unapproved devices if they can provide adequate clinical justification for a particular indication of a new drug or device.
3. **Personal import**: an individual may bring an unapproved device into Australia on their person or may organise for a therapeutic good to be sent to them from an overseas supplier so long as the device complies with quarantine laws, does not contain prohibited substances, does not contain human or animal samples, is not on-sold or given to a relative or friend, and does not include more than 3 months of supply.
4. **Clinical trials**: devices used in clinical trials are exempt from inclusion on the ARTG.

For all other devices, a key step in the conformity assessment process for inclusion on the ARTG is ensuring that medical devices comply with the Essential Principles; a set of regulatory guidelines informed by work conducted by the GHTF. The Essential Principles are outlined in the *Therapeutic Goods Act (1989)* (Cth), and establish the minimum requirements for compliance necessary for a device to be considered for inclusion on the ARTG. There are six general principles that apply to all devices, which aim to ensure new medical devices:\(^{(16)}\)

1. Do not compromise the health and safety of consumers.
2. Are designed and constructed in a manner that conforms to the safety principles outlined in the first principle.
3. Are suitable for their intended purpose.
4. Have data supporting their long-term safety.
5. Are not adversely affected by transport or storage.
6. Have therapeutic or diagnostic benefits that outweigh any potential adverse effects.

In addition to the general principles, there are nine additional principles relating to the design and construction of devices, which are applied on a case-by-case basis.\(^{(12)}\) These principles relate to device-specific features such as radiation dose, infection and contamination, chemical properties and construction properties. As not all of the additional principles are relevant for all medical devices, the level of conformity assessment a device must face is dependent upon on the class of device being assessed. In this regard the TGA, as with many similar agencies, takes a risk-based approach to conformity assessment in Australia.

### 1.2.2 Risk management approach to medical device regulation

Medical devices are subject to varying levels of pre-market regulatory scrutiny, based primarily on their ability to cause physical harm to a patient. The classification of medical devices is also based on a device’s intended use, its degree of invasiveness in the human body, and the duration of its use.\(^{(13)}\) Under the current classifications, Class I devices represent the lowest risk to patients, Class IIa and IIb represent low to moderate risk, and Class III and active implantable devices (AIMD) are considered to present the highest risk. Examples of devices assigned to various risk categories are presented in Table 1.2.

#### Table 1.2 Examples of medical devices under different risk categories

<table>
<thead>
<tr>
<th>Device Classification</th>
<th>Example of Device(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Spectacle frames, urine collection bottles, medical adhesive tape</td>
</tr>
<tr>
<td>Class Is</td>
<td>Sterile adhesive dressing strips</td>
</tr>
<tr>
<td>Class Im</td>
<td>Clinical thermometers, medicine measuring cups</td>
</tr>
<tr>
<td>Class IIa</td>
<td>Non-invasive breast imaging devices, cannulas, scalpel blades, blood pressure measurement systems, X-ray films</td>
</tr>
<tr>
<td>Class IIb</td>
<td>In-vitro fertilisation culture medium kit</td>
</tr>
<tr>
<td>Class III</td>
<td>Press-fit femur prostheses, aortic arch cannulas, eye lubricant</td>
</tr>
<tr>
<td>Active Implantable Devices</td>
<td>Implantable pacemakers, cochlear implants</td>
</tr>
</tbody>
</table>

Examples sourced directly from the ARTG.\(^{(11)}\)

The manufacturer of a medical device is responsible for assigning the risk classification to a new medical device when applying for ARTG inclusion, as guided by a set of classification rules outlined by the TGA.\(^{(13)}\) These rules are derived from the Essential
Principles, and pertain to a device's level of invasiveness, side effect profile, design, and the severity of the condition for which it is intended to be used. The TGA's model for selecting the appropriate level of risk classification for an active medical device, that is, a device with a power source, is presented in Figure 1.1. Using this model, active medical devices that are used to diagnose diseases or conditions are classified as Class IIa. In contrast, active medical devices used for diagnosis, which are also used to monitor vital processes that could place a patient in direct or immediate danger, are classified as Class IIb. Using this framework, non-invasive imaging devices would be classified as Class IIa.

**Figure 1.1 Algorithm to determine the risk classification of an active medical device**

Adapted from TGA, 2011.

The level of pre-market conformity assessment a medical device is subject to increases alongside its associated risk classification. Higher-risk devices (Class III and AIMDs) are subject to a more rigorous level of assessment before being included on the ARTG, whereas lower-risk devices are required to pass minimal conformity assessment procedures. A summary of the most common conformity assessment procedures required for each class of device, as described by the TGA, is outlined in Table 1.3. It is important to note that while all devices above Class I must have quality assurance systems in place, only AIMDs and Class III medical devices are required to submit clinical evidence for assessment.
prior to ARTG inclusion. Class IIb devices must have clinical evidence available if requested for auditing purposes, but are not formally required to submit this evidence prior to gaining market approval. In addition to these requirements, specific devices may face additional regulatory assessment prior to ARTG inclusion. However, these cases are rare due to the TGA’s limited capacity and funding to carry out more resource-intensive assessments.\(^{(13)}\)

**Table 1.3** **Australian conformity assessment requirements for different classes of medical devices, adapted from the Australian regulatory guidelines for medical devices**

<table>
<thead>
<tr>
<th>Class of device</th>
<th>Most commonly used conformity assessment requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>The manufacturer must ensure that the device(s) comply with the Essential Principles, and must have a Declaration of Conformity available if the TGA requests. This declaration is not required to be submitted to, or assessed by, the TGA.</td>
</tr>
<tr>
<td>Class I (measuring), and Class IIa (non-sterile)</td>
<td>The manufacturer must ensure that the device(s) comply with the Essential Principles, and must have a Declaration of Conformity available if the TGA requests. This declaration is not required to be submitted to, or assessed by, the TGA. The manufacturer must also implement a quality management system which encompasses the final inspection and testing of a medical device. This quality management system needs to be audited by either the TGA or a European Notified Body.</td>
</tr>
<tr>
<td>Class I (sterile), and Class IIa (sterile)</td>
<td>The manufacturer must ensure that the device(s) comply with the Essential Principles, and must have a Declaration of Conformity available if the TGA requests. This declaration is not required to be submitted to, or assessed by, the TGA. The manufacturer must also implement a quality management system which encompasses the production and final inspection a medical device. This quality management system needs to be audited by either the TGA or a European Notified Body, and is also required to review a sample of the manufacturer’s technical documentation for the devices.</td>
</tr>
<tr>
<td>Class IIb</td>
<td>The manufacturer must design and implement a full quality management system, encompassing product design, production, packing, labelling and final inspection and arrange for the TGA or European Notified Body to audit this system. The manufacturer must also have technical documents and available clinical evidence on hand if the TGA or European Notified Body requests it for auditing purposes.</td>
</tr>
<tr>
<td>Class III, and Class AIMD</td>
<td>The manufacturer must design and implement a full quality management system, encompassing product design, production, packing, labelling and final inspection and arrange for the TGA or European Notified Body to audit this system. The manufacturer must also provide the TGA or European Notified Body with technical documentation supporting the device(s), including all available clinical evidence for assessment. This assessment aims to ensure that the device complies with the Essential Principles.</td>
</tr>
</tbody>
</table>

AIMD: active implantable medical device. TGA: Therapeutic Goods Administration. Source: TGA, 2011.\(^{(13)}\)
The pathway to ARTG inclusion, and therefore market approval in Australia, is summarised in Figure 1.2. In this pathway, the manufacturer and sponsor of the device have different responsibilities in order for a medical device to be approved for use in Australia. The manufacturer of a medical device refers to the person or company that designs, produces, packages and labels a device, whereas the sponsor refers to a person or company that exports or imports a device to Australia, or manufacturers a device within Australia.\(^{(6)}\) There are three key steps to market approval involving manufacturers and sponsors, which differ depending on the class of device as discussed earlier:

1. First, the manufacturer must submit evidence that the device conforms to the Essential Principles. Conformity assessment with the Essential Principles may be self-certified by the manufacturer, evaluated by the TGA, or assessed by an approved European regulatory body.
2. If the device complies with the Essential Principles, the manufacturer will receive a conformity assessment certificate, which the sponsor may submit to the TGA.
3. Once the conformity assessment certificate is approved by the TGA, the sponsor may then apply to have the device listed on the ARTG. The evidence supporting devices lower than Class III may be evaluated by the TGA at this stage, as they are not assessed for efficacy prior to this step.

**Figure 1.2** Pathway of supply for medical devices in Australia

Once a medical device satisfies the conformity assessment requirements and is included on the ARTG, it can legally be supplied, manufactured, imported to, or exported from Australia. As outlined by the principles of diffusion theory, new health technologies entering the health system often move through a standard diffusion curve. An example of a standard diffusion curve with possible diffusion patterns is presented in Figure 1.3. Ideally, Horizon Scanning should identify new technologies during the early adoption phase, approximately three to five years prior to widespread diffusion. Health technology assessment is traditionally conducted at the peak inflection point in the curve, with reimbursement policy considered when the technology is established. During the early stage of the diffusion cycle, medical devices are less likely to be publicly funded compared to an established device or technology, and as such are often reliant on out-of-pocket, or “user pays” markets.

**Figure 1.3  Technology adoption curve with possible patterns of diffusion**

<table>
<thead>
<tr>
<th>Innovators</th>
<th>Early Adopters</th>
<th>Early Majority</th>
<th>Late majority</th>
<th>Laggards</th>
</tr>
</thead>
<tbody>
<tr>
<td>The prognosis-signature technique is developed and the first organizations adopt (introduce) the technology in their daily practice.</td>
<td>The early adoption phase describes the implementation a priori in 10-15 hospitals.</td>
<td>The implementation in other participating hospitals, relying on opinion leaders and well established logistics.</td>
<td>The late majority is conservative and waits until there is no further debate on the validity and the logistics are further improved.</td>
<td>The laggards are very hard to convince.</td>
</tr>
</tbody>
</table>

1.3 Medical devices advertised directly towards consumers

The definition of DtCA is varied in the literature, partly due to disciplinary differences in what qualifies as “DtCA”, and partly due to the changing nature of advertisements via the internet and web 2.0 initiatives.\(^{20-22}\) In Australia, the Therapeutic Goods Act (1989) (Cth) defines advertising in relation to therapeutic goods as:

“Any statement, pictorial representation or design, however made, that is intended, whether directly or indirectly, to promote the use of supply of the goods”.\(^{5}\)

In the context of medical devices, this applies to marketing endeavours by a provider of a medical device, which promotes information regarding a device to the general public without the involvement of a healthcare professional.\(^{20}\) The potential public health impact of DtCA of therapeutic goods is likely to increase, as information seeking behaviour and internet access increase. Research suggests that healthcare information sought online is highly valued by both patients and caregivers,\(^{23, 24}\) and that Australians are actively seeking healthcare information at increasing rates.\(^{24}\) In 2008, 34 per cent of a representative sample of 3,034 South Australian residents reported having sought healthcare information online, of which 82 per cent found the information “useful”, and 12.5 per cent changed the way they managed their healthcare as a result.\(^{24}\) Although there appears to be interest in online information about therapeutic products in Australia, researchers have raised concerns regarding the quality of online DtCA.\(^{25}\) Debate around this area has inevitably brought into question the current regulatory framework to regulate online information for therapeutic products in Australia.\(^{26}\)

1.3.1 Regulating DtCA of medical devices in Australia

Direct-to-consumer advertising (DtCA) of healthcare products, such as prescription medicines, complementary and alternative medicines and medical devices, is a contentious issue in health policy.\(^{27}\) Like other western countries, with the exception of the United States and New Zealand, DtCA of pharmaceutical products and selected pharmacist only medications is currently prohibited in Australia. While DtCA of over-the-counter (OTC) medicines and complementary and alternative medicine (CAM) is currently permitted, advertisements are required to meet a set of standards for advertising approval, as outlined in the Therapeutic Goods Act (1989) (Cth), the Therapeutic Goods Advertising Code, and the Competition and Consumer Act (2010) (Cth).\(^{5, 28}\) In addition to these Acts and guidelines, CAMs and OTC medicines must also adhere to further guidelines outlined by the Complementary Healthcare Council (CHC) Code of Practice, and the Australian Self-Medication Industry (ASMI) Code of Practice. Under these guidelines, direct-to-consumer
advertisements for CAMs and OTC medicines require prior approval by the CHC and ASMI respectively, before being presented to consumers in Australia.

Regulation of these guidelines is carried out by a combination of industry self-regulation, and co-regulation by the TGA, the Therapeutic Goods Advertising Code Council, the Australian Competition and Consumer Commission (ACCC), the ASMI, and the CHC. However, there are no industry bodies tasked with pre-approving medical device advertising, and medical device advertising does not require pre-approval from the TGA. As such, the quality of medical device advertising is dependent upon undefined industry self-regulation and consumer complaints to the TGA and/or ACCC. Given the poor track record of industry self-regulation of advertising in the Australian pharmaceutical and CAM industries, it raises the question of whether medical device advertising is adequately regulated in Australia to ensure that claims are not false or misleading.

1.4 Challenges to the effective regulation of medical devices and related advertising material

Within health services research, divergent schools of thought exist in relation to why, how, and to what extent medical devices should be regulated. Foremost in this debate are three considerations that provide context regarding the current state of the medical device industry, and medical device regulation in Australia:

1. The medical device industry is outpacing the pharmaceutical industry in terms of revenue growth internationally, with similar trends experienced in Australia.  
2. There are limited resources available to fund the regulation of medical devices and medical device advertising.
3. The regulatory framework for medical devices has not been successful at ensuring the safety of “high-risk” devices, which are the most rigorously assessed devices prior to market.

When combined, these statements highlight the increasing demand on resource-limited regulators, whose decisions can have a potentially large impact on the health of the population. Although the current landscape for medical devices indicates that effective regulation of the industry is warranted, considerations must be addressed in regards to whether, or at least to what extent, medical devices should be regulated. Leading this debate are considerations of the co-existence of public and private healthcare markets, and consumer autonomy versus state-enforced paternalism.
Publicly funded health care markets do not operate in isolation in Australia. Services that are supplied through private markets, either through user-pays or third-party payer (private insurer) systems, co-exist alongside the public market. These devices and services fall outside the rigorous health technology assessment (HTA) processes that government-funded procedures and therapeutic goods are subject to.\(^{(36)}\) Therefore there is less certainty around the safety, effectiveness and cost-effectiveness of medical devices that exist in out-of-pocket markets. This is particularly important in healthcare, as direct-to-consumer devices may be accessed by circumventing general practitioners and specialists, the traditional gatekeepers to safe and effective care.

Despite direct-to-consumer products existing within private markets, the public provision of health is not completely shielded from the transactions that take place in private markets. When a private market exists alongside an established public market, the public market invariably absorbs some indirect costs (externalities) that result from the private transaction of services or goods.\(^{(37, 38)}\) Any deficiencies in the guarantees provided in the private market are likely to be borne as a cost in the public system. For example, a user-pays out-of-pocket diagnostic test for breast cancer may send the patient into the public sector for treatment, or further investigation of an inconclusive or positive test result.

When it comes to private markets, the political, philosophical and ethical issues of whether people should have the ability to purchase any technology or service they desire is a constant source of debate, and there are inevitably proponents of a ‘buyer beware’ system.\(^{(35)}\) However, Australia has an existing framework of ‘fair trading’ law that stipulates the necessary guarantees that suppliers must make to consumers during transactions within private markets, through the *Competition and Consumer Act* (2010) (Cth) and the *Therapeutic Goods Act* (1989) (Cth).\(^{(5, 28)}\) As such, arguments around whether or not medical devices should be regulated are not directly relevant to this thesis, as Australian law dictates that they must. Instead, a more relevant question for this thesis is whether or not the promotion of medical devices provides a net benefit or harm to public health.

### 1.4.1 Debate around the benefit of DtCA

Although the majority of research around the public health impacts of DtCA has focused on prescription drugs,\(^{(39-41)}\) the principal areas of debate for and against the use of DtCA are broadly applicable to all healthcare products, including medical devices.

A primary benefit of DtCA claimed for public health is its ability to educate the public about health conditions and treatment options.\(^{(40)}\) Increasing the awareness of diseases and treatment options through educational media campaigns has been shown to increase the uptake of healthcare services in population-based screening initiatives,\(^{(42-44)}\) and it can be
argued that the same principles may apply to educational campaigns run through DtCA. This argument is based on two key assumptions: first, that the information presented in DtCA has educational value, and second, that the uptake of healthcare services promoted towards consumers always results in a positive outcome. The educational potential of DtCA, however, is often adversely affected by misleading and biased advertisements presented by companies selling healthcare products.\(^{(25, 45-47)}\) Furthermore, the conditions often advertised in this manner do not always warrant medical intervention, in which case DtCA can contribute to the overuse of medicines,\(^{(48)}\) and the medicalisation of normal human processes.\(^{(49)}\) To address the issue of unbalanced information provided in DtCA material, legislation in the United States mandates that prescription drug advertisements list all possible side effects of the drug being promoted, although no such arrangements are currently in place for medical devices or CAMs. Similarly, the ability of consumers to understand the information in DtCA may be limited due to low levels of health literacy, and has been suggested as a key factor contributing to market failure in private health markets.\(^{(50)}\)

The relationship between patients and health care providers, whereby clinicians act as gatekeepers to safe and effective health care, is also affected by DtCA of therapeutic goods. Proponents of DtCA argue that advertising therapeutic products directly towards consumers empowers individuals to engage in informed discussions with healthcare providers.\(^{(41)}\) This view is contrary to the established evidence of the educational benefit of DtCA. Evidence from the United States has also demonstrated that patients who are aware of DtCA often place pressure on healthcare providers to prescribe an advertised medicine, potentially resulting in inappropriate prescribing practices and overuse of prescription medicines.\(^{(48, 51)}\) In the instance that a request is denied, some patients may simply seek a prescription from another physician, or terminate the relationship with their healthcare provider.\(^{(39, 52)}\) Although there is currently little evidence to support the misuse of other healthcare products in the same manner, concerns have been noted over the potential for this to occur.\(^{(26, 53)}\)

It has also been argued that DtCA has the ability to increase the perceived clinical effectiveness of advertised health care products, due to an increase in the placebo effect.\(^{(20, 54)}\) Almasi and Stafford offer two models to explain the increased placebo effect witnessed with advertised products.\(^{(54)}\) Firstly, advertising may generate a conditioning effect in consumers, who are led to associate the products with positive emotions elicited by advertising material. Secondly, advertising may generate expectations of efficacy in consumers, which have been shown to increase the placebo effect through the expectancy-value theory.\(^{(54)}\) By raising consumers’ expectations about how well a therapeutic good may
work, and training an emotionally conditioned response to a healthcare product, it may be possible to increase the efficacy of healthcare interventions for a net public gain. The main challenge facing these models is that advertising which evokes heightened expectations of efficacy and emotional responses can also lead to over-demand for therapeutic goods beyond their reasonable usefulness.\(^{48}\) Over-prescription and overuse of medicines is a well-cited outcome of DtCA, and it is foreseeable that the same outcomes are possible for certain classes of medical devices, as DtCA for these products gains momentum.\(^{48, 55, 56}\)

Given that medical device advertising is not proactively regulated by an independent regulatory body in Australia, the potential harms associated with DtCA of these devices may be heightened. The issues discussed thus far in relation to the regulation of medical devices and DtCA are briefly summarised in Box 1. The remainder of this thesis will focus on a subset of medical devices which are currently advertised DtCA in Australia, namely, emerging breast cancer imaging devices.

**Box 1  Summary of issues related to the regulation of medical devices marketed direct-to-consumer**

<table>
<thead>
<tr>
<th>Summary of issues related to the regulation of medical devices in Australia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The TGA employs a risk-based classification system to determine the level of assessment a medical device must face prior to gaining market approval in Australia. Non-invasive medical imaging devices are most often classified as Class IIa or Class IIb devices, depending on their intended use.</td>
</tr>
<tr>
<td>Class IIb devices must have clinical evidence available if requested for auditing purposes, but are not formally required to submit this evidence prior to gaining market approval. Class IIa devices and below are not required to submit clinical evidence prior to market.</td>
</tr>
<tr>
<td>Devices at an early stage of uptake and diffusion often exist primarily in user-pays markets, and are advertised directly to consumers.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary of issues related to DtCA of medical devices.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DtCA can increase consumer awareness of healthcare interventions,(^{40}) promote informed discussions between patients and healthcare providers,(^{48, 51}) and generate a placebo effect.(^{20, 54})</td>
</tr>
<tr>
<td>The benefits of DtCA are contrasted against potential harms due to unbalanced or misleading information presented in advertisements,(^{25, 45, 46}) the overuse of therapeutic goods,(^{48}) and the medicalisation of normal human processes.(^{49})</td>
</tr>
<tr>
<td>The circumvention of clinicians as gatekeepers to safe and effective healthcare necessitates the regulation of DtCA in order to ensure that promotional material is balanced and accurate.</td>
</tr>
</tbody>
</table>
1.5 Case study: emerging breast cancer imaging devices

The term ‘breast cancer’ is used to define a group of diseases that are collectively characterised by the rapid, uncontrolled replication of poorly differentiated cells within the breast. This uncontrolled replication develops into malignant tumours which destroy local tissue, and can spread to other sites in the body through the lymphatic or vascular systems.\(^{(57)}\) Evidence shows that the early detection of breast cancer through population-based screening programs can mitigate the morbidity and mortality associated with breast cancer.\(^{(58-63)}\) In addition to conventional X-ray mammography, a number of alternative imaging tests currently exist to screen or diagnose breast cancer. The diversity of screening and diagnostic tests available beyond mammography, combined with the high profile and public health impact of breast cancer make this an appropriate case study for investigating the real-world application and impact of the current regulatory framework for direct-to-consumer medical tests in Australia.

1.5.1 Clinical relevance and burden of disease in Australia

Registry data from 2010 indicates that breast cancer had the highest age-standardised incidence rate of all notifiable cancers in Australian women (113.2 cases per 100,000 females), accounting for approximately 28 per cent of all newly diagnosed female cancers.\(^{(64)}\) In 2012, there were 14,560 new cases of invasive breast cancer in Australia, accounting for 40 new diagnoses of breast cancer per day on average.\(^{(64)}\) While the overall incidence rate of breast cancer in Australia is high, age specific incidence rates indicate a positive association between breast cancer incidence and age (Figure 1.4). Consequently, the risk of developing breast cancer is approximately six times higher in women aged 70 years or above compared to women under the age of 50, and 69 per cent of cases are diagnosed in females aged 40 to 69 years of age.\(^{(65)}\)

Although the age-standardised incidence of breast cancer has increased from 80.7 cases per 100,000 in 1982 to 113.2 cases per 100,000 in 2010, age-standardised death rates due to breast cancer have decreased by 27 per cent over the same period, from 30.2 per 100,000 to 21.6 per 100,000.\(^{(64, 66)}\) The observed increase in breast cancer incidence over this period can be partially explained by improved detection of early-stage tumours through the national breast screening program, BreastScreen. Improvements in survival outcomes have been largely attributed to improvements in treatment due to oestrogen receptor antagonists such as Tamoxifen, as well as early detection of the disease through BreastScreen.\(^{(58, 67, 68)}\) Despite recent advances in long-term survival, breast cancer remains the second leading cause of cancer-related death, and fifth leading cause of all death in
Australian women.\textsuperscript{(66)} In 2010, breast cancer contributed to 15.3 per cent of all female cancer-related deaths (2,840 deaths), behind lung cancer (3,165 deaths).\textsuperscript{(64)}

\textbf{Figure 1.4} Age standardised incidence of breast cancer by age at diagnosis, females, 1982-2009

Source: Australian Institute of Health and Welfare (AIHW), 2009.\textsuperscript{(69)}

It is estimated that breast cancer contributed to 61,300 disability adjusted life years (DALYs) in Australian women in 2012, accounting for four per cent of the total estimated burden of disease (>1.4 million DALYs). In comparison, all cancers in females contributed to 256,900 DALYs in 2012. Breast cancer remains the sixth leading contributing factor to the overall burden of disease in Australian women.\textsuperscript{(65)} Only dementia, type 2 diabetes, ischaemic heart disease, stroke and anxiety and depression carry a higher burden of disease in Australian women.\textsuperscript{(65)} DALYs consist of years of life lost (YLL) and years lost to disability (YLD). Around two thirds of the burden of disease in breast cancer consists of lost life years due to premature mortality (YLL), whereas one third consists of healthy life lost due to disability (due to side effects of treatment, potential changes in menopause).\textsuperscript{(65)}

Breast cancer also imposes a significant financial burden on the healthcare system. In 2008-09, the total expenditure attributable to breast cancer was $236.9 million, of which $147.24 million was due to hospital admissions, $29.2 million due to out-of-hospital care, and $60.5 million due to prescription pharmaceuticals.\textsuperscript{(70)} In 2008-09, breast cancer had the 6\textsuperscript{th} highest expenditure of all notifiable cancers, behind colorectal ($427.4 million), non-melanoma skin cancer ($367.4 million), prostate ($346.6 million), non-Hodgkin lymphoma
($262.5 million) and leukaemia ($256.6 million). Healthcare expenditure attributable to breast cancer is not only attributable to the treatment of the disease, but also through screening programs aimed at detecting non-invasive, early stage breast cancer. In 2008-09, the total expenditure of the national breast cancer screening program, BreastScreen, was $174.5 million, up from $95.9 million in 2000-01.\(^{70}\)

There are several known risk factors for breast cancer, including older age, exposure to ionising radiation, late menopause, early menstruation, long-term use of hormone replacement therapy, and being nulliparous.\(^{57,71-73}\) Women with a family history of breast cancer are twice as likely to develop the disease before the age of 50 compared to women without a family history,\(^{57}\) and mutations in the BRCA1 and BRCA2 genes are responsible for up to 10 per cent of breast cancer diagnoses in Western countries.\(^{57}\) Lifestyle factors associated with a higher risk of breast cancer include low physical activity, alcohol consumption and obesity.\(^{65}\) As the majority of risk factors for breast cancers are not modifiable, the emphasis within public health research has been placed on finding secondary, rather than primary preventative methods, such as early detection through targeted screening programs.

### 1.5.2 Australia’s national breast cancer screening program

Australia implemented a national, publicly funded mammographic screening program, BreastScreen, in 1991 with an aim to detect breast cancer in its earliest stages and reduce the overall burden of the disease on the public health sector.\(^{69}\) BreastScreen invites women aged 50-69 years of age to receive a biennial mammographic X-ray to check for early signs of breast cancer. In 2010-11, a total of 1,373,731 Australian women aged 50-69 received a mammographic X-ray through the BreastScreen program, representing 55 per cent of the target population.\(^{69}\) The current clinical pathway for breast cancer imaging through the BreastScreen program, including clinical follow-up of equivocal or symptomatic cases is show in Figure 1.5.
Breast cancer is an appropriate candidate for a targeted screening program, as it meets or exceeds all of the principles of early disease detection defined by Wilson and Jungner on behalf of the World Health Organization:

1. Breast cancer carries a large public health burden, affecting one in eight women before the age of 85.\(^\text{69}\)
2. There are effective treatments for breast cancer in the form of breast surgery, chemotherapy, radiotherapy, human epidermal growth factor receptor targeted therapy, and oestrogen receptor antagonist therapy.\(^\text{76-78}\)
3. Australia has the necessary facilities available to diagnose and treat the disease.\(^\text{69, 70}\)
4. Breast cancer has recognisable asymptomatic and early symptomatic stages, identified as low-stage tumours and ductal carcinoma in-situ.
5. There are suitable tests or examinations able to detect breast cancer, including X-ray and digital mammography, magnetic resonance imaging, breast ultrasound, and biopsy.\(^{(69)}\)

6. Mammographic screening is reasonably well-accepted by the population, as evidenced by annual screening rates of 55 women per 100 in 2010-2011 in the target population.\(^{(69)}\)

7. The natural history of the disease is adequately understood, however, there remains some ambiguity in regard to which cancers would lead to death in the natural course of a woman’s life if left untreated.\(^{(79, 80)}\)

8. There is a clearly indicated target population, defined as women aged between 50-69 years of age. This population has the highest risk for developing breast cancer.\(^{(69)}\)

9. Screening for breast cancer is cost-effective. While limited in many respects, the International Agency of Research on Cancer has demonstrated that the cost-effectiveness of mammographic screening is best described in countries with a high-incidence of breast cancer, but is also affected by the mortality rate, the quality of the screening program, the health care setting and economics.\(^{(81)}\)

10. Screening for breast cancer occurs as a continuing process and not a once-off intervention. Women are invited for screening either annual or biannually depending on their associated risk.\(^{(65)}\)

Mammography, while accepted as the current best practice in breast cancer screening,\(^{(82-84)}\) has been the target of debate regarding its safety and effectiveness as a breast cancer screening tool. Conventional X-ray mammography exposes patients to ionising radiation, is not suited to women with dense breasts, overdiagnose between 10 and 30 percent of patients.\(^{(85)}\) Despite the available evidence demonstrating the effectiveness of mammographic screening in Australia and overseas, there remains continued debate around whether mammographic screening programs reduce breast cancer mortality.\(^{(79, 85)}\) Early detection initiatives have been shown to decrease the mortality burden of breast cancer and lead to increased survival in certain populations,\(^{(58-63)}\) and it has been well established that mammographic screening is able to detect tumours which are smaller and better differentiated than those detected when symptoms are present.\(^{(80, 86, 87)}\)
1.6 Emerging breast imaging devices

In 2009, the Australia and New Zealand Horizon Scanning Network (ANZHSN) identified three classes of imaging devices that were being promoted at that time for use as breast cancer screening and diagnostic tools, including digital infrared thermal imaging (DITI),\(^{(88)}\) electrical impedance scanning (EIS),\(^{(89)}\) and electronic palpation imaging (EPI), also referred to as computerised breast imaging.\(^{(90)}\) Two features distinguish these devices from conventional imaging methods such as X-ray mammography: first, these devices can be used for breast imaging without the necessary involvement of a registered healthcare practitioner, and second, their use as a screening or diagnostic service is paid for entirely out-of-pocket by consumers.\(^{(91)}\)

1.6.1 Digital infrared thermal imaging (DITI)

Clinical thermography is a method of recording the distribution of temperature on surfaces of the body. In clinical practice, thermography is used to measure changes in the temperature of skin, as it is suggested that this enables the detection of physiological abnormalities.\(^{(92)}\) There are two main types of thermography, contact thermography and DITI. Contact thermography involves either the insertion of a needle into the tissue to measure the temperature of an area with a suspected lesion, or covering the area in a heat-sensitive liquid crystal film.\(^{(93)}\) In contrast, DITI is non-invasive, and involves the use of cameras to detect infrared radiation emitted from the skin.\(^{(94)}\) The information collected by infrared cameras is converted into a visual map of the target area known as a thermogram. Both methods have been utilised for the detection of breast cancer in the past, however, DITI has evolved into the most widely accepted form of thermal breast imaging due to its suggested higher sensitivity, ease of use, and low level of invasiveness.\(^{(92)}\)

The use of thermography for the detection of breast cancer operates under the theory that changes in the perfusion of blood into tissues is related to an underlying pathology, as blood is the primary medium for heat exchange in the body.\(^{(95,96)}\) In the case of breast cancer, there are three underlying causes that can disrupt the regular perfusion of blood within the breast: cancerous cells and immune cells release nitric oxide causing vasodilation and therefore increased blood flow;\(^{(97)}\) developing tumours stimulate angiogenesis to supply the area with increased nutrients; and inflammatory cells are recruited to the site of developing tumours.\(^{(95)}\) All of these factors can contribute to increased blood perfusion at the site of a developing breast tumour, and will result in increased temperatures relative to healthy tissue. In clinical practice, the likelihood of a breast tumour being present is indicated by temperature asymmetry between breasts, a change in thermal
patterns over time, or focal areas of increased temperature.\(^{(98)}\) Examples of normal and abnormal thermograms are presented in Figure 1.6.

**Figure 1.6  Examples of thermography imaging results**

A: An abnormal thermogram showing a unilateral increase in heat in the left breast. B: A normal thermogram showing no signs of temperature asymmetry or focal hot spots. Source: Kontos et al, 2011.\(^{(98)}\)

The first iterations of thermographic technology were suggested as a method for breast cancer diagnosis in 1956 by Lawson.\(^{(99)}\) In the following decades the medical community showed a strong interest in the applications of thermography for both breast cancer screening and diagnosis, as it offered a potential alternative to X-ray mammography without the need for radiation exposure or compression of the breast. However, in a study of 16,000 asymptomatic women, Feig et al. reported the sensitivity and specificity of thermography to be 39 per cent and 82 per cent respectively; lower than both mammography and clinical breast examination (CBE).\(^{(100)}\) Following the release of the report, thermography was no longer considered a viable alternative for breast cancer screening.\(^{(100)}\) However, recent advances in the use of modern DITI hardware and techniques have generated interest in the use of thermography as a tool for breast cancer detection. It is estimated that DITI has been promoted by at least 24 companies in Australia for breast cancer imaging since 2011.\(^{(101)}\)

**1.6.2 Electrical impedance scanning (EIS)**

Electrical impedance scanning (EIS), also referred to as electrical impedance mammography, is a non-invasive, radiation-free imaging technique promoted for use as both a screening tool and an adjunctive diagnostic tool for breast cancer.\(^{(84, 102)}\) EIS functions as an imaging device under the premise that biological tissues have different levels of electrical conductivity depending on their structure.\(^{(103, 104)}\) In the case of breast cancer, pathological changes in malignant breast cancer cells lead to an increase in electrical conductivity, and hence lower electrical impedance compared to healthy cells.\(^{(104)}\) This increase in electrical
conductivity is able to be detected by an EIS imaging scan (Figure 1.7), which involves placing an electrical probe on the surface of the skin. While EIS has shown promising signs as an adjunctive diagnostic tool, it is currently limited by the inability of the electrical probe to capture high-resolution images.

**Figure 1.7 Examples of electrical impedance imaging results**

A: EIS image of healthy breast tissue. B: EIS image of breast pathology. Graph indicates normal electrical impedance levels (green) compared to lowered electrical impedance due to pathology (yellow). Source: Impedance Medical Technologies, 2008.

The theoretical basis for EIS was first established by Fricke and Morse in 1926. They found a significant difference between the electrical capacitance of malignant breast cancer cells compared to healthy tissue. Although EIS has existed since the 1920s, it has only recently been adopted commercially for breast cancer detection. The first commercial EIS device, the T-SCAN™ 2000, was approved for commercial sale in the United States by the FDA in 1999, before being listed on the ARTG in 2008. It is currently estimated that at least 10 private companies have advertised EIS scans for breast imaging in Australia since 2011.
1.6.3 **Electronic palpation imaging (EPI)**

EPI, also referred to as breast elasticity imaging and breast elastography, is currently advertised in Australia as a non-invasive, radiation-free imaging technique used for breast cancer screening in women of all ages and breast types. EPI operates under the same theoretical principle as CBE, whereby systematically applying pressure to the breast is thought to detect the presence of palpable breast cancers at an early stage of progression before they become symptomatic.\(^{110}\) There are currently three classes of devices capable of carrying out elastography scans: ultrasound elastography (USE) devices; magnetic resonance elastography devices; and a newly developed device referred to as an electronic palpation imaging (EPI) device by its manufacturer (also known as tactile breast imaging, mechanical breast imaging, and computerised breast imaging). While all three elastography devices are currently in an early development stage, EPI has been marketed directly towards women in Australia for breast imaging by at least two companies since 2011.\(^{101}\)

EPI uses a hand-held transducer, reportedly four times more sensitive than human touch,\(^{111}, 112\) to produce images of palpable masses (Figure 1.8). Besides this information, little is known about the specifics of how the device works. One EPI device currently being advertised directly to consumers in Australia is listed on the ARTG. However, the public listing states that it should not be used for clinical decision-making, and that a mammogram or ultrasound should be used to further evaluate any suspicious findings from an EPI scan.

**Figure 1.8  Examples of elastography imaging results**

A: Elastography imaging of a round or oval mass. B: Elastography image of a lobulated or spiked mass. Source: Kaufman et al, 2006,\(^{112}\)
1.6.4 The evidence base for DITI, EIS and EPI

When work on this thesis commenced, the most recent review of DITI and EIS for screening and diagnosis of breast cancer had been conducted in 2009 by the ANZHSN,\(^{(109)}\) in the form of a horizon scanning overview of new and emerging cancer technologies. This brief, non-systematic report found little evidence supporting the use of DITI or EIS for breast cancer screening or diagnosis. Based on the limited search strategy, the report presented diagnostic accuracy data from two DITI studies that reported the device to have a diagnostic sensitivity between 72 and 96.7 per cent, and specificity between 11.8 and 44.1 per cent. In contrast, EIS was reported to have a diagnostic sensitivity ranging between 26 and 38 per cent, and a diagnostic specificity of approximately 81 per cent based on the result of five primary studies.\(^{(102, 109, 113)}\) Screening accuracy results for EIS could not be presented due to limitations in the methodology of primary studies. There was no evidence identified on the use of DITI for breast cancer screening, although one included DITI study tested the use of a “screening mode” on a symptomatic population.

In addition to the ANZHSN report, one systematic review had been identified that investigated DITI, EIS and several other imaging technologies for breast cancer screening. The review was conducted in 2004 by Irwig et al.,\(^{(114)}\) and found no evidence to support either device for use in this setting. However, this review employed strict inclusion and exclusion criteria that were likely to have excluded studies with lower methodological quality, and did not evaluate their use as a diagnostic tool. The ANZHSN report also indicated that there was some, albeit limited, evidence for screening published since the 2004 review.

Beyond the systematic review, one narrative review of EIS had also been identified, which investigated the first commercial EIS scanners as adjunct diagnostic tools to complement mammography. The review, conducted by Zou and Guo, reported promising results from multiple clinical studies that assessed the diagnostic accuracy of EIS when used for this indication.\(^{(115)}\) The authors reported an increased specificity (51% up from 39%) and sensitivity (88% up from 82%) associated with the use of EIS as an adjunct diagnostic tool, however, they did not identify the primary research from which these data were obtained, and did not provide any detail on their search strategy or data analysis methods.

Based on the available evidence at the start of the research in this thesis, it was difficult to estimate the accuracy of these tests. The horizon scanning reports and narrative review evidence covered different studies for DITI and EIS, and reported different ranges of diagnostic accuracy. Compared to DITI and EIS, EPI is in a much earlier stage of development, and there have not been any systematic or narrative reviews of its evidence base to date.
1.7 Gaps in evidence base and research justification

Following the release of the 2009 ANZHSN report, several official complaints were raised against companies promoting these devices in 2010 and 2012, citing advertising material that claimed DITI, EIS and EPI were suitable alternatives to mammography for breast cancer screening and diagnosis. These complaints have since raised questions around whether the regulatory framework adequately ensures that these breast imaging devices are safe and effective prior to gaining market approval, and whether the advertising material for these products reflects the available evidence base. Australian research into DtCA has highlighted limitations in the current system of regulation for CAMs. However, the pathway onto market for CAMs is different to medical devices, requiring different levels of pre-market conformity assessment. It is possible that similar limitations witnessed in the pathway to market for CAMs are reflected in the context of devices, though this has not been explored in the literature.

When work first began on this thesis, there remained a lack of systematic review evidence investigating the safety and effectiveness of these devices for breast cancer screening and diagnosis. As such, assumptions about the evidence base for the use of DITI, EIS and EPI for these indications were drawn by non-systematic, non-peer reviewed horizon scanning reports. Despite the absence of a defined evidence base, these devices have been promoted in Australia for both breast cancer screening and diagnosis, often as a direct alternative to conventional mammography. Given the potential harms associated with screening and diagnostic tests, a formal, up-to-date systematic literature review to determine the appropriateness of DITI, EIS and EPI for breast cancer screening and diagnosis was warranted.

While there have been numerous reports surrounding the type and quality of information found on websites for different complementary medicines, prescription medicines and specific medical tests, to date there have been no reviews of the content found in online advertisements for these breast imaging devices. Since these devices do not require a referral from a medical practitioner, it is possible that a patient’s decision to use one of these devices may be influenced solely by promotional material, which may have limited educational value. As the evidence base for DITI, EIS and EPI is not well defined, it is difficult to assess the validity of advertising claims that suggest these devices are suitable for breast cancer imaging. Thus, it is argued that a review of the advertising content for DITI, EIS, and EPI alongside a review of the available evidence of the safety and effectiveness of these devices is justified.
1.8 Research aims and questions

The primary aims of this thesis are to determine whether the current regulatory framework for medical devices in Australia adequately ensures that emerging breast cancer imaging devices have sufficient evidence to support their safety and effectiveness, and whether the advertising material for these devices is supported by evidence. In light of any defined limitations in the current regulations, this project will further aim to use the evidence collected to explore ways in which medical device regulation in Australia may be improved. In order to achieve these aims and address the highlighted research gaps, this thesis will utilise a mixed methods case study methodology to explore the following research questions.\(^{(123,124)}\)

To address the current lack of systematic reviews of the safety and effectiveness for these devices, which are prominently marketed towards consumers:

- **Research question 1**: What are the safety, effectiveness and diagnostic accuracy of digital infrared thermal imaging (DITI), electrical impedance scanning (EIS) and electronic palpation imaging (EPI) for breast cancer screening and diagnosis?

To describe the types of claims made in product-oriented websites for these devices, and to illustrate the relationship between claims made and the evidence supporting their diagnostic accuracy and safety:

- **Research question 2**: What is the nature and frequency of information presented on direct-to-consumer websites for DITI, EIS and EPI?
- **Research question 3**: To what extent are claims of safety, effectiveness and diagnostic accuracy made on direct-to-consumer websites for DITI, EIS and EPI supported by evidence?

To explore options to reform the pre-market arrangements for medical devices and their related advertising material:

- **Research question 4**: What are the perspectives and recommendations of key stakeholders in breast cancer research, patient advocacy and screening, on the proposed changes to the regulatory framework for advertising and pre-market approval of breast cancer screening and diagnostic devices in Australia?
- **Research question 5**: Which characteristics of medical devices and medical device advertising do stakeholders in breast cancer research, patient advocacy and screening, consider should be assessed by an independent regulator?
1.9 Thesis outline

The proposed research questions are addressed in the following five chapters, three of which have been either accepted or published in peer-reviewed journals. In order to make the following published chapters easier to read, the material from the peer-reviewed journal articles has been formatted in a style consistent with the body of the thesis. This allows chapter headings, tables and figures to be more easily traced in the table of contents, and allows the references to be compiled at the end of the thesis instead of after each chapter. Cover pages from the published chapters are available in Appendix A.

Chapter 2 provides a commentary outlining the benefits and limitations of the current regulatory framework for the pre-market assessment of medical devices, and the regulation of therapeutic goods advertising in Australia. This chapter was published in Internal Medical Journal, and represents the first time the regulatory framework for medical devices has been critically discussed in published literature.\(^{125}\)

Chapter 3 presents the results from a systematic review investigating the available evidence for safety, effectiveness and efficacy of DITI, EIS and EPI for breast cancer screening and diagnosis.\(^{126}\) This review, published in Breast Cancer Research and Treatment, presents the first comprehensive review of the diagnostic accuracy of these devices for use as both diagnostic and screening tools.

Chapter 4 presents the results from a content analysis, aimed at describing the advertising claims being made in online website advertisements for these devices. The advertising claims presented in this analysis are compared with the evidence collected in Chapter 3, in order to determine the degree to which claims being made in the advertising material for these devices are supported by evidence. This chapter was accepted for publication in the Medical Journal of Australia in October 2013.

Chapter 5 synthesises the results from the policy discussion, systematic review, and content analysis, and uses this information to engage with stakeholders in breast cancer around possible methods to reform pre-market medical device and therapeutic goods advertising regulation in Australia. The results from this chapter were incorporated in a submission to the governing bodies, as part of a broad review of regulatory processes in Australia (See Appendices E and F).

Chapter 6 provides a summary and critique of the previous chapters, and discusses the policy implications of the research findings of this thesis. Recommendations for future research and reform around the regulation of medical devices and DtCA in Australia are discussed.
CHAPTER 2

Policy issues with DtCA of breast imaging devices in Australia

2.1 Preface to Chapter 2

In 2010, several emerging breast imaging devices were removed from the Australian Register of Therapeutic Goods (ARTG), following a series of complaints about the advertising material for these devices.\textsuperscript{[116-118, 127]} The removal of these devices from the ARTG raised questions around the ability of pre-market regulations to ensure that registered devices are adequately supported by evidence. In the previous chapter, the regulatory frameworks for medical devices and medical device advertising were broadly described. The following chapter describes the Australian regulatory frameworks for the pre-market assessment of medical devices and the regulation of therapeutic goods advertising in greater detail, within the specific context of emerging breast imaging devices. The roles of multiple regulatory bodies and legislation are also discussed, and limitations that allow devices onto the market without a thorough review of their evidence are described. Some information found in Chapter 1 is repeated, in order to provide the context required for a peer-reviewed article on this topic.
2.2 Statement of authorship


Thomas Vreugdenburg (Candidate)
Conceptualised the structure and content of the manuscript, wrote the manuscript and acted as corresponding author.

Signed: . . . . . . . . . . . . . . . . . . . . . . Date: . . . . . . .

Cameron Willis
My contribution to this paper involved assisting with conceptualisation, writing and evaluation of the manuscript. I give consent for Thomas Vreugdenburg to present this paper for examination towards the Doctor of Philosophy

 Signed: . . . . . . . . . . . . . . . . . . . . . . Date: . . . . . . .

Linda Mundy
My contribution to this paper involved assisting with the conceptualisation and evaluation of the manuscript. I give consent for Thomas Vreugdenburg to present this paper for examination towards the Doctor of Philosophy

Signed: . . . . . . . . . . . . . . . . . . . . . . Date: . . . . . . .

Janet Hiller
My contribution to this paper involved assisting with the conceptualisation and evaluation of the manuscript. I give consent for Thomas Vreugdenburg to present this paper for examination towards the Doctor of Philosophy

Signed: . . . . . . . . . . . . . . . . . . . . . . Date: . . . . . . .
2.3 Abstract

While research investigating direct-to-consumer advertising (DtCA) of therapeutic goods in Australia has historically focused on prescription medicines, recent action taken by regulators against companies promoting medical devices has placed the industry into the spotlight. Despite the need to effectively regulate DtCA of medical devices due to its potential harms, inadequacies in the current regulatory system have been noted. Under the present system, devices with a questionable evidence base may enter the Australian marketplace without an evaluation of their effectiveness, and regulators are reliant on industry self-regulation and consumer complaints to draw attention to cases of advertising misconduct. Although some successes in the present system have been observed, we argue that the outlined inadequacies continue to enable the promotion of medical devices to consumers without thorough or sufficient examination of evidence.

2.4 Introduction

Research on DtCA of therapeutic goods in Australia and overseas has historically focused on prescription pharmaceuticals.\(^\text{27, 29}\) In contrast, DtCA in the rapidly expanding medical devices industry has received relatively little attention, with the exception of the burgeoning area of genetic testing. However, a recent succession of complaints raised against several companies marketing medical devices in Australia has recently turned the spotlight on to DtCA of these products, as well as the wider medical devices industry.\(^\text{128, 129}\)

The merits of DtCA for the promotion of therapeutic goods have been extensively debated. Proponents argue that DtCA educates members of the public about health conditions and available treatment options, and empowers individuals to engage in informed discussions with healthcare providers.\(^\text{130}\) Opponents suggest, however, that the ability of DtCA to function as an educational and empowering tool is often adversely affected by poor quality, biased, and unbalanced information presented in advertisements.\(^\text{25, 45}\) For medical screening and diagnostic devices specifically, DtCA may carry significant risks relating to both safety, through misdiagnosis of disease presence or absence, and also confidentiality, as test results may impact the future acquisition of employment, healthcare or life insurance.\(^\text{53, 91}\) DtCA of screening and diagnostic devices also carries financial implications for both the patient and the wider healthcare system, as while a test using a device may be funded out-of-pocket, the results of the test can lead to further investigation in the public system.
Owing to the potential risks associated with DtCA of diagnostic and screening devices, there is a need for an effective regulatory framework governing this practice. Recent action taken by the Therapeutic Goods Administration (TGA), the Complaints Resolution Panel (CRP) and the Australian Competition and Consumer Commission (ACCC) against several diagnostic/screening device suppliers for presenting false or misleading advertising claims has highlighted some strengths of the current regulatory system. However, a significant number of pre-market and post-market regulatory deficiencies have been noted. This paper explores the major difficulties facing the current regulatory system for medical imaging devices and their related advertising in Australia, and presents a case study of breast cancer imaging devices to demonstrate how these difficulties manifest in practice.

2.5 Importance of breast cancer screening and diagnostic devices

Increases in early detection due to mammographic screening, combined with improved treatment options, have contributed to a reduction in the Australian age-standardised mortality rate of breast cancer from 66 deaths per 100,000 women in 1995, to 47 deaths per 100,000 women in 2007. Although mammography has a well-established evidence base to support its use in asymptomatic populations, it remains an imperfect gold standard in breast cancer screening and has been the target of much debate and controversy regarding the magnitude of its effectiveness relative to its potential risks.

The risks and limitations associated with X-ray mammography have motivated the development of new adjunct screening and diagnostic tools. In recent times, numerous new products advertised for these purposes have entered the Australian market, including electrical impedance tomography, digital infrared thermography, and electronic palpation imaging. All of these products are currently available at various clinics across the country, however, none require a referral from a doctor. The potential for devices of this nature to do harm is significant, as product marketing directly targets women of all ages, not only those deemed to have an increased risk of breast cancer and therefore eligible for mammography screening.
The major concern with these devices is the limited primary research investigating their safety and accuracy for screening and/or diagnosis of breast cancer.\textsuperscript{(93, 114)} Despite this, these products are listed on the ARTG; a requirement for importation, supply, manufacture and exportation of therapeutic goods in Australia. Following a series of media attention and anonymous complaints raised about these devices (Box 2), this case study highlights a number of peculiarities of the current regulatory environment relating to both the pre-market approval and the post-market regulation of DtCA for medical screening and diagnostic devices.

**Box 2  Events surrounding breast cancer screening and diagnostic devices**

In 2008-2009, advertisements for emerging thermography, electrical impedance, and palpation imaging devices began to draw the attention of various interest groups, as they promoted the use of these devices for breast cancer screening and/or diagnosis with stated claims of safety and effectiveness.

Concerns were raised over advertisements claiming “wonderful accuracy”\textsuperscript{(118)} that “can show cellular changes years ahead of any other screening method”\textsuperscript{(116)}, and which compared these new devices with mammography either directly - “a safe alternative to mammograms”\textsuperscript{(116)} - or indirectly - “no squeezing”, “no harmful radiation”\textsuperscript{(117)}

In response to the advertising claims, The Cancer Council of Western Australia released a paper in collaboration with BreastScreen WA, the University of WA and the Department of Health in May 2010, cautioning women over the lack of evidence supporting the advertising claims made for these new technologies.\textsuperscript{(138)}

Following a flurry of media attention, a series of complaints about advertisements for the devices were considered by Therapeutic Goods Advertising Complaints Resolution Panel (CRP) at the end of 2010.\textsuperscript{(116-118)} The CRP upheld each of the complaints. The CRP’s determinations, pressure from health groups, and the growing concern over the devices perpetuated in the media motivated investigations by the Therapeutic Goods Administration (TGA)\textsuperscript{(127)} and Australian Competition and Consumer Commission (ACCC)\textsuperscript{(129)} into the advertising claims.

As of September 2011, neither the TGA nor ACCC have arrived at official conclusions on the matter, however, sponsors have voluntarily removed several devices from the Australian Register of Therapeutic Goods following TGA requests to produce evidence supporting the efficacy of the device.\textsuperscript{(127)}
2.6 Pre-market regulation of medical devices in Australia

For regulatory purposes, the TGA classifies medical devices into two subcategories: medical devices (e.g., diagnostic imaging devices) and in-vitro medical devices (e.g., genetic testing kits). In this discussion, the focus is on the former. A medical device is defined by the *Therapeutic Goods Act (1989)* (Cth) to be any instrument, apparatus, machine, software or other similar device, which is used for supporting or sustaining life, or for the diagnosis, prevention, monitoring or investigation of a disease or physiological process, such as computed radiography machines commonly employed in investigations of breast cancer.

While Australia’s system of pre-market regulation is considered to be relatively effective, several issues have recently been identified that challenge the rigour of assessment placed on devices before they are approved for use:

First, while the broad definition of a medical device encompasses the physical device itself, it does not account for the application of the device. For example, the definition may refer to a specific diagnostic device, such as a computed radiography machine; however, it does not include the diagnostic test carried out using the device (e.g. a breast scan). Therefore, unless an audit is specifically commissioned, any test, service or other application of a medical device supplied on a user-pays basis does not require listing on the ARTG, and thus typically evades evaluation of its efficacy and effectiveness before being approved for market in Australia. However, in order for a diagnostic test or other service to become publicly funded by Medicare it must pass a rigorous health technology assessment review, ensuring that ineffective or dangerous tests are not publicly funded.\(^{(139)}\)

Second, all medical devices must satisfy the ‘Essential Principles’ listed in the *Therapeutic Goods Act (1989)* (Cth), which outlines the minimum level of evidence supporting the safety and performance of the device necessary for market approval. However, only manufacturers of certain ‘high risk’ therapeutic goods, such as implantable devices, are required to present this information for market approval. For therapeutic goods classified as ‘low risk’, including new breast cancer imaging devices and a large number of complementary medicines, sponsors are able to self-certify their compliance with the Essential Principles.\(^{(140)}\) To this end, it is only required that sponsors have the required documentation readily available, should a post-market audit of the device be commissioned; a process which the TGA carries out at random to a limited extent, or in response to consumer complaints about a specific device. A recent post-market review conducted by the TGA has shown the reliance on self-certification for ‘low risk’ therapeutic goods is ineffectual in the complementary medicines industry,\(^{(141)}\) and while a review of the same scale has not
been completed for the medical devices industry, several breaches in regulations have been found in targeted reviews of breast cancer imaging devices. This lack of pre-market scrutiny allows devices with an uncertain or absent evidence base onto the Australian market without any form of quality appraisal, and as only limited audits are conducted, the size of this problem is currently unknown.

Third, while the TGA conducts limited post-market reviews of medical devices, there appears to be a lack of regulatory capacity to enforce sanctions on companies found to breach relevant regulations. Examples of this have been observed recently, as breast cancer imaging devices reportedly removed from the ARTG in January 2011 have continued to be promoted to consumers by various clinics around the country. While these instances may represent isolated cases, the lack of transparency by the TGA in providing information about devices that have been removed from the register make the size of this problem impossible to determine.

Finally, the manner in which risk is classified by the Therapeutic Goods Act (1989) does not adequately account for the types of risks associated with diagnostic and/or screening devices. In the current system, perceived safety risks are indicated only by the potential for physical harm to occur as a result of using a device. However, for diagnostic and screening devices safety risks not only relate to physical harm, but are also linked to the accuracy of the tests for which the devices are applied. For example, false positive results may lead to further, potentially more invasive testing (often in the publicly funded system), while false negative results may lead to treatable disease being ignored. This presents a significant issue, as the classification of risk dictates the level of pre-market evaluation applied to a medical device.

These deficiencies have created an environment in which certain medical devices, or their application, may be marketed in Australia without a rigorous evaluation of their safety and effectiveness. Although these deficiencies in the current pathway to market for medical devices present significant challenges for a range of stakeholders, they tell only half the story in a wider regulatory system that also encompasses DtCA, a practice for which regulation is also lacking.
2.7 Post-market regulation of DtCA in Australia

In Australia, the responsibility of regulating DtCA of all classes of medical devices is shared between the TGA, ACCC, and industry. The TGA is tasked with regulating the quality of information presented in DtCA of medical devices through administration of the *Therapeutic Goods Act* (1989) (Cth) and the *Therapeutic Goods Advertising Code 2007* (Cth), while the ACCC administers the *Competition and Consumer Act (2010)* (Cth), formerly known as the *Trade Practices Act* (1974) (Cth). However, the extent to which the present regulatory framework adequately patrols the quality and content of advertisements has been questioned.\(^{(131)}\)

There are several characteristics of the current system that raise questions about the quality of content found in advertisements for medical devices. Arguably of most importance, there is no independent body funded or resourced to assess advertisements prior to dissemination, nor to carry out active monitoring of existing advertising content. In lieu of an active monitoring system, there are two systems in place to ensure that advertisements for medical devices meet some level of quality appraisal. First, consumer complaints are relied on to draw the attention of regulators to advertisements that breach the Therapeutic Goods Advertising Code and relevant legislation, and second, industry codes of conduct are used to provide a foundation for the self-regulation of advertisements aimed at both consumers and health practitioners.\(^{(131)}\) In this regard, regulators such as the TGA and ACCC are responsible for regulating the content of advertisements only after their attention has been drawn to evidence of advertising misconduct by self-regulatory bodies or consumer complaints.

Complaints about advertisements for medical devices are primarily handled by the CRP; a collaboration of representatives from industry, consumer groups, advertising agencies, the government and healthcare professionals.\(^{(144)}\) If the CRP finds a complaint to be justified, it can request the advertisement be either amended, or replaced with a notice of retraction. In 2010, six complaints regarding companies advertising breast cancer imaging devices directly to consumers were registered on the CRP website, all of which were found to be justified.\(^{(116-118)}\) In situations where companies have refused to cooperate with the CRP’s request for an advertisement to be removed or amended, the case is typically forwarded to the TGA or ACCC for further action.

Although the highlighted cases indicate some successes of the current system, concerns have been raised in a recent government consultation around the sustainability of the CRP, as well as its ability to achieve compliance with its requests across the wider medical devices industry.\(^{(131)}\) Among the major concerns raised, the CRP is under-resourced
to deal with an ever-increasing workload associated with evaluating the quality of evidence supporting claims made in advertisements; a process that is made more cumbersome due to the lack of assessment placed on ‘low risk’ medical devices during the pre-market approval process. Furthermore, the CRP has no authority to enforce its recommendations or impose more stringent civil penalties, and must rely on the TGA and/or ACCC to enforce its sanctions if companies do not comply voluntarily.\(^{131}\) Forwarding complaints to another regulator in this manner slows the complaints process, and concerns have been raised about the transparency of the follow-up protocols in these instances.\(^{145}\)

The current reliance on industry self-regulation for the promotion of therapeutic goods in Australia has been placed under scrutiny.\(^{131}\) Self-regulation in the Australian pharmaceutical and complementary medicine industries has proven to be inadequate, as companies continue to promote products with false or misleading claims, and in a manner that often sidesteps conventional methods of regulation.\(^{29, 31, 141}\) Similar patterns have also begun to emerge in the medical devices industry, where, despite suggestions that the evidence base for emerging breast cancer screening and diagnostic devices is limited, these products continue to be advertised with stated claims of safety and effectiveness (Box 1). While the eventual forced retraction of such advertisements represents the success of the current regulatory system, it also offers further evidence that industry self-regulation is not an adequate replacement for independent review of advertisements, and that advertisements need to be either assessed prior to release, or subsequently monitored for accuracy of their content.

In addition to the issues associated with industry self-regulation, evolving forms of online media are presenting challenges affecting the capacity of regulators to supervise medical device advertising. Online marketing through Web 2.0 initiatives such as social media pages (eg. Facebook, Twitter), sponsored websites, YouTube channels, blogs and Really Simple Syndication (RSS) feeds present regulators with the challenge of controlling international material in a local environment.\(^{146}\) That is not to say that companies who advertise on these mediums cannot be held accountable for their content. The ACCC, TGA and CRP have the power to act against companies who present false or misleading content in online advertisements, a power that they have been utilising in recent times.\(^{128, 147, 148}\) Of particular note, a company promoting allergy treatments was recently fined for not removing misleading testimonials from its Facebook page, even though they were published by a third party.\(^{144}\) While these examples illustrate some successes of regulation, the role of industry self-regulation and consumer complaints to draw attention to such cases of misconduct remains a major weakness in the current regulatory system.
2.8 Conclusion and implications

Currently, the regulatory environment for pre-market approval and post-market DtCA of medical devices is inadequately patrolled by the TGA and ACCC. While the issues raised in this article have been framed in the context of screening and diagnostic devices, they are also relevant to the wider medical devices industry. These inadequacies have resulted from peculiarities of existing legislation relating to regulation of devices and DtCA, such as: the misclassification and lack of pre-market scrutiny of perceived ‘low risk’ devices, the lack of regulation for the application of a device, and the reliance on industry self-regulation for monitoring of advertising material. The ability of the TGA and ACCC to carry out active monitoring is largely affected by a lack of funding and resources, addressing a wider problem beyond the legislative framework in which they operate.

The situation is becoming increasingly complex with the emergence of new advertising methods on the internet, including social media pages such as Facebook and Twitter. While the ACCC has started to assert some authority in this area, its continued reliance on consumer complaints to draw attention to cases of misconduct remains a significant barrier to effective, independent regulatory procedures.

In recognition of these issues, the TGA opened a public consultation process in October 2010 to discuss strategies to improve the current arrangements for the regulation of therapeutic goods advertising in Australia. Among other concerns raised, the submissions have highlighted the substantial dependence of the current regulatory framework for advertising on industry self-regulation and complaints as being ineffective and unethical. It has also become clear in these discussions that the current model of advertising regulation involving multiple bodies, administering multiple regulations, with varying levels of power to enforce sanctions, is inefficient and needs to be streamlined.

Limitations of the regulatory environment for both the pre-market approval and post-market advertising allow medical devices with limited supporting evidence to make it to onto the Australian market, and be advertised directly to consumers without an assessment of the content found in advertisements. While these limitations pose genuine concerns for public safety, the number of devices breaching regulations is currently unknown because of the lack of comprehensive post-market evaluation of advertising content. A better understanding of the size of this problem is needed in order to determine its potential impact on patient health and finance, and to guide efforts for reform in this area.
CHAPTER 3

Evaluating the evidence base: a systematic review of emerging breast imaging devices

3.1 Preface to Chapter 3

In the previous chapters, the limitations of the current pathway to market for medical devices were described. It was demonstrated that a non-invasive medical device intended to diagnose or screen for breast cancer can be included on the Australian Register of Therapeutic Goods (ARTG) in the Class IIa risk category. As a result, the current pre-market regulations do not require sponsors of non-invasive breast imaging devices to submit evidence of efficacy or effectiveness prior to gaining inclusion on the ARTG, and therefore market approval.

As discussed, digital infrared thermal imaging (DITI), electrical impedance scanning (EIS), and electronic palpation imaging (EPI) have been marketed directly towards consumers in Australia. These devices have been promoted as suitable alternatives to mammography for breast cancer screening and diagnosis, although they have not been assessed for these indications by the TGA. The aim of this chapter, therefore, is to determine the evidence of the safety, effectiveness and diagnostic accuracy of DITI, EIS and EPI devices. This chapter also addresses the absence of systematic reviews of the evidence for these devices, which are prominently marketed directly towards consumers. In doing so, this chapter will address the first research question of the thesis:

**Research question 1:** What are the safety, effectiveness and diagnostic accuracy of DITI, EIS and EPI for breast cancer screening and diagnosis?

Supplementary material to support the results of Chapter 3, including online-only eTables and eFigures, are available in Appendix B. While not specifically relevant to the current case study, ultrasound elastography was also included in the review in order to more broadly investigate the elastography class of devices. However, only the EPI device in this device class is marketed directly towards consumers in Australia.
3.2 Statement of authorship


**Thomas Vreugdenburg (Candidate)**

Developed the systematic review protocol and data extraction form, conducted the literature search, screened studies for inclusion by title, abstract and full text, extracted data, synthesised and analysed the extracted data with assistance from a statistician (See acknowledgement), wrote the manuscript and acted as corresponding author.

Signed: . . . . . . . . . . . . . . . . . . . . . . . Date: . . . . . . . .

**Cameron Willis**

My contribution to this paper involved assisting with the design of the study protocol, study selection, data extraction, and manuscript evaluation. I give consent for Thomas Vreugdenburg to present this paper for examination towards the Doctor of Philosophy

Signed: . . . . . . . . . . . . . . . . . . . . . . . Date: . . . . . . . .

**Linda Mundy**

My contribution to this paper involved assisting with the design of the study protocol, study selection, data extraction, and manuscript evaluation. I give consent for Thomas Vreugdenburg to present this paper for examination towards the Doctor of Philosophy

Signed: . . . . . . . . . . . . . . . . . . . . . . . Date: . . . . . . . .

**Janet Hiller**

My contribution to this paper involved assisting with the design of the study protocol, study selection, and manuscript evaluation. I give consent for Thomas Vreugdenburg to present this paper for examination towards the Doctor of Philosophy

Signed: . . . . . . . . . . . . . . . . . . . . . . . Date: . . . . . . . .
3.3 Abstract

The objective of this study aimed to systematically identify and evaluate all the available evidence of safety, effectiveness and diagnostic accuracy for three emerging classes of technology promoted for breast cancer screening and diagnosis: digital infrared thermal imaging (DITI), electrical impedance scanning (EIS) and elastography. A systematic search of seven biomedical databases (EMBASE, PubMed, Web of Science, CRD, CINAHL, Cochrane Library, Current Contents Connect) was conducted through March 2011, along with a manual search of reference lists from relevant studies. The principal outcome measures were safety, effectiveness, and diagnostic accuracy. Data were extracted using a standardised form, and validated for accuracy by the secondary authors. Study quality was appraised using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool, while heterogeneity was assessed using forest plots, Cooks’ distance and standardised residual scatter plots, and $I^2$ statistics. From 6,808 search results, 267 full text articles were assessed, of which 60 satisfied the inclusion criteria. No effectiveness studies were identified. Only one EIS screening accuracy study was identified, while all other studies involved symptomatic populations. Significant heterogeneity was present among all device classes, limiting the potential for meta-analyses. Sensitivity and specificity varied greatly for DITI (Sens 0.25-0.97, Spec 0.12-0.85), EIS (Sens 0.26-0.98, Spec 0.08-0.81), and ultrasound elastography (Sens 0.35-1.00, Spec 0.21-0.99). It is concluded that there is currently insufficient evidence to recommend the use of these technologies for breast cancer screening. Moreover, the high level of heterogeneity among studies of symptomatic women limits inferences that may be drawn regarding their use as diagnostic tools. Future research employing standardised imaging, research and reporting methods is required.
3.4 Introduction

In light of the continued controversy surrounding established breast imaging modalities such as mammography, a number of new and emerging technologies are being developed for breast cancer screening and diagnosis internationally. Three of these respective technologies include DITI, EIS and elastography. While these devices all use non-invasive imaging methods, which neither emit ionising radiation, nor compress the breast, they do operate under differing physiological principles.

DITI aims to detect localised skin temperature increases, which are thought to occur as a result of increased vascularisation, vasodilation and recruitment of inflammatory cells to the site of a developing tumour. Localised differences in skin temperature are captured by infrared cameras, which produce a heat map of the breast called a thermogram. Early iterations of thermal imaging technology for breast cancer detection had poor sensitivity (39%), however the recent development of high-resolution infrared cameras has generated new interest in the use of DITI as a tool for breast cancer detection.

In contrast, EIS operates under the principle that malignant breast cancer cells have increased electrical conductivity, and therefore lower electrical impedance compared to healthy cells. Currently there are three methods for interpreting EIS images employed in practice: the presence of a bright white spot indicating a region of lower impedance, the use of an algorithm which grades lesions on a level of suspicion (LOS) index from one (no finding) to five (high suspicion of malignancy) and the use of a modified version of the previous algorithm which classifies tumours as either malignant (red indicator) or benign (green indicator).

Elastography is a broad class incorporating multiple techniques or technological approaches. Two subclasses of elastography - ultrasound elastography (USE) and electronic palpation imaging (EPI) - are considered in this review. EPI is a new technology that generates pressure maps of breast tissue, identifying tumours as more rigid structures than healthy tissue. In contrast, USE has a longer history of development, and can be interpreted as a measure of comparative strain between healthy and cancerous tissue, a five-point elasticity score index, or as an automatic classification of benign or malignant tumours using an artificial neural network.

The aim of this review was to systematically collect and evaluate the evidence of safety, effectiveness and diagnostic accuracy for DITI, EIS, USE and EPI devices used for breast cancer screening and diagnosis.
3.5 Methods

3.5.1 Search strategy

A comprehensive research protocol was developed by the principal author, reviewed by all co-authors, and then approved by an external reviewer prior to commencement. In total, seven biomedical and specialist electronic databases (EMBASE, PubMed, Web of Science, CRD, CINAHL, Cochrane Library, Current Contents Connect) were systematically searched for peer-reviewed studies through March 2011 (eTable 1 in Appendix B), along with a manual search of reference lists from included studies. Search filters and limits were not employed during database searching.\textsuperscript{158}

3.5.2 Study selection

Search results were initially screened by title and abstract by the principal author, using selection criteria that were determined \textit{a priori}. Inclusion of full-text articles was decided by consensus with secondary authors (LM, CDW).

Studies were eligible for inclusion if they investigated the use of a relevant index test for the detection of breast lesions in human participants (eTable 2 in Appendix B). The principal outcomes of interest included measures of diagnostic and screening effectiveness (a reduction in breast cancer mortality attributable to imaging), safety and diagnostic accuracy. Safety in this context was defined as the risk of physical harm from the device, as well as the risk of false positive and false negative test results. Diagnostic accuracy studies were included if they compared the accuracy measures of a relevant index test with a valid reference test, such as biopsy with histopathological confirmation. Foreign language studies were excluded by title and abstract if they did not offer a higher level of evidence than included English language studies, as scored by the National Health and Medical Research Council (NHMRC).\textsuperscript{8} Due to advances in digital thermal imaging, thermography studies published before 1980 were excluded.

3.5.3 Data extraction and quality appraisal

Data from all included studies were extracted by the principal author using a standardised extraction form. Extracted forms were reviewed by co-authors and a research assistant to ensure accuracy (CDW, LM, DR), with discrepancies settled by consensus. Data were extracted for author affiliations and funding, sample characteristics, study design, index and reference test characteristics, length of follow-up, severity of disease, diagnostic and screening effectiveness, diagnostic accuracy, safety, and changes to patient management.
Diagnostic accuracy data were extracted into 2x2 tables of test performance indicating true positive, false positive, false negative and true negative results.

Quality appraisal was conducted by the principal author using a standardised scoring sheet and validated by co-authors. Diagnostic accuracy studies were appraised using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool developed by Whiting et al.,\(^{(159)}\) while studies investigating screening and/or diagnostic effectiveness were appraised using the Downs and Black quality appraisal checklist for health care interventions.\(^{(160)}\) The level of bias introduced by study design was also scored according to the NHMRC levels of evidence (eTable 3 in Appendix B).\(^{(18)}\)

### 3.5.4 Data synthesis

Where authors reported accuracy measures without providing 2x2 data, a 2x2 table was populated for each study by multiplying the reported estimates of sensitivity against the number of disease confirmed participants, and multiplying the reported estimates for specificity against the confirmed benign or disease-free participants. The calculated estimates of diagnostic accuracy varied by no more than ± one per cent compared to the reported values, likely due to rounding.

Heterogeneity was assessed visually by examining forest plots of sensitivity and specificity, Cook’s distance scatter plots, and standardised residual scatter plots, and quantitatively using Cochran’s Q test and \(I^2\) statistics.\(^{(161)}\) Using the \(I^2\) statistic, 25 per cent was considered low heterogeneity, 50 per cent moderate heterogeneity and >75 per cent substantial heterogeneity.\(^{(162)}\) Subgroup analyses, predetermined during data extraction, were conducted to investigate sources of heterogeneity; however these were limited due to the availability of data. The presence of potential publication bias was assessed using Deeks’ funnel plot asymmetry test for meta-analyses of diagnostic accuracy studies.\(^{(163)}\) All analyses were conducted using Stata 12.0 (StataCorp, USA).
3.6 Results

3.6.1 Literature search results

The search identified 6,808 studies, of which 267 were reviewed by full-text, and 60 were selected for inclusion in the review. Justification for excluding articles by title-and-abstract and full-text is outlined in Figure 3.1. Further detail relating to individual study exclusion is available from the corresponding author upon request. In total, eight DITI studies, 11 EIS studies, 39 USE studies, and two EPI studies were included. Twenty two studies were carried out in Europe, 12 in the United States of America (USA), 22 in Asia, two in South America, and two in the Middle East. No foreign language studies identified by title and abstract presented higher levels of evidence than the included English language studies.

Figure 3.1 PRISMA flow diagram of study inclusion

![PRISMA Flow Diagram]

Studies identified through database searching:
\[ N = 6,726 \]

Studies identified through other sources:
\[ N = 82 \]

Duplicates removed:
\[ N = 1,367 \]

Records excluded with reasons:
- 1980 or earlier: 1,841
- Foreign language: 103
- Population: 39
- Intervention: 2,426
- Outcomes: 41
- Index test: 499
- Publication type: 225

Full-text articles assessed for eligibility:
\[ N = 267 \]

Full-text articles excluded, with reasons:
- Population: 11
- Outcome measures: 73
- Index test: 51
- Intervention: 4
- Publication type: 55
- Article series: 11
- No full text access: 1
- No reference standard: 1

Studies included in final review:
\[ N = 60 \]
Extracted data relating to study characteristics are presented in Table 3.1. From the 11 EIS studies, four investigated the application of the five point LOS index\(^{(154, 164-166)}\) six investigated the ‘bright white spot’ technique\(^{(153, 167-171)}\) and one implemented a modified detection algorithm\(^{(113)}\). DITI methods varied greatly, as only two of eight studies used the same device and method of interpreting the thermograms\(^{(172, 173)}\). For USE, 23 studies implemented elasticity scores, one used strain ratios, six reported both elasticity and strain ratios, four used a neural network, and six implemented unique methods of interpretation. The results of included studies are presented in eTable 4 in Appendix B.

No identified studies reported measures of diagnostic or screening effectiveness for DITI, EIS, EPI or USE. All studies included in this review are thus diagnostic accuracy studies (Table 3.1). Only one EIS study investigated the use of an index test for the detection of breast cancer in an asymptomatic population, however, the study did not utilise a valid reference test to confirm the disease status of study participants in the specificity cohort.\(^{(113)}\) All other included studies were conducted on symptomatic populations, typically involving women scheduled for breast biopsy for the investigation of breast symptoms. Hence, most studies are relevant to a discussion of diagnosis rather than screening.

One DITI study and one USE study utilised a diagnostic case-control study design, in which cases were enrolled with a confirmed diagnosis of breast cancer, and controls were enrolled as either healthy individuals, or individuals with a confirmed benign breast mass (e.g. tumour, cyst etc).\(^{(174, 175)}\) All other included studies adopted a diagnostic cohort study design, whereby participants were enrolled under the suspicion of disease without a confirmed diagnosis, with disease status confirmed during the study with a valid reference standard.

### 3.6.2 Risk of bias within studies

Adherence to the QUADAS quality appraisal criteria by included studies was variable (eTable 6 in Appendix B). The majority of studies (85%-100%) scored highly on their explanation of withdrawals, description of the index test and reference test, independence of the index test from the reference test, and consistent application of the reference test to all participants. However, spectrum bias featured in a large percentage of studies (41.7%) due to inadequate description of the sample, selective inclusion of participants with advanced disease severity, and selective inclusion of a narrow age range of participants. Selection bias was present in 63.3 per cent of studies due to inadequate or incomplete reporting of inclusion criteria. Similarly, blinding of the index test and reference test was only reported in 41.7 per cent and 10 per cent of studies respectively. The level of bias inherent in the study design is presented as levels of evidence in Table 3.1. The majority of DITI (88%) and EIS (82%)
studies were ranked level III-2 diagnostic, while USE was distributed between level II diagnostic (33%) and level III-2 diagnostic (66%).

3.6.3 Publication bias

Deeks’ funnel plot asymmetry test produced no evidence of significant asymmetry, and thus no evidence of publication bias for DITI (p = 0.77), EIS (p = 0.61), or USE (p = 0.91). As only two studies were identified for EPI, there were insufficient data to determine the presence of publication bias.

3.6.4 Investigation of heterogeneity

Forest plots of sensitivity and specificity indicated a high level of heterogeneity among studies for DITI, EIS and USE (Figure 3.2, Figure 3.3, Figure 3.4, eFigure 2, eFigure 3, eFigure 4 in Appendix B). Further investigation of heterogeneity with Cochrane’s Q test and $I^2$ statistics quantified a significant level of heterogeneity in estimates of sensitivity and specificity, and likelihood ratios (eTable 5 in Appendix B). Removal of high-impact studies identified on Cooks’ distance and standardised residual scatter plots had no effect on reducing the amount of heterogeneity in any subgroups.

Subgroup analyses of EIS studies revealed significant heterogeneity among studies that were both blinded and non-blinded, those with a mean patient/participant age of 50-69 and those which used the ‘bright white spot’ technique. While there did not appear to be any statistically significant heterogeneity between studies which utilised the five point LOS technique ($\hat{I} = 0, Q = 0.79, p = 0.38$), the wide confidence interval for the $I^2$ statistic (0-100) and low statistical power of Cochrane’s Q test in instances of small sample sizes (e.g. < 4 studies), limit the strength of these findings.\(^{(176)}\) Subgroup analyses for DITI were limited due to the availability of data, however, significant heterogeneity was observed among studies with a prospective study design, and those that did not blind the index test to the results of the reference standard. Significant heterogeneity was also present among all USE subgroups, with the exception of studies that investigated strain ratio ($\hat{I} = 0, Q = 0.44, p = 0.401$). However, variation in this group cannot be ruled out due to the small number of included studies and wide confidence intervals.
### Table 3.1 Characteristics of studies included in the systematic review

<table>
<thead>
<tr>
<th>Citation</th>
<th>Included patients</th>
<th>Included lesions</th>
<th>Excluded patients</th>
<th>Excluded lesions</th>
<th>Study design*†‡</th>
<th>Inclusion Criteria</th>
<th>Patient enrolment</th>
<th>Blind to reference?**</th>
<th>Blind to comparator?††</th>
<th>Mean age</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>DITI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arora et al, 2008 (172)</td>
<td>92</td>
<td>94</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>NR</td>
<td>Blind</td>
<td>Unclear</td>
<td>51</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Button et al, 2004 (177)</td>
<td>29</td>
<td>29</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>NR</td>
<td>Unclear</td>
<td>Unclear</td>
<td>NR</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Keyserlingk et al, 1998 (174)</td>
<td>200</td>
<td>200</td>
<td>28</td>
<td>NR</td>
<td>Retrospective case-control</td>
<td>Confirmed diagnosis</td>
<td>Consecutive</td>
<td>Not blind</td>
<td>Not blind</td>
<td>53</td>
<td>III-3 diagnostic</td>
</tr>
<tr>
<td>Kontos et al, 2011 (99)</td>
<td>126</td>
<td>126</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Breast symptoms</td>
<td>NR</td>
<td>Blind</td>
<td>Blind</td>
<td>48</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Parisky et al, 2003 (170)</td>
<td>769</td>
<td>875</td>
<td>524</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>NR</td>
<td>Blind</td>
<td>Not blind</td>
<td>NR</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Tang et al, 2008 (170)</td>
<td>117</td>
<td>117</td>
<td>NR</td>
<td>NR</td>
<td>NR Cohort</td>
<td>Scheduled for biopsy</td>
<td>NR</td>
<td>Blind</td>
<td>N/A</td>
<td>NR</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Wang et al, 2010 (100)</td>
<td>276</td>
<td>298</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>NR</td>
<td>Not blind</td>
<td>Not blind</td>
<td>51</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Wishart et al, 2010 (173)</td>
<td>100</td>
<td>106</td>
<td>13</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>NR</td>
<td>Blind</td>
<td>Blind</td>
<td>57</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>EIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diebold et al, 2005 (164)</td>
<td>256</td>
<td>256</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>NR</td>
<td>Unclear</td>
<td>Not blind</td>
<td>NR</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Fuchsjaeger et al, 2005 (164)</td>
<td>121</td>
<td>128</td>
<td>114</td>
<td>141</td>
<td>Prospective cohort</td>
<td>Biopsy of lesion/s</td>
<td>Consecutive</td>
<td>Blind</td>
<td>Not blind</td>
<td>52</td>
<td>II diagnostic</td>
</tr>
<tr>
<td>Glickman et al, 2002 (165)</td>
<td>NR</td>
<td>461</td>
<td>NR</td>
<td>NR</td>
<td>NR Cohort</td>
<td>Identified lesion/s</td>
<td>NR</td>
<td>Unclear</td>
<td>Not blind</td>
<td>NR</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Malich et al, 2003 (167)</td>
<td>353</td>
<td>387</td>
<td>NR</td>
<td>63</td>
<td>Prospective cohort</td>
<td>Identified lesion/s</td>
<td>NR</td>
<td>Not blind</td>
<td>Not blind</td>
<td>57</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Malich et al, 2007 (168)</td>
<td>NR</td>
<td>295</td>
<td>NR</td>
<td>NR</td>
<td>Retrospective cohort</td>
<td>Identified lesion/s</td>
<td>NR</td>
<td>Not blind</td>
<td>NR</td>
<td>NR</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Martin et al, 2002 (169)</td>
<td>74</td>
<td>74</td>
<td>60</td>
<td>NR</td>
<td>NR Cohort</td>
<td>Identified lesion/s</td>
<td>NR</td>
<td>Unclear</td>
<td>Unclear</td>
<td>56</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Melloul et al, 1999 (170)</td>
<td>121</td>
<td>121</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Identified lesion/s</td>
<td>NR</td>
<td>Unclear</td>
<td>Unclear</td>
<td>53</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Stojadinovic et al, 2008 (113)</td>
<td>390</td>
<td>390</td>
<td>207</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>No breast symptoms</td>
<td>Consecutive</td>
<td>Blind</td>
<td>Not blind</td>
<td>40</td>
<td>II diagnostic</td>
</tr>
<tr>
<td>Citation</td>
<td>Included patients</td>
<td>Included lesions</td>
<td>Excluded patients</td>
<td>Excluded lesions</td>
<td>Study design*</td>
<td>Inclusion Criteria</td>
<td>Patient enrolment</td>
<td>Blind to reference?**</td>
<td>Blind to comparator?††</td>
<td>Mean age</td>
<td>Level of evidence</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>---------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-----------------------</td>
<td>------------------------</td>
<td>---------</td>
<td>------------------</td>
</tr>
<tr>
<td>Szabo et al, 2005</td>
<td>137</td>
<td>145</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Identified lesion/s</td>
<td>NR</td>
<td>Not blind</td>
<td>Not blind</td>
<td>56</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Wang et al, 2010</td>
<td>583</td>
<td>583</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>NR</td>
<td>Blind</td>
<td>Blind</td>
<td>36</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Wesebe et al, 2002</td>
<td>117</td>
<td>129</td>
<td>NR</td>
<td>NR</td>
<td>NR Cohort</td>
<td>Scheduled for biopsy</td>
<td>NR</td>
<td>Not blind</td>
<td>Not blind</td>
<td>55</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Egorov et al, 2009</td>
<td>179</td>
<td>179</td>
<td>40</td>
<td>NR</td>
<td>NR Cohort</td>
<td>Identified lesion/s</td>
<td>NR</td>
<td>Not blind</td>
<td>Not blind</td>
<td>43</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Kaufman et al, 2006</td>
<td>110</td>
<td>110</td>
<td>NR</td>
<td>NR</td>
<td>NR Cohort</td>
<td>Breast symptoms</td>
<td>NR</td>
<td>Not blind</td>
<td>Not blind</td>
<td>NR</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>USE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Athanasicu et al, 2010</td>
<td>46</td>
<td>48</td>
<td>16</td>
<td>14</td>
<td>NR Cohort</td>
<td>Scheduled for biopsy</td>
<td>Consecutive</td>
<td>Unclear</td>
<td>Not blind</td>
<td>58</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Barr, 2010</td>
<td>208</td>
<td>251</td>
<td>71</td>
<td>87</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>NR</td>
<td>Unclear</td>
<td>Not blind</td>
<td>NR</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Burnside et al, 2007</td>
<td>397</td>
<td>403</td>
<td>NR</td>
<td>42</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>Consecutive</td>
<td>Blind</td>
<td>Not blind</td>
<td>49</td>
<td>II diagnostic</td>
</tr>
<tr>
<td>Chang et al, 2011</td>
<td>NR</td>
<td>291</td>
<td>25</td>
<td>30</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>Consecutive</td>
<td>Not blind</td>
<td>Not blind</td>
<td>46</td>
<td>II diagnostic</td>
</tr>
<tr>
<td>Chen et al, 2006</td>
<td>86</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td>Prospective case-control</td>
<td>Confirmed diagnosis</td>
<td>Consecutive</td>
<td>Unclear</td>
<td>Unclear</td>
<td>45</td>
<td>III-3 diagnostic</td>
</tr>
<tr>
<td>Cho et al, 2008</td>
<td>100</td>
<td>100</td>
<td>104</td>
<td>104</td>
<td>NR Cohort</td>
<td>Scheduled for biopsy</td>
<td>Consecutive</td>
<td>Blind</td>
<td>Not blind</td>
<td>46</td>
<td>II diagnostic</td>
</tr>
<tr>
<td>Cho et al, 2010</td>
<td>94</td>
<td>99</td>
<td>155</td>
<td>155</td>
<td>NR Cohort</td>
<td>Scheduled for biopsy</td>
<td>Consecutive</td>
<td>Blind</td>
<td>Not blind</td>
<td>45</td>
<td>II diagnostic</td>
</tr>
<tr>
<td>Chung et al, 2010</td>
<td>120</td>
<td>120</td>
<td>69</td>
<td>NR</td>
<td>Retrospective cohort</td>
<td>Scheduled for biopsy</td>
<td>Consecutive</td>
<td>Blind</td>
<td>Not blind</td>
<td>47</td>
<td>II diagnostic</td>
</tr>
<tr>
<td>Evans et al, 2010</td>
<td>52</td>
<td>53</td>
<td>NR</td>
<td>NR</td>
<td>NR Cohort</td>
<td>Identified lesion/s</td>
<td>Consecutive</td>
<td>Unclear</td>
<td>Unclear</td>
<td>53</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Fleury et al, 2009</td>
<td>188</td>
<td>228</td>
<td>19</td>
<td>19</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>NR</td>
<td>Unclear</td>
<td>Not blind</td>
<td>44</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Garra et al, 1997</td>
<td>28</td>
<td>28</td>
<td>NR</td>
<td>NR</td>
<td>NR Cohort</td>
<td>Scheduled for biopsy</td>
<td>NR</td>
<td>Blind</td>
<td>Not blind</td>
<td>NR</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Citation</td>
<td>Included patients</td>
<td>Included lesions</td>
<td>Excluded patients</td>
<td>Excluded lesions</td>
<td>Study design***</td>
<td>Inclusion Criteria</td>
<td>Patient enrolment</td>
<td>Blind to reference?**</td>
<td>Blind to comparator?††</td>
<td>Mean age</td>
<td>Level of evidence</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>-----------------</td>
<td>--------------------</td>
<td>-------------------</td>
<td>------------------------</td>
<td>----------------------------</td>
<td>----------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Giuseppetti et al, 2005</td>
<td>82</td>
<td>91</td>
<td>NR</td>
<td>NR</td>
<td>NR Cohort</td>
<td>Identified lesion/s</td>
<td>NR</td>
<td>Unclear</td>
<td>Not blind</td>
<td>55</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Itoh et al, 2006</td>
<td>111</td>
<td>111</td>
<td>24</td>
<td>34</td>
<td>NR Cohort</td>
<td>Identified lesion/s</td>
<td>Consecutive</td>
<td>Not blind</td>
<td>Not blind</td>
<td>NR</td>
<td>II diagnostic</td>
</tr>
<tr>
<td>Ko et al, 2011</td>
<td>264</td>
<td>275</td>
<td>42</td>
<td>42</td>
<td>Retrospective cohort</td>
<td>Scheduled for biopsy</td>
<td>NR</td>
<td>Blind</td>
<td>Not blind</td>
<td>47</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Kumm et al, 2010</td>
<td>288</td>
<td>310</td>
<td>4</td>
<td>6</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>Consecutive</td>
<td>Blind</td>
<td>Not blind</td>
<td>NR</td>
<td>II diagnostic</td>
</tr>
<tr>
<td>Lee et al, 2011</td>
<td>278</td>
<td>315</td>
<td>82</td>
<td>91</td>
<td>Retrospective cohort</td>
<td>Scheduled for biopsy</td>
<td>Consecutive</td>
<td>Unclear</td>
<td>Not blind</td>
<td>47</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Leong et al, 2010</td>
<td>99</td>
<td>110</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>Consecutive</td>
<td>Unclear</td>
<td>Not blind</td>
<td>47</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Moon et al, 2005</td>
<td>86</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>Consecutive</td>
<td>Unclear</td>
<td>Unclear</td>
<td>45</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Moon et al, 2009</td>
<td>181</td>
<td>181</td>
<td>NR</td>
<td>NR</td>
<td>NR Cohort</td>
<td>Scheduled for biopsy</td>
<td>Consecutive</td>
<td>Not blind</td>
<td>Not blind</td>
<td>47</td>
<td>II diagnostic</td>
</tr>
<tr>
<td>Moon et al, 2010</td>
<td>140</td>
<td>140</td>
<td>31</td>
<td>NR</td>
<td>Retrospective cohort</td>
<td>Scheduled for biopsy</td>
<td>Consecutive</td>
<td>Not blind</td>
<td>Not blind</td>
<td>46</td>
<td>II diagnostic</td>
</tr>
<tr>
<td>Navarro et al, 2011</td>
<td>116</td>
<td>124</td>
<td>6</td>
<td>7</td>
<td>Retrospective cohort</td>
<td>Identified lesion/s</td>
<td>NR</td>
<td>Unclear</td>
<td>Not blind</td>
<td>46</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Parajuly et al, 2010</td>
<td>150</td>
<td>170</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Identified lesion/s</td>
<td>NR</td>
<td>Blind</td>
<td>Not blind</td>
<td>45</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Raza et al, 2010</td>
<td>175</td>
<td>188</td>
<td>11</td>
<td>12</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>Consecutive</td>
<td>Unclear</td>
<td>Not blind</td>
<td>47</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Regini et al, 2010</td>
<td>NR</td>
<td>104</td>
<td>NR</td>
<td>16</td>
<td>NR Cohort</td>
<td>Identified lesion/s</td>
<td>NR</td>
<td>Unclear</td>
<td>Unclear</td>
<td>51</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Regner et al, 2006</td>
<td>88</td>
<td>89</td>
<td>13</td>
<td>13</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>Consecutive</td>
<td>Blind</td>
<td>Not blind</td>
<td>58</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Satake et al, 2011</td>
<td>104</td>
<td>115</td>
<td>NR</td>
<td>26</td>
<td>Retrospective cohort</td>
<td>Identified lesion/s</td>
<td>NR</td>
<td>Blind</td>
<td>Not blind</td>
<td>55</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Scaperrotta et al, 2008</td>
<td>278</td>
<td>293</td>
<td>17</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>NR</td>
<td>Blind</td>
<td>Not blind</td>
<td>52</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Schaefer et al, 2009</td>
<td>193</td>
<td>193</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Identified lesion/s</td>
<td>NR</td>
<td>Unclear</td>
<td>Not blind</td>
<td>54</td>
<td>III-2 diagnostic</td>
</tr>
</tbody>
</table>
### Table 3.1 continued

<table>
<thead>
<tr>
<th>Citation</th>
<th>Included patients</th>
<th>Included lesions</th>
<th>Excluded patients</th>
<th>Excluded lesions</th>
<th>Study design</th>
<th>Inclusion Criteria</th>
<th>Patient enrolment</th>
<th>Blind to reference?</th>
<th>Blind to comparator?</th>
<th>Mean age</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sohn et al, 2009</td>
<td>267</td>
<td>281</td>
<td>NR</td>
<td>NR</td>
<td>Retrospective cohort</td>
<td>Scheduled for biopsy</td>
<td>NR</td>
<td>Blind</td>
<td>Not blind</td>
<td>NR</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Tan et al, 2008</td>
<td>415</td>
<td>550</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Identified lesion/s</td>
<td>Consecutive</td>
<td>Not blind</td>
<td>Not blind</td>
<td>39</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Thomas et al, 2006</td>
<td>108</td>
<td>108</td>
<td>42</td>
<td>NR</td>
<td>NR Cohort</td>
<td>Identified lesion/s</td>
<td>Consecutive</td>
<td>Blind</td>
<td>Not blind</td>
<td>54</td>
<td>II diagnostic</td>
</tr>
<tr>
<td>Thomas et al, 2007</td>
<td>50</td>
<td>50</td>
<td>25</td>
<td>NR</td>
<td>NR Cohort</td>
<td>Identified lesion/s</td>
<td>NR</td>
<td>Blind</td>
<td>Not blind</td>
<td>49</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Thomas et al, 2010</td>
<td>227</td>
<td>227</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Identified lesion/s</td>
<td>Consecutive</td>
<td>Blind</td>
<td>Not blind</td>
<td>54</td>
<td>II diagnostic</td>
</tr>
<tr>
<td>Wojcinski et al, 2010</td>
<td>779</td>
<td>779</td>
<td>NR</td>
<td>NR</td>
<td>NR Cohort</td>
<td>Identified lesion/s</td>
<td>NR</td>
<td>Unclear</td>
<td>Not blind</td>
<td>54</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Yerli et al, 2011</td>
<td>71</td>
<td>78</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>Consecutive</td>
<td>Blind</td>
<td>Not blind</td>
<td>52</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Yoon et al, 2011</td>
<td>53</td>
<td>65</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>Consecutive</td>
<td>Blind</td>
<td>Not blind</td>
<td>46</td>
<td>II diagnostic</td>
</tr>
<tr>
<td>Zhi et al, 2007</td>
<td>232</td>
<td>296</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Identified lesion/s</td>
<td>NR</td>
<td>Blind</td>
<td>Not blind</td>
<td>42</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Zhi et al, 2010</td>
<td>437</td>
<td>559</td>
<td>NR</td>
<td>NR</td>
<td>NR Cohort</td>
<td>Identified lesion/s</td>
<td>NR</td>
<td>Blind</td>
<td>Not blind</td>
<td>39</td>
<td>III-2 diagnostic</td>
</tr>
<tr>
<td>Zhu et al, 2008</td>
<td>112</td>
<td>139</td>
<td>NR</td>
<td>NR</td>
<td>Prospective cohort</td>
<td>Scheduled for biopsy</td>
<td>Consecutive</td>
<td>Blind</td>
<td>Not blind</td>
<td>46</td>
<td>II diagnostic</td>
</tr>
</tbody>
</table>

**USE:** Ultrasound Elastography, EPI: Electronic Palpation Imaging, EIS: Electrical Impedance Scanning, DITI: Digital Infrared Thermography. NR: Not Reported.

*Diagnostic case-control study. Cross-sectional in design, cases enrolled into the study with a confirmed diagnosis of breast cancer, controls enrolled into the study as either healthy, or with a confirmed diagnosis of benign breast mass (e.g. tumor, cyst).

†Diagnostic cohort study. Cross-sectional in design, participants enrolled under the suspicion of breast disease without a confirmed diagnosis. Confirmation of disease status occurs with a valid reference standard during the study.

‡NR Cohort: Diagnostic cohort study which did not specify whether it was prospective or retrospective.

**Were the results of the index test, e.g. DITI, EIS, interpreted without knowledge of the results of the reference standard, e.g. biopsy?

††Was the index test carried out or interpreted without knowledge of the results of a comparator test, e.g. mammography, ultrasound (N/A where no comparator was used)?


3.6.5 Synthesis of results

Due to the presence of significant heterogeneity across subgroups, it was not appropriate to calculate pooled estimates of diagnostic accuracy [26]. The majority of EIS studies reported sensitivities between 62.0 per cent and 97.5 per cent (median 83%), with the exception of Stojadinovic et al. (26.4%). Specificity values for EIS were lower, ranging between 42.0 per cent and 80.9 per cent (median 68%), with the exception of Martin et al. (8.3%). DITI studies were also highly variable, reporting sensitivities between 25.0 per cent and 96.7 per cent (median 82%), and specificities between 11.8 per cent and 84.9 per cent (median 55%). USE studies reported sensitivities between 35.4 per cent and 100.0 per cent (median 84%), and specificities between 21.1 per cent and 98.9 per cent (median 88%).
Figure 3.3  Forest plot of estimated sensitivity and specificity reported in digital infrared thermal imaging studies, all methods

![Forest plot of sensitivity and specificity for digital infrared thermal imaging](image)

Figure 3.4  Forest plot of estimated sensitivity and specificity reported in electrical impedance scanning studies that employed the 5 point “Level of Suspicion” method

![Forest plot of sensitivity and specificity for electrical impedance scanning](image)

Figure 3.5  Forest plot of estimated sensitivity and specificity reported in electrical impedance scanning

![Forest plot of sensitivity and specificity for electrical impedance scanning](image)
3.7 Discussion

This comprehensive, systematic review found no studies evaluating whether breast cancer screening or diagnosis with DITI, EIS or elastography leads to a reduction in mortality or morbidity. As these devices are in the early stages of adoption into practice, accuracy data from both symptomatic and asymptomatic populations were also collected as a secondary outcome measure to determine their performance in the absence of effectiveness data. From all three classes of device, only one EIS study investigated the accuracy of a device in asymptomatic women,\textsuperscript{(113)} with all remaining studies reporting diagnostic accuracy parameters in symptomatic populations.

Selection bias due to non-consecutive enrolment of study participants was prominent in diagnostic accuracy studies of USE, EPI and EIS. Individual study results are therefore likely to have been affected, as non-consecutive study enrolment can inflate diagnostic odds ratios by up to 50 per cent compared to consecutive enrolment.\textsuperscript{(218)} Likewise, the presence of selection bias due to selective inclusion of participants may have also inflated the reported values of diagnostic accuracy within individual studies,\textsuperscript{(218)} although the extent of which is unclear due to the large amount of inadequate reporting on participant selection.

Review bias due to inadequate blinding of the index test to the results of the reference standard and vice versa was also highly prevalent. Inadequate blinding in diagnostic accuracy studies has been shown to increase reported estimates of diagnostic accuracy, particularly when the results of a reference test are made available when interpreting the results of an index test.\textsuperscript{(219)} Moreover, the presence of review bias ultimately impacts the clinical relevance of the test, as the results of a reference test will rarely be available when the index test is interpreted in practice. Unfortunately it was not possible to investigate the differences in pooled estimates of accuracy between blinded and un-blinded studies in this review, due to the presence of significant heterogeneity among studies.

The largest limitations identified in the evidence base were the wide range of methodological approaches applied within each class of device, and high degree of variation between results of individual studies that applied each method. Subgroup analyses were conducted in order to determine the likely cause of variation, with significant variation observed in all subgroups. The wide range of specific devices used to carry out each imaging method may also account for the variation. For example, within USE there were four main methods of conducting imaging, and up to eight unique devices within each method. This was also a significant issue for DITI, where there were seven unique devices, each of which had its own method of classifying diseased and disease-free participants. Other factors that
may have affected the spread of data that could not be accounted for due to a lack of data include lesion size, grade and stage, BRCA1/2 status and family history of breast cancer.

Due to high levels of variation among study results, and the large degree of variation among the methods and devices used for imaging, it was deemed inappropriate to produce pooled estimates of diagnostic accuracy for any of the three classes as a whole. As pooled estimates of positive predictive value and negative predictive value could not be estimated, it was not possible to compare these new technologies with mammography in screening populations. Therefore, in order to compare these new devices with mammography, a review of diagnostic accuracy is required. A recent systematic review identified one low quality and three high quality studies investigating the accuracy of digital mammography for breast cancer diagnosis in high risk and symptomatic women. The review concluded that there was limited evidence of test accuracy, with reports of sensitivity between 66-72 per cent and specificity between 67-98 per cent. In contrast, the evidence base for the technologies included in this review reported a large amount of variation among the accuracy results reported in DITI, EIS, and USE studies. Differences in the evidence base for these new technologies are indicative of the variation in methodology and device type, as well as the large influence of heterogeneity among subgroups.

Both the included EPI studies scored poorly against the QUADAS criteria and reported a low level of evidence, and neither blinded investigators to the clinical diagnosis when interpreting EPI images, nor stated whether participants were enrolled consecutively. The study by Kaufman et al. measured the ability of the device to detect any palpable mass, i.e. any lesion detected by the device was classified as a true positive, and as such their reported results of sensitivity and specificity are not appropriate in the context of diagnosis where benign and malignant disease must be differentiated. The remaining study by Egorov et al., involving 179 patients with clinically confirmed breast lesions, met more QUADAS criteria than the previous study. However, the investigators emphasised an average sensitivity and specificity from all sites, thus smaller sites had equal impact on the reported outcomes as larger ones. When combined data were reported instead of averaged data the results were lower (sens 87.5%, spec 84.4%).

In regards to safety, there was no evidence of physical harm arising from use of the devices in any of the included studies. All of the relevant index tests are non-invasive, do not compress the breast, and do not expose patients to ionising radiation. The main potential harms associated with these devices therefore relate to their ability to correctly identify diseased and disease-free patients. Due to the high degree of variation found among studies reporting on each class of device, it is difficult to suggest the risk of harm from potentially
treatable disease being ignored, and clinically irrelevant disease being investigated with more invasive diagnostic tools.

Although the evidence base for these devices is still developing, DITI, EIS and EPI are currently available internationally without a referral from a healthcare practitioner. DITI can currently be accessed directly by both symptomatic and asymptomatic women for breast cancer imaging in 10 countries,\(^{(220, 221)}\) EPI is available in eight countries,\(^{(155)}\) and EIS is available in Australia and the USA.\(^{(222, 223)}\) Given the availability of these devices in practice, both patients and clinicians should be aware of the large degree of variation in the evidence base for these devices.

This study has minor limitations. First, one identified study was not included in the review due to a lack of full-text access.\(^{(224)}\) The study, published in 1986, had no available abstract, and no reported citations in Embase. In addition, due to the age of the publication it is likely that it adopted an older iteration of thermal imaging technology that would not have met the inclusion criteria for the review. The exclusion of non-English language studies that did not present a higher level of evidence than included English language studies may affect the generalisability of the results of this review. Finally, as these are emerging devices, it is possible that long-term studies investigating their use for diagnosis and screening are currently being undertaken, which may warrant an update of this review in the future.

### 3.8 Conclusions

This review did not identify any studies that evaluated the diagnostic or screening effectiveness of DITI, EIS, USE or EPI for breast cancer detection. Similarly, there were no studies that evaluated the accuracy of these devices in asymptomatic populations, with the exception of one EIS study. Due to the lack of available data evaluating the use of these devices in asymptomatic women, these devices cannot be recommended for safe use in healthy, screening populations at this time. It is recommended that future research should aim to determine the performance of these devices in asymptomatic populations before they are adopted more widely into practice as a screening tool.

Although USE shows promise as a diagnostic or adjunct diagnostic tool, the high degree of heterogeneity in the evidence base for all devices investigated in this review, at both the class level and subgroup level, prohibits any recommendation for their adoption into practice. In particular, there was a lack of consensus around which technological approach for each class yields the best results, and which individual devices within each class were the most accurate at detecting breast cancer. More research, conducted with adequate blinding of the index test, and uniformly defined methods for both imaging with, and interpreting the
test results of these devices, is needed in order to better define their performance as diagnostic imaging tools for breast cancer.

3.8.1 Acknowledgements

The authors would like to thank Dagmara Riitano and Thomas Sullivan from the University of Adelaide for their invaluable contributions to the data extraction and analysis completed in this review. TDV is supported by an Australian Commonwealth PhD scholarship, with a top-up from Adelaide Health Technology Assessment. CDW is supported by an NHMRC Sidney Sax Fellowship.
CHAPTER 4

Content analysis of online DtCA of emerging breast imaging devices

Chapter 4 | Content Analysis

4.1 Preface to Chapter 4

In the previous chapter, a comprehensive systematic review of the evidence for digital infrared thermal imaging (DITI), electrical impedance scanning (EIS) and electronic palpation imaging (EPI) was conducted. As discussed, the review did not find sufficient evidence to support the use of these devices for breast cancer screening, and heterogeneous, low quality evidence for diagnosis. Given the findings of the review, an investigation of the direct-to-consumer advertising (DtCA) for these devices was planned in order to determine the extent to which advertising claims were consistent with the available evidence.

An analysis of the online advertising material for DITI, EIS and EPI devices, as it compares to the available evidence of safety and effectiveness, is relevant to Australian policy on advertising regulation. As outlined in Chapter 2, advertising material for medical devices is not pro-actively regulated in Australia, and instead is largely monitored for accuracy by industry bodies and members of the public. In June 2011, the Australian Competition and Consumer Commission (ACCC), the Therapeutic Goods Administration (TGA) and Cancer Council of Australia submitted a joint media release, warning consumers about the promotion of these devices, suggesting that they may not be supported by evidence. A review of advertising material for these devices in the context of the available safety and effectiveness evidence has not yet been conducted.

The aim of this chapter is to describe the manner in which Australian companies promote DITI, EPI and EIS devices directly towards consumers online. Specifically, this entails an analysis of the types of advertising claims being made on websites for these devices. Advertising claims are then compared narratively with the evidence collected in Chapter 3, thereby addressing Research Questions 2 and 3:

Research question 2: What is the nature and frequency of information presented on direct-to-consumer websites for DITI, EIS and EPI?

Research question 3: To what extent are claims of safety, effectiveness and diagnostic accuracy made on direct-to-consumer websites for DITI, EIS and EPI supported by evidence?
4.2 Statement of authorship


Thomas Vreugdenburg (Candidate)

Developed the study protocol and search strategy, conducted the search to identify relevant websites, collected website data over a 12 month period, managed the dataset, developed the code book, trained external coders, coded part of the data, analysed the coded data, wrote the manuscript and acted as corresponding author.

Signed: . . . . . . . . . . . .  Date: . . . . . .

Caroline Laurence

My contribution to this paper involved assisting with the design of the study protocol, codebook development, data analysis and manuscript evaluation. I give consent for Thomas Vreugdenburg to present this paper for examination towards the Doctor of Philosophy

Signed: . . . . . . . . . . . .  Date: . . . . . .

Cameron Willis

My contribution to this paper involved assisting with the design of the study protocol and manuscript evaluation. I give consent for Thomas Vreugdenburg to present this paper for examination towards the Doctor of Philosophy

Signed: . . . . . . . . . . . .  Date: . . . . . .

Linda Mundy

My contribution to this paper involved assisting with the design of the study protocol and manuscript evaluation. I give consent for Thomas Vreugdenburg to present this paper for examination towards the Doctor of Philosophy

Signed: . . . . . . . . . . . .  Date: . . . . . .
Janet Hiller

My contribution to this paper involved assisting with the design of the study protocol and manuscript evaluation. I give consent for Thomas Vreugdenburg to present this paper for examination towards the Doctor of Philosophy

Signed: .....................  Date: ........

**NOTE:**
This publication is included on pages 67-77 in the print copy of the thesis held in the University of Adelaide Library.

It is also available online to authorised users at:

CHAPTER 5

Exploring options to reform the regulation of medical devices and medical device advertising


5.1 Introduction

In Chapter 3 and Chapter 4, two concerns with the promotion of breast cancer imaging devices directly to consumers were highlighted. Firstly, the current level of pre-market assessment placed on emerging breast imaging devices does not ensure that they are safe or effective at detecting breast cancer in either symptomatic or asymptomatic populations. Secondly, the current reliance on industry self-regulation is not effective in ensuring that advertisements for emerging breast imaging devices are supported by evidence. Given the highlighted issues with these devices, it is argued that the current regulatory system responsible for their pre-market approval and advertising material is in need of reform.

In 2011, six official complaints about the advertising material for breast cancer imaging devices were lodged with the Complaints Resolution Panel (CRP) – a partnership of industry and government stakeholders, including the Therapeutic Goods Administration (TGA), tasked with overseeing complaints made about the advertisement of therapeutic goods. Although these complaints raised the profile of emerging breast imaging devices with the TGA, they also indicated a broader problem with the regulation of the medical devices industry. Complaints about the medical devices industry have become increasingly prevalent since 2007, equalling the total number of complaints lodged against complementary and alternative medicines (CAM) and over-the-counter (OTC) medicines combined in 2010. In recognition of this growing burden on the CRP, the TGA has been proactive in reforming many aspects of its role as Australia’s principal therapeutic goods regulator.

Through a series of public reform consultations initiated in 2009, the TGA created a platform for members of the community to provide input into proposed changes to the regulation of therapeutic goods in Australia. In light of this opportunity, it was considered how the results of this thesis may pragmatically contribute to the ongoing reform process. This chapter describes a stakeholder engagement that aimed to translate knowledge gained from this thesis into policy recommendations for regulatory reform. In order to achieve this, the research findings from Chapter 3 and Chapter 4 were disseminated to members of the breast cancer community, who were subsequently engaged in discussion around the policy issues affecting emerging breast cancer imaging devices. The primary focus of this engagement was to assess a series of options proposed by the TGA to reform the regulation of medical devices and medical device advertising, within the context of the case study of non-invasive breast cancer imaging devices. The key advantages and disadvantages of the TGA’s proposed reforms are presented, and recommendations to guide the reform process were developed and fed back into the TGA’s reform consultation process.
5.1.1 The TGA reform process

The public consultations initiated by the TGA in 2009 aimed to develop options to reform the advertising arrangements for therapeutic goods and the pre-market approval process for medical devices.\textsuperscript{(131, 132)} These consultations contributed to a series of reviews, which also aimed to investigate the transparency of the TGA’s regulatory processes, and the TGA’s role in health technology assessment (HTA) and complementary and alternative medicine regulation.\textsuperscript{(253)} An outline of the review process is presented in Figure 5.1, with the consultations most relevant to emerging breast imaging devices outlined in bold: the advertising regulatory framework options for reform, the medical devices regulatory framework consultation, and the pre-market assessment of medical devices consultation.

**Figure 5.1 Approximate timeline of the major reviews contributing to the TGA’s blueprint for reform package**

CAM: complementary and alternative medicine. TGA: Therapeutic Goods Administration.
5.1.1.1 **The 2012 Advertising Regulatory Framework Consultation**

In 2010, the Therapeutic Goods Advertising Consultation (Figure 5.1) aimed to assess the regulations for therapeutic goods advertising in Australia.\(^\text{131}\) Submissions were received from a broad range of industry, professional, and consumer stakeholder groups, who suggested that the existing regulatory framework did not adequately prevent consumers from being exposed to false or misleading advertisements for therapeutic goods. The lack of pre-approval of CAM and medical device advertising by an independent regulator were highlighted as a key limitations in the existing system.\(^\text{131}\)

In response to these findings, the TGA initiated the 2012 Advertising Regulatory Framework Consultation, aimed at improving the regulation of therapeutic goods advertising.\(^\text{131}\) Three options to reform the regulatory arrangements for therapeutic goods advertising in Australia were proposed:

- **Option 1**: Strengthen the current pre-approval system, by expanding it to include medical devices and CAMs; or
- **Option 2**: Remove the existing pre-approval system in favour of active monitoring of advertisements for therapeutic goods (including devices), and increased penalties for companies that breach regulations; or
- **Option 3**: Develop a new regulatory system, involving an auditable database of therapeutic goods advertising (including devices) to highlight repeat offenders that breach regulations. Repeat offenders would be subject to pre-approval of their advertisements in future.

This consultation opened for discussion during the course of this thesis, and presented an opportunity for stakeholders to offer feedback on the proposed options directly to the TGA.

5.1.1.2 **The 2010 Medical Devices Regulatory Consultation**

The 2010 Medical Devices Regulatory Consultation sought to update the way in which medical devices obtain pre-market approval in Australia. The consultation highlighted four key areas in need of reform, based on recommendations made during the Australian 2009 HTA Review. These options included: reclassifying joint implants as high-risk devices; increasing the level of scrutiny required for the pre-market approval of implantable devices; improving the transparency of medical devices that are included on the Australian Register of Therapeutic Goods (ARTG); and publishing product information about devices on the TGA website.\(^\text{132}\) Three additional proposals for reform were also suggested, that will affect the quality and transparency of assessments placed on emerging breast imaging devices.\(^\text{132}\)
- **Proposal 1**: Allow third-party assessment bodies to certify medical devices manufactured by Australian companies;
- **Proposal 2**: Enhance the transparency of approved medical devices, and amend the way in which a device is registered on the ARTG; and
- **Proposal 3**: Publish medical device product information on the TGA website.

As this consultation opened for discussion during the course of this thesis, it presented an opportunity for stakeholders to provide input into the regulation of breast imaging devices in Australia. However, in January 2013, the TGA released a series of additional proposals to amend the regulation of medical devices prior to market.

### 5.1.1.3 The 2013 Pre-market Assessment of Medical Devices Consultation

Building on the 2010 consultation, the 2013 Pre-market Assessment of Medical Devices Consultations aimed to refine the framework of amendments to the pre-market assessment of medical devices in Australia. Submissions to this consultation were elicited from the medical devices industry, consumer advocacy groups, and government departments. The consultation discussed the following proposals for reform:

- **Proposal 1**: Increase the scrutiny of conformity assessment for medical devices that apply for ARTG inclusion;
- **Proposal 2**: Publish regulatory decisions for medical devices online; and
- **Proposal 3**: Allow third party verification of conformity assessment for Australian manufacturers of lower class medical devices (expanding from proposal 1 in the previous consultation).

### 5.1.2 Research aims and objectives

The current regulatory framework for medical devices in Australia allows emerging breast cancer imaging devices to be marketed directly towards consumers without an assessment of efficacy or effectiveness. Once listed on the ARTG, the content of advertisements for these devices is self-regulated by the medical devices industry, which does not guarantee that advertising claims are evidence-based. This practice appears in contrast to the national mammographic screening program, BreastScreen, which was required to pass a rigorous HTA prior to its commencement, as well as ongoing reviews of safety and effectiveness and constant monitoring for adherence to performance standards.
The public consultation process initiated by the TGA presented an opportunity for members of the breast cancer community to provide input into the manner in which new breast imaging devices may be regulated in the future. It also presented an opportunity to raise the importance of the noted limitations in the current regulatory framework, by disseminating the research findings from previous chapters of this thesis amongst relevant stakeholder groups. The aim of this chapter is to explore key stakeholders’ perspectives on how the TGA reform options might impact the regulation of breast cancer imaging devices in Australia, by investigating the following research questions:

**Research question 4:** What are the perspectives and recommendations of key stakeholders in breast cancer research, patient advocacy and screening, on the proposed changes to the regulatory framework for advertising and pre-market approval of breast cancer screening and diagnostic devices in Australia?

**Research question 5:** Which characteristics of medical devices and medical device advertising do stakeholders in breast cancer research, patient advocacy and screening, consider should be assessed by an independent regulator?
5.2 Methods

5.2.1 Design

Semi-structured interviews were conducted with key stakeholders in breast cancer research, patient advocacy and screening using the qualitative description (QD) approach.\textsuperscript{(256-258)} Based on qualitative research principles, QD aims to describe the ‘what’, ‘how’ and ‘why’ of individuals’ perceptions and experiences of phenomena.\textsuperscript{(256)} The QD approach involves less transformation of data compared to other methods such as grounded theory or phenomenology, and instead produces findings that are closely aligned to the original data.\textsuperscript{(258)} In this regard, the QD approach is suited to health services research that deals with specific, policy-based research questions, as it provides a clear synthesis of the views and opinions of stakeholder groups that can be used to inform policy decisions.\textsuperscript{(257)}

5.2.2 Stakeholder selection and recruitment

A purposive sampling strategy was applied in order to identify key stakeholders within the Australian breast cancer community.\textsuperscript{(259)} Positional sampling, a form of purposive sampling, involves selecting individuals who are established in leadership positions, or who represent organisations fulfilling a leadership role within the community.\textsuperscript{(259, 260)} National, not-for-profit organisations were viewed as having leadership roles in three key areas: breast cancer research, breast cancer screening, and consumer advocacy. Stakeholders from these three distinct areas were sought to provide diversity of opinion on the TGA’s options for reform. Opinions of the breast cancer community were sought, as it has a unique perspective on patient groups that are relevant to the case study of emerging breast imaging devices. Not-for-profit organisations were targeted specifically, as there was a strong response from the medical devices industry to prior public reform consultations. As such, study participants were required to meet two requirements for inclusion into the study:

1. Individuals must represent a national, not-for-profit organisation involved in providing support or leadership within breast cancer research, patient advocacy and screening.
2. Individuals must have working knowledge of breast cancer screening and diagnosis.

Participants were approached via a three-phase process aimed at reducing the likelihood that participants would feel pressure to enrol from their host organisation.\textsuperscript{(261)} In the first instance, an approach letter was sent via e-mail to 10 key stakeholder organisations, with the aim to seek in-principle interest in the project. Organisations that showed interest in the project were contacted via telephone in order to shortlist potential participants from within
the organisation who met the inclusion criteria for the study listed above. Finally, individual participants were sent a personalised approach letter and background information about the study via email, and were asked if they were willing to participate in the study. Stakeholders were not offered financial or other incentives to participate in the study.

5.2.3 Interview schedule

Stakeholders that agreed to participate were presented with an information sheet that summarised the results from Chapters 2, 3 and 4 of this thesis (Appendix D). The semi-structured interview schedule included both targeted and open-ended interview questions. Targeted interview questions aimed to address research question 4, regarding the specific options for reform proposed by the TGA. Open-ended questions were also developed to address research question five, in order to discern which characteristics of a breast imaging test should be assessed prior to market. The full interview schedule is presented in Appendix D, and was based around the following areas of inquiry:

1. The advantages and disadvantages of the proposed changes to the current system of regulating these devices and their advertising material in Australia, recently proposed by the TGA.
2. The characteristics of a new device that stakeholders believe should be assessed before it is made available and promoted as a screening or diagnostic tool in Australia.

Interviews were held between 12 December 2012 and 22 February 2013. However, on 14 January 2013 the TGA released the Pre-market Assessment of Medical Devices consultation. The interview schedule was updated to reflect the new list of reforms. As a result, the first three of 13 participants were not able to offer a response to two additional interview questions that were related to the new consultation. Interviews were conducted until data saturation had been reached. In the context of this study, data saturation was defined as the point at which additional interviews had minimal or no effect on the coding scheme, that is, the point at which no new themes emerged from interview transcripts. Two additional interviews were conducted after it was thought that saturation had been achieved.
5.2.4 Data analysis

Interviews were recorded with consent from participants, and transcribed for analysis. Thematic analysis was used to identify, synthesise and interpret recurrent themes within the collected data. Analysis of interview responses addressing research question four was targeted towards generating themes related to the advantages and disadvantages of the TGA’s proposed reform options. Coding of themes related to research question four were checked by an independent coder (CL) in collaboration with the candidate.

Due to the open-ended nature of research question five, an inductive approach to data coding allowed the identification of emergent themes without adhering to a predetermined coding framework. The entire sample of thematic data addressing research question five was duplicated by an external researcher (DJ) in order to lend reliability to the coded themes. During the duplicate coding, disagreements between coders around the definition of themes were settled through discussion. Data were coded using QSR NVivo, version 9.2 (QSR International). Coding of themes was completed in four iterative rounds, allowing for reflexivity in the coding process:

- **Round 1**: Familiarisation with interview transcripts, coding large portions of transcripts into their respective interview questions/topics for synthesis.
- **Round 2**: Broad grouping of data to characterise initial themes.
- **Round 3**: Combination, expansion or revision of initial themes, and identification of outlying themes.
- **Round 4**: Final check to ensure the defined themes supported the data with revisions where necessary.

The number of respondents that indicated a preference for a particular option for reform is reported in order to demonstrate the general agreement within the stakeholder group. These numbers are not intended to be generalisable beyond the stakeholders included in this study.

5.2.5 Ethical requirements

This study received ethical approval from the University of Adelaide Human Research Ethics Committee approval H-2012-146. Provisions of ethical approval for this project included de-identifying participants from the data analysis and reporting of the study results and avoiding organisations from nominating participants involuntarily. All participants included in the study gave permission to be audio recorded so that interviews could be transcribed at a later date.
5.3 Results

5.3.1 Stakeholder demographics

From the 10 organisations that were approached via email, four self-identified as not having the skills or knowledge to contribute to the project, one did not reply to repeat invitations, and five showed in-principle interest in the study. The interested organisations recommended a total of 14 potential participants, 13 of whom accepted the invitation, and one who did not - stating time pressures. Additional individuals were snowball sampled from the included organisations in order to achieve saturation. These additional participants were recommended by interview participants, resulting in 16 study participants in total. Sample demographics are presented in Table 5.1.

Table 5.1 Participant demographics

<table>
<thead>
<tr>
<th>Interview</th>
<th>Occupation</th>
<th>Identifier</th>
<th>Gender</th>
<th>Interview Type</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Advocacy</td>
<td>A1</td>
<td>M</td>
<td>Telephone</td>
<td>Metropolitan</td>
</tr>
<tr>
<td>2</td>
<td>Advocacy</td>
<td>A2</td>
<td>F</td>
<td>Face-to-face</td>
<td>Metropolitan</td>
</tr>
<tr>
<td>3</td>
<td>Screening</td>
<td>S1</td>
<td>F</td>
<td>Telephone</td>
<td>Metropolitan</td>
</tr>
<tr>
<td>4</td>
<td>Screening</td>
<td>S2</td>
<td>F</td>
<td>Telephone</td>
<td>Metropolitan</td>
</tr>
<tr>
<td>5</td>
<td>Advocacy</td>
<td>A3</td>
<td>F</td>
<td>Face-to-face</td>
<td>Metropolitan</td>
</tr>
<tr>
<td>6</td>
<td>Advocacy</td>
<td>A4</td>
<td>F</td>
<td>Face-to-face</td>
<td>Metropolitan</td>
</tr>
<tr>
<td>7</td>
<td>Research</td>
<td>R1</td>
<td>F</td>
<td>Telephone</td>
<td>Metropolitan</td>
</tr>
<tr>
<td>8</td>
<td>Screening</td>
<td>S3</td>
<td>M</td>
<td>Face-to-face</td>
<td>Metropolitan</td>
</tr>
<tr>
<td>9</td>
<td>Screening</td>
<td>S4</td>
<td>F</td>
<td>Face-to-face</td>
<td>Metropolitan</td>
</tr>
<tr>
<td>10</td>
<td>Research</td>
<td>R2</td>
<td>F</td>
<td>Face-to-face</td>
<td>Metropolitan</td>
</tr>
<tr>
<td>11</td>
<td>Research</td>
<td>R3</td>
<td>M</td>
<td>Face-to-face</td>
<td>Metropolitan</td>
</tr>
<tr>
<td>12</td>
<td>Advocacy</td>
<td>A5</td>
<td>F</td>
<td>Telephone</td>
<td>Metropolitan</td>
</tr>
<tr>
<td>13</td>
<td>Research</td>
<td>R4</td>
<td>M</td>
<td>Face-to-face</td>
<td>Metropolitan</td>
</tr>
<tr>
<td>14</td>
<td>Screening</td>
<td>S5</td>
<td>M</td>
<td>Telephone</td>
<td>Metropolitan</td>
</tr>
<tr>
<td>15</td>
<td>Advocacy</td>
<td>A6</td>
<td>F</td>
<td>Face-to-face</td>
<td>Metropolitan</td>
</tr>
<tr>
<td>16</td>
<td>Advocacy</td>
<td>A7</td>
<td>F</td>
<td>Face-to-face</td>
<td>Metropolitan</td>
</tr>
</tbody>
</table>
As this study addresses multiple research questions and topics, the remainder of the results section is reported in three sections:

- **Section 1** outlines stakeholders’ responses to the pre-market assessment of medical devices reform options, addressing research question four of the thesis.
- **Section 2** outlines stakeholders’ responses the regulation of therapeutic goods advertising reform options, addressing research question four of the thesis.
- **Section 3** describes stakeholders’ recommended criteria for the pre-market assessment of medical devices, and medical device advertising, addressing research question five of the thesis.

### 5.3.2 Section 1: The TGA’s proposals to reform the pre-market assessment of medical devices

The following section presents a synthesis of participant responses relating to the TGA’s proposed changes to the pre-market assessment of medical devices in Australia. All of the proposals presented to participants were considered for adoption by the TGA, so feedback was requested on the overall support, key benefits, and key limitations of each proposal. Key themes identified for each proposal are outlined in Table 5.2, including the key advantages and disadvantages of each proposal, as well as any extra conditions that should be considered as part of the proposed option.

<table>
<thead>
<tr>
<th>Proposal</th>
<th>Key Advantages</th>
<th>Key Disadvantages</th>
<th>Extra Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reform Proposal 1</td>
<td>Less duplication, fewer regulatory resources.</td>
<td>Lack of Australian context in review of devices.</td>
<td>Clear explanation of credentialing process for external regulators.</td>
</tr>
<tr>
<td></td>
<td>Faster access to medical device and services.</td>
<td>Quality of external regulators.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>May impede access to decision-making documents.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference in risk-classification between Australia overseas.</td>
<td></td>
</tr>
<tr>
<td>Reform Proposal 2</td>
<td>Increase transparency of TGA processes and decision making.</td>
<td>Requires increased resources for TGA.</td>
<td>Qualification on type of modification that would need to be registered.</td>
</tr>
<tr>
<td></td>
<td>Increase information about device modifications.</td>
<td>Requires increased resourced for industry.</td>
<td>Qualification for when a variation becomes an entirely new device.</td>
</tr>
<tr>
<td></td>
<td>Increase ease in identifying similar products from same sponsor.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5.2 Stakeholder perspectives on the proposals for reform to the pre-market assessment of medical devices
### Table 5.2 continued

<table>
<thead>
<tr>
<th>Proposal</th>
<th>Key Advantages</th>
<th>Key Disadvantages</th>
<th>Extra Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reform Proposal 3</strong></td>
<td>Increase ease of access to ARTG data for consumers and clinicians.</td>
<td>Increase use of resources for industry.</td>
<td>Increase community awareness of ARTG entry numbers and website.</td>
</tr>
<tr>
<td></td>
<td>Increase transparency of TGA processes and decision making.</td>
<td>Lack of community knowledge about ARTG.</td>
<td>Include expiry date of ARTG entry number on labelling.</td>
</tr>
<tr>
<td></td>
<td>Increase visibility of approved use of device compared with actual use in practice.</td>
<td>Entry numbers may not be presented if device is on-sold to community provider.</td>
<td>Prevent separation of ARTG number from device - may not be available at point of service.</td>
</tr>
<tr>
<td><strong>Reform Proposal 4a</strong></td>
<td>Increase transparency of TGA processes and decision making.</td>
<td>Does not prevent inappropriate use of device in practice.</td>
<td>Demonstrate utility of device for its intended purpose.</td>
</tr>
<tr>
<td></td>
<td>Inform consumers and clinicians on best-use for new devices.</td>
<td>Regular consumers unlikely to access ARTG.</td>
<td>Understandable to lay persons.</td>
</tr>
<tr>
<td></td>
<td>Precedent from prescription medicine industry (AusPARs).</td>
<td>Opens review decisions to criticism over quality of evidence considered.</td>
<td>Applied retrospectively.</td>
</tr>
<tr>
<td><strong>Reform Proposal 4c</strong></td>
<td>Provides reason for lack of access to devices approved internationally.</td>
<td>Requires increased resources for TGA.</td>
<td>Applied retrospectively.</td>
</tr>
<tr>
<td></td>
<td>Identifies quality control issues in companies with repeated rejections.</td>
<td>Regular consumers unlikely to access ARTG.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increases transparency of TGA processes and decision making.</td>
<td>Allows companies to exploit application system, dispute rejections visibly.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alerts neighbouring countries to products not up to standard.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Proposal 1: Allow Australian companies that manufacture low-risk devices to be certified by an independent third party instead of the TGA. This option would also involve a process of certifying third party assessment bodies (within Australia and overseas) for competency.

Proposal 2: Amend the way in which medical devices are registered on the ARTG by requiring every model or variation of a device to be listed under the same ARTG entry.

Proposal 3: Enhance the ability to identify devices that have been approved by the TGA for supply in Australia by having the ARTG identifier on the label.

Proposal 4a: Increase the information contained in ARTG registry entries to include information about the basis upon which a device is allowed onto the market, as well as the evidence that was considered in reaching this decision.

Proposal 4b: Which kinds of devices should option 4a be applicable to?

Proposal 4c: Publish information online pertaining to the reasons for ARTG applications that are rejected.
5.3.2.1 Proposal 1: Allow Australian companies that manufacture low-risk devices to be certified by an independent third party instead of the TGA. This option would also involve a process of certifying third party assessment bodies (within Australia and overseas) for competency

Participants shared majority in-principle support for Proposal 1 (n = 11/16), which aimed to remove TGA conformity assessment requirements for Australian manufacturers of low-risk devices. This was viewed as a cheaper and faster option for getting devices on the market, due to the removal of duplication in regulatory processes. It was noted that: “[the] cost disadvantage to require new technologies in Australia to be separately and completely certified in Australia, [will] just be reinventing the wheel for a very small market.” [R3] One participant highlighted a precedent from the prescription medicines industry, whereby an evaluation of a drug by a recognised regulator is often considered during the Australian assessment of the same drug. This reduces the regulatory burden associated with approving the drug for use in Australia, and could be applied in a similar way for devices. While there was in-principle support for Proposal 1, this support was dependent upon whether the TGA could address the key limitations of this proposal.

The most significant disadvantage identified by participants was limited trust in the third party regulator. One participant highlighted concerns with European Commission (CE) certification processes specifically, particularly in the complementary medicines industry, and indicated that similar issues may also exist in the certification of medical devices. Comparatively, participants placed greater trust in the Food and Drug Administration’s (FDA) process for certifying medical devices in the United States. However, context was key; it was suggested that any international regulator considered in this proposal, including the FDA, should be required to pass: “a very transparent process of how are they defining a regulator that has a similar standard to Australia, how are they monitoring these processes, and how sure [we are] that the off-shore regulator is as good, if not better than, or a higher standard than Australia.” [A7]

One participant also questioned whether the potential exists for this proposal to impede or diminish the value of Proposal 4a (that is, to increase the information contained in ARTG registry entries to include information about the basis upon which a device is allowed onto the market, as well as the evidence that was considered in reaching this decision). It was questioned how, or if, external conformity assessment procedures may affect the publication of decision-making documents for medical devices given that the conformity assessment would not be conducted by the TGA.
5.3.2.2 Proposal 2: Amend the way in which medical devices are registered on the ARTG by requiring every model or variation of a device to be listed under the same ARTG entry

Under the current system for including a medical device on the ARTG - with the exception of class III devices, active implantable medical devices, and class IV in-vitro devices - multiple devices entering the register can be included under the same group of devices if they have the same sponsor, manufacturer, risk classification, and Global Medical Device Nomenclature (GMDN) code. Proposal 2 aimed to amend this process, by requiring devices applying for registration to be itemised under the same ARTG entry, so that modifications and different models of devices can be identified easily.\(^{(132)}\)

There was majority support for Proposal 2 (n = 14/16). One participant required further qualification of the manner in which the proposal would be carried out, and one participant did not offer an opinion. Participants highlighted the increased transparency of ARTG registered devices, and additional information relating to devices as most significant benefits to Proposal 2. In terms of consumer advocacy: “It would make it a lot easier for people [in advocacy], who are trying to track these devices and their use, to understand what is actually being registered, what’s off the list and what’s in use in the community as a result of that.” [A7] It was noted that the current arrangements for registering devices on the ARTG make it difficult to identify similar classes of device, and that: “this [proposal] wouldn’t completely overcome that problem but it would certainly be a step in the right direction.” [S2]

Participants were mindful of the increased costs to both industry and the TGA associated with implementing this proposal: “we do need to think about the costs of regulation, not only the benefits of them but what sort of imposition they put on.” [S2] An important consideration was also raised, regarding the differentiation between changes to a device and the requirements for registering changes as a completely new device: “The problem comes when you get to the edge of all this, when does a new model or variation become a new device rather than a variation of an existing device? [...] If something starts off as a thermal camera but it becomes a thermal camera with a biopsy device, then it is a totally different kettle of fish.” [R3]
5.3.2.3 Proposal 3: Enhance the ability to identify devices that have been approved by the TGA for supply in Australia by having the ARTG identifier on the label

As with Proposals 1 and 2, the majority of participants were supportive of Proposal 3 (n = 14/16), which aims to enhance the visibility of the TGA's regulatory processes by labelling registered devices with an ARTG identification number. Participants noted increased visibility and transparency of the regulatory status of devices listed on the ARTG as key benefits of this proposal. It was also suggested that this would allow healthcare practitioners to more easily identify and seek information on medical devices, and may also prompt consumers to access information about registered devices. On this issue, one breast cancer researcher commented that: “patients, particularly nowadays, are much more inquisitive than they previously were, and they have every right to ask ‘has something been certified?’ It would be reassuring to be able to provide that information immediately to the patient.” [R4] Therefore, a proposal aimed at providing the ARTG registration number for devices could conceivably act as a cue to action for a consumer to look for further information about the device online. However, this point was rebutted: “the person in the street has no idea what the ARTG is or what it means, but I do think that at least you can say to someone, ‘look, have you got the information on that device?’… and at least we can identify if it is or it isn’t [registered].” [S2] It was suggested that an initiative to increase community awareness of the ARTG would be necessary for this proposal to have an effect on improving patient access.

Aside from the limited community knowledge of the ARTG, the limitations of this proposal (presented in Table 5.2) were deemed to be minor in comparison to the proposed benefits. However, one key consideration was raised about this proposal. It was suggested that processes would need to be in place to ensure that the ARTG entry number is made available to consumers at the time a device or service using a device is purchased. This effectively highlighted the potential risk, in that “the machine of course can be on-sold [in the community], and the information may or may not travel with it.” [S2] This issue is less concerned with high-cost medical devices that hold a well-established role in clinical practice, but may often present as a problem in the direct-to-consumer market in which devices are purchased or accessed in the community without the involvement of a healthcare practitioner. It was suggested that the proposal could be further improved by adding the expiry date for ARTG certification on the label of the device.
5.3.2.4 Proposal 4a: Increase the information contained in ARTG registry entries to include information about the basis upon which a device is allowed onto the market, as well as the evidence that was considered in reaching this decision

As discussed earlier, the first three participants could not respond to this question due to a change in the interview schedule. Of those participants who could respond, there was unanimous support (n = 13/13) for Proposal 4a. Participants suggested this proposal would increase the transparency of TGA decision-making, which will allow clinicians, technologists and patients to make better-informed decisions. It was also noted that increasing transparency in this manner may open the TGA to criticism over the quality of evidence considered in the decision making process, but that this should not detract from the additional benefits of improving transparency: “It’s wide open to criticism because it’s a subjective measure of what’s sufficient, and you could say there is mountains of evidence or will it be a one liner, so that’s the criticism I would have of that.” [R3]

One participant highlighted a precedent from within the prescription medicine industry to expand the information presented on regulatory decisions, namely the successful Australian Public Assessment Reports (AusPAR) initiative. An equivalent initiative intended to broaden the information provided on registered medical devices in the same vein as AusPAR would inform consumers and clinicians about the best use for new medical devices, particularly those that are not yet established in practice.

A key limitation of this option was the increase in resources required by the TGA, including time, money and staff. It was also suggested that the average consumer is unlikely to visit the ARTG website to access this additional information: “I think it is useful but the public are not going to be the people who access this website. I doubt that many members of the public are aware of what the TGA does and what its role is, and that this information is available.” [S2] However, it was noted that this information would be valuable to consumer advocates who act on behalf of consumers, and to employ knowledge translation strategies to make the information about decisions more accessible to consumers where deemed necessary:

“I don’t know if your average Joe public consumer is going to jump onto the ARTG whether, you know, they come across a medical device, but it is certainly important for NGOs working in this space to be able to access that kind of information on efficacy for basic consumer protection.” [A7]
5.3.2.5 Proposal 4b: Which kinds of devices should option 4a be applicable to?

For Proposal 4b, participants were given a choice between five types of devices that Proposal 4a may be applied to. As with Proposal 4a, only 13 of 16 participants were asked this question. The majority of participants indicated a preference to have the additional information approved for all medical devices (n = 7/13), while a minority indicated support for high risk devices only (n = 1/13), high risk and “interesting” devices only (n = 1/13), and devices applying for ARTG registration only (n = 1/13). There was no support indicated for only devices that are already listed on the ARTG (n = 0/13). The remaining three participants had no opinion. In this context, an “interesting” device is defined as technology that is new or innovative. Beyond this broad definition, no further clarification on what constitutes an “interesting” device has been offered by the TGA. Stakeholders suggested that identifying the evidence considered during the certification process for devices will help inform consumers and clinicians when deciding whether to use or recommend a breast imaging device.

5.3.2.6 Proposal 4c: Publish information online pertaining to the reasons for ARTG applications that are rejected

Participants expressed majority support for the publication of decisions for rejected devices (n = 15/16). The most commonly noted benefit of Proposal 4c was to provide justification for why devices available internationally are not also available in Australia. This point was illustrated with examples from the prescription medicine industry:

“It has often been an issue, at least for years, at the European level and at the Australian level, not to give information on drugs which are not approved, and it’s really what we want as well, because otherwise it’s very misleading for people that say “[why] isn’t [the drug] approved in Australia”, and the drug has been rejected for maybe safety reasons, but nobody ever knows.” [R1]

It was suggested that this information would be valuable for clinicians and consumer advocacy groups that are regularly faced with queries about devices that are not available in Australia. Furthermore, participants suggested this option would increase the transparency of the TGA’s decision-making process, which would have the added benefit of highlighting quality control issues in companies that are repeatedly rejected for certification. Participants also noted that identifying these issues may also be useful for regulatory bodies in neighbouring countries, such as New Zealand. This proposal shared the same limitations as Proposal 4a. In addition, one participant suggested this may also allow companies that have been repeatedly rejected on reasonable grounds to publicly dispute these rejections through various media platforms, increasing time and resources needed.
5.3.3 Section 2: The TGA’s options to reform the advertising arrangements for medical devices in Australia

The following section presents a synthesis of participant responses relating to the TGA’s options to reform the regulation of medical device advertising in Australia. Perspectives were sought on which of the three options was seen as the most suitable alternative to the current regulatory system. Key themes identified for each option are outlined in Table 5.3.

Table 5.3 Stakeholder perspectives on options to reform advertising regulations for medical devices

<table>
<thead>
<tr>
<th>Reform Option</th>
<th>Key Advantages</th>
<th>Key Disadvantages</th>
<th>Extra Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reform Option 1</td>
<td>Increase consumer confidence in advertising claims. Impetus on regulator, not consumer, to discern accuracy of advertising claims. Standardised process adds consistency to regulatory decisions. Advertisements have less ability to present false or misleading information.</td>
<td>May slow down access to new devices. Including internet advertising may be unachievable due to off-shore hosting of websites.</td>
<td>Requiring approval for high-risk devices only will save resources. Administration would have to be by the TGA, not industry.</td>
</tr>
<tr>
<td>Reform Option 3</td>
<td>Less bureaucratic than Option 1. Faster access to medical device and services.</td>
<td>Open to exploitation – companies can re-register under new trading name. Highly resource intensive. Difficult to define “repeat offenders”. Less impetus to regulate. Damage is done before audit will identify repeat offenders.</td>
<td>Clarification of how new companies will be impacted by this system. Tenacity of auditing.</td>
</tr>
</tbody>
</table>

Option 1: Extend the Australian pre-market approval process for therapeutic goods advertising to include medical devices and internet websites.

Option 2: Remove the current Australian pre-market approval system for therapeutic goods advertising in favour of an efficient monitoring system.

Option 3: Develop a new regulatory system in which only “repeat offenders” will be required to submit advertising for approval by the TGA.
5.3.3.1 **Option 1: Extend the Australian pre-market approval process for therapeutic goods advertising to include medical devices and internet websites.**

Currently, the approval process for therapeutic goods advertising material in Australia is limited to non-prescription, pharmacist-only medicines. Option 1 aimed to expand the current system to include medical devices. Under this arrangement, all medical device sponsors would be required to submit their advertising material to the TGA for approval prior to promotion in Australia.

Of the proposed options, participants shared a preference (n = 11/16) for Option 1. A pre-market approval scheme was thought to reduce the likelihood that advertisements could present false or misleading information to the general public. Harms associated with the misleading advertisement of medical devices were highlighted by participants:

“I think that it is absolutely essential to recognise the potential public health harm associated with misleading advertising of therapeutic devices, such as devices used commercially for breast imaging, is akin to the potential harm associated with misleading advertising of non-prescription medicines… It follows that there is an undeniable public health benefit to regulating the advertising of imaging devices through a pre-approvals process.” [A7]

Participants acknowledged the current approvals process for pharmacist-only medicines as a precedent for establishing an approval process for medical device advertising: “We have an existing precedent for non-prescription medicines that recognises the strong needs for appropriate advertising and processes by which advertising can be pre-vetted; that same recognition should apply to devices.” [A7] Consumer advocates also noted that this option places the responsibility of determining the accuracy of advertising claims on a regulator instead of consumers. It was suggested that this option would lead to the greatest increase in consumer confidence of advertising claims.

The main disadvantages of Option 1 identified by stakeholders were the increased costs and resources required for the expanded pre-approvals process. The associated costs would be carried by companies seeking approval for a device, but TGA would also require an increase in resources to carry out the approval process. One participant also questioned how a pre-approvals process would affect promotional material for government-funded health services, such as a national breast screening campaign. Finally, it was suggested that sole-practitioners promoting breast imaging devices may not be members of a relevant industry self-regulatory body, and therefore may not be aware of their obligation to submit their advertising material for pre-approval.
The general opinion towards Option 1 was summarised by Participant A1: “My doubt is not whether this is the best arrangement, my doubt is about the extent to which it can be successfully introduced.” [A1] A more nuanced approach to considering this option was provided by Participant A7, who suggested that the TGA’s risk-based approach to regulation could also be applied to a pre-market approval system for advertising material:

“Whether pre-approval should be extended to all devices is another matter; I can see that there are devices on the ARTG that should not be part of this process, the lower risk devices in particular, and so I think it would be reasonable to extend the pre-approval requirement automatically to high risk devices, and to ‘interesting’ lower risk devices. This is a feasible threshold, although it would stand or fall upon the process by which the TGA determined a lower risk device to be ‘interesting’.” [A7]

5.3.3.2 Option 2: Remove the current Australian pre-market approval system for therapeutic goods advertising in favour of an efficient monitoring system.

Option 2 aimed to remove the current pre-market approval system for non-prescription medicine advertising, in favour of a post-market monitoring system coupled with increased penalties for breaches of advertising regulations. This system would include non-prescription medicines, CAMs, and medical devices. There was very little support for this option (n = 3/16), reflecting a lack of trust in the TGA and industry to implement such a system effectively. Participants noted examples of ineffectiveness in the self-regulation of advertising in the CAM industry:

“Industry self-regulation of advertising in any sector can generally be considered a failure because it is fundamentally flawed by conflict of interest. It is reasonable to say that public health will never be paramount in a body set up to promote the commercial interests of its members. Alcohol advertising is a primary example.” [A7]

Participants noted three advantages to Option 2. It was suggested that a monitoring system would decrease the time-to-market for companies to broadcast their advertising for new therapeutic goods, and may prove to be an appropriate deterrent against false and misleading advertising if coupled with appropriate increases in penalties for misconduct. This strategy would reduce the immediate resource requirements for pre-approval for both the TGA (by removing their responsibility to pre-approve advertisements) and for industry bodies (by removing the fees required for TGA approval). However, if the monitoring system were to be administered by the TGA, it would require the same volume of resources as a pre-approval system, except that it would be applied retrospectively, as “In many ways that’s just
as difficult as Option 1. So if you’re going to put in the procedures for Option 1 I’d rather do it before the ad ever got out, than try to catch it after it went out, because to me it requires the same sort of workload." [A1]

5.3.3.3 **Option 3: Develop a new regulatory system in which only “repeat offenders” will be required to submit advertising for approval by the TGA.**

Option 3 offers an alternative, risk-based approach to the current pre-approvals process, in which all advertisements would be entered onto a central database. An audit of the database would identify companies that repeatedly breach advertising regulations. Companies found to repeatedly breach regulations would then be required to gain pre-approval for all future advertisements. Only one participant indicated support for this option (n = 1/16), while also conceding that it may not solve some issues relating to breast imaging devices: “I am still not sure if it’s able to overcome that issue of, really, the difference between sponsors of devices and the people who may actually provide services and advertise out in the community.” [S2] The only advantage of this proposal was limited to removing “some of the bureaucratic process which may prevent ethical people from advertising.” [S3]

There are a number of disadvantages and qualifications with Option 3. The first and most commonly reported disadvantage of this option is that it is open to exploitation. Smaller companies can re-register under new trading names relatively easily, in order to void their ‘repeat offender’ status. Participants also desired clarification around how the term ‘repeat offender’ would be defined, "What do you mean by ‘repeat offenders’? As far as I know, all drug companies in Australia are repeat offenders if you take a 10 year period" [R1]. The final major limitation was highlighted by Participant S5:

“It comes back to the appetite for doing the audit. So when you have a positive approval system then it has to happen, when you have more negative or retrospective sort complaints or problem identification, then … often the appetite for actually doing the audit … fades over time and so it’s never done, and then you have a database of millions of ads sitting there and nobody has ever looked at them.” [S5]
Section 3: Recommended criteria for the pre-market assessment of medical devices, and medical device advertising

The results in this section present a synthesis of participant responses regarding criteria that participants deem essential to the assessment of emerging breast imaging prior to market, and how their advertising material should be regulated. The secondary aim of this section is to identify any significant issues relating to the regulation of these devices that were potentially overlooked in the TGA reform process.

Characteristics of devices that should be considered during the pre-market assessment of breast imaging devices

Themes identified in relation to participants’ perspectives on the pre-market assessment of medical devices are presented in Table 5.4. These include themes of safety, comparative safety, efficacy, comparative efficacy, application in practice and cost-effectiveness.

Safety was conceptualised by participants in a number of ways, including both physical harm and psychological harm. Physical harm was seen to play an essential role in the pre-market assessment of medical devices, as: “you don’t want to be electrocuted by it… that it doesn’t have asbestos in it... that it doesn’t give off any noxious substances. That type of thing. Just purely the technical specifications of the device… the minimum thing it’s got to be actually safe in terms of its function” [A1]. However, a greater emphasis was placed on the safety of the device due to its efficacy, which was also identified as a key criterion for pre-market assessment, including the ability of the device to produce false negative and false positive results:

“Sorry before you go on this whole concept of risk, I think that [concept] just needs to be reconsidered, and ask the people who are likely to use these things if they consider getting a false/negative or false/positive… is going to impact on their quality of life. If you suddenly find out you’re pregnant and you’re not, or suddenly discover you’ve got breast cancer and you haven’t, that has a huge risk, that is not low risk.” [A6]

Assessment of the use of a device in practice was seen as an important criterion for the evaluation of medical devices beyond its registered use on the ARTG. In the case of breast cancer imaging devices, they are often advertised for a particular clinical use that is different to its registered use on the ARTG. This issue has implications for patient safety, as:

“whilst the device itself may not, in general, do a lot of harm if it is advertised for the purpose for which it has been approved, it’s how that’s used in
practice is where we really get into trouble, and … we can't bring people under any professional codes of practice when it has been used by non-health professionals.” [S2]

The themes of relative efficacy and relative safety were also seen as important factors that should be considered during the pre-market approval of devices. These themes shared the same fundamental principles as the themes of safety and efficacy, but expanded upon them to include comparisons with existing devices. How well the safety and efficacy of a new device compares to an existing device was seen as paramount to ensuring that devices work well, but also so that patients do not access a device which is not as good as something already on the market. Cost-effectiveness was the final characteristic of importance to stakeholders; however, this was only identified by in small minority of interviews. This theme was referenced in terms of both out-of-pocket costs, and government spending for new technology.

Table 5.4  Illustrative quotes demonstrating themes identified from participants regarding the pre-market approval of devices

<table>
<thead>
<tr>
<th>Theme</th>
<th>Illustrative quote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>“Harm can be from a variety of ways, it’s not just physical harm. It could also be some sort of psychological harm, either about the way that testing is done or the way the device is used or implanted or deployed in some way as well.” [A2]</td>
</tr>
<tr>
<td></td>
<td>“I can see why it might be a lower risk assessment because obviously it’s not invasive, but it’s got to have the full range of risks assessed, and so to me effectiveness has to be, you know… ‘does this device actually, on an evidence base, do what it claims to do’ has got to be a criterion.” [A6]</td>
</tr>
<tr>
<td></td>
<td>“Just purely the technical specifications of the device, which is of course different from whether it’s harmful or not if misused. But the minimum thing it’s got to be actually safe in terms of its function.” [A1]</td>
</tr>
<tr>
<td>Application in Practice</td>
<td>“There is a real schism, particularly with these breast imaging devices, between intended purpose, actual use and advertised use, and somebody needs to follow that up at some point to make the inclusion onto the ARTG a regulated and useful and meaningful thing.” [A7]</td>
</tr>
<tr>
<td></td>
<td>“The TGA look at the safety of the machine for a purpose, what they are unable to do is to look at how that will be used in practice… they look at the technical data about a machine and any evidence from trials, but how something is used under trial conditions and how something is used out in normal clinical practice - or even in the case here of non-clinical practice - is where it gets really tricky.” [S2]</td>
</tr>
<tr>
<td></td>
<td>“The TGA takes the device description for inclusion onto the ARTG at face value - the intended purpose that the sponsor nominates the device for - but there is no follow-up of [the application of] the device.” [A7]</td>
</tr>
<tr>
<td>Cost-Effectiveness</td>
<td>“I think the government should put a lot more emphasis on the necessity to prove efficacy and safety, but actually efficacy, the cost benefit that things are not just a waste of resources… I think we’ve wasted a lot of government money really, over the years, on fashion.” [S1]</td>
</tr>
<tr>
<td></td>
<td>“You are going to drain the population of money if they think that this is going to be something which will find a cancer that other systems can’t find, and they will go out and spend good money if there is good marketing, [but] it might … take some years for people to realise that maybe it’s not going to do what it’s cracked up to do.” [R3]</td>
</tr>
</tbody>
</table>
Table 5.4 continued

<table>
<thead>
<tr>
<th>Theme</th>
<th>Illustrative quote</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>“I would expect that it was going to be fairly accurate, and that there would be some processes in place to follow up after screening or make sure that people got results and understood the results... all of the interpretation around it.” [A2]</td>
</tr>
<tr>
<td></td>
<td>“It’s essential before any screening test is allowed [onto the market] it needs to be able to identify a disease before a pre-disease state, and that you can treat this pre-disease state in a better way than if you diagnosed it after.” [R1]</td>
</tr>
<tr>
<td></td>
<td>“What needs to be absolutely thoroughly assessed is the image quality, the diagnostic efficacy - and by diagnostic efficacy I mean sensitivity and specificity.” [R4]</td>
</tr>
</tbody>
</table>

**Comparative Efficacy**

| “The rigour is their relative performance against what is being used at the moment, and that it doesn’t matter how safe they are, they could harm someone by not working as well as whatever’s on the market.” [A1] |

| “You need determine whether it has additional benefits to what we already have, so we have mammography, ultrasound, MRI. If it can’t match in performance sensitivity, or really accuracy not just sensitivity, accuracy then it really has no place.” [S3] |

**Comparative Safety**

| “The other aspect that needs to be thoroughly assessed is, is it truly non-invasive, is it truly safe and compare that with the risks of mammography and X-rays.” [R4] |

| “You’d have to [compare with] what test it was going to replace... and its cost effectiveness compared to [a comparator] and its safety, so its likelihood of complications and its likelihood of tumour recurrence.” [S1] |

5.3.4.2 Characteristics of breast imaging device advertising that should be assessed by an independent regulator

As with the pre-market assessment of medical devices, the themes of safety and efficacy were highlighted by participants as being of key importance for medical device advertising. There were, however, some minor differences between how these concepts were conceptualised for advertising material as opposed to the pre-market registration of medical devices. In particular, it was suggested that promotional material that may dissuade women from accessing a conventional diagnostic test should also be considered harmful:

“The use of a test such as thermography to preclude people from having mammographic screening is a harm, even though the thermography may not be actually physically doing any harm in its execution, as the omission of a reasonable test is a harm in itself.” [S5]

Four additional areas of importance to stakeholders for advertising regulations were derived from the data (Table 5.5), including comparative benefits, extraordinary claims, change in practice, and comparative efficacy. The theme of ‘comparative benefit’ was conceptualised as a balance of the advertised advantages and disadvantages of an imaging device, compared to
an appropriate comparator device or test. This theme was commonly referenced in relation to emerging breast cancer imaging devices, as they are often promoted with selective evidence that does not adequately reflect the whole evidence base for their use in breast imaging. In the same manner, ‘comparative efficacy’ was also seen to be an important aspect of medical device advertising that should require pre-market approval: “Obviously we have got to sell the product, you’ve got to push it out there. You will hear about the advantages, but those advantages need to be put into some sort of context by comparing it with the gold standard.” [R4]

Participants referred to ‘extraordinary claims’ in relation to advertising material concerning significant disease, or that could affect patients’ health in a significant way, for example, by reducing breast-cancer related mortality. The similar theme of ‘change in practice’ occurs when the advertising material for a new imaging device dissuades people from accessing another established imaging tool, such as mammography, thereby changing the standard clinical pathway of care. These themes were viewed by participants as relevant to clinical practice, as they directly affect patient decision making around the use of a particular screening or diagnostic tool.

<table>
<thead>
<tr>
<th>Theme</th>
<th>Illustrative quote</th>
</tr>
</thead>
</table>
| Safety  | “Look, you can have your breast imaged without having compression done, and that’s a lot more comfortable. Well sure it is, but what it doesn’t tell you is that we’ve got no idea on the relative false-positive false-negative rate compared to mammography, and that’s dangerous.” [A1]  
“The serious issue about this has always been that, while a device may not cause acute injury, the belief that the device is effective can cause long term injury, in that people put faith in the outcome of whatever that device does, which is mislaid.” [S1]  
“If consumers are misled by false advertising for devices claiming benefits to breast cancer detection, this could lead to widespread harm: missed cancers and delayed diagnoses, or false alarms requiring unnecessary further investigation.” [A7] |
| Efficacy| “It’s got to be that the claims are accurate, so that in terms of the imaging devices, that yes they do detect cancer without having a high rate of false positives.” [A6]  
“Efficacy is the main reason why you would be doing this test, I guess if there were some of the more niceties around it like warmth and comfort or something, characteristics like that, which are really window dressings, trimmings on it, but they are not the core functions.” [A2]  
“If they were advertised as a breast imaging device that take a photo of heat spots on your breast, there is no problem … The problem is if they are advertised as “it will take heat images, pictures of your breast and it’s been shown to detect breast cancers or to be equally effective to mammography or is a breast screening device”, that is where it is misleading.” [S2] |
### Table 5.5 continued

<table>
<thead>
<tr>
<th>Theme</th>
<th>Illustrative quote</th>
</tr>
</thead>
</table>
| **Comparative efficacy** | “I actually think that the device has got to be compared with, you know, devices that do the same thing. I mean you wouldn’t want to put onto the market something that was so inferior to something that’s already on the market that, you know, the only thing that could sell it was a slick advertising campaign.” [A1]  
“If they claim that it’s more effective than a mammogram… you have got to be able to judge within the framework of an ad - which is clearly promoting the best aspect of these devices - that that is what [the device can] actually do.” [A6]  
“If it’s being marketed as a diagnostic test or as a therapeutic device, then it needs to be compared with current modalities that it’s going to replace.” [S1] |
| **Comparative benefits** | “Most of the advertising issues are issues of omission rather than commission, because if you frankly say something does X and it doesn’t then it’s too easy to counter that, but if you only play up the benefits… without talking about the risks or without talking about the relative benefit compared to the market leader, then you’re not being fully honest.” [A1]  
“Obviously we have got to sell the product, you’ve got to push it out there. You will hear about the advantages, but those advantages need to be put into some sort of context by comparing it with the Gold Standard.” [R4]  
“If they are saying that better than mammograms for say woman over 50 then I would want to know that it’s been confirmed by some sort of scientific analysis.” [A6] |
| **Change in practice** | “If the medication or treatment stops people doing the usual treatment or the usual process, that also would need to be defended.” [S5]  
“The use of a test such as thermography to preclude people from having mammographic screening is a harm, even though thermography may not be actually physically doing any harm in its execution. The omission of a reasonable test is a harm in itself.” [S5]  
“What I understand is the medical screening tests are considered low risk, and from my perspective it becomes an issue especially if they are advertised as an alternative to better screening, and so it means that in this, with this perspective they are not low risk anymore, because they can detract people, consumers, from getting a better test.” [R1] |
| **Extraordinary claims** | “If a medication [or device] say, for example, says it can cure cancer, that is an extraordinary statement, and it can’t be left without defence.” [S5]  
“[I] would really be careful in making sure that claims are not implying, for standard consumers, that this device can save lives if they have not been shown to do that, or … distracting people to get the correct advice.” [R1] |
5.5 Discussion

Through a transparent consultation process, the TGA has sought to facilitate public discussion and engagement around proposed regulatory reforms to both the pre-market approval process for medical devices and therapeutic goods advertising in Australia.\(^{(131, 132)}\) The present study aimed to translate the knowledge gained in previous chapters into recommendations that could contribute to this policy decision-making process.\(^{(18, 255)}\) Rather than devise recommendations based on the research findings alone, the results of prior research presented in this thesis were disseminated to stakeholders within breast cancer research, patient advocacy and screening. Stakeholders highlighted a number of benefits and limitations in the proposed reforms, as well as a range of conditions or considerations that aim to increase the rigour of regulatory actions.

The first proposal to reform the pre-market assessment of medical devices aimed to allow the TGA to accept FDA clearance for devices applying for low-risk registration on the ARTG, as proposed in the 2010 medical devices reform consultation.\(^{(132)}\) While there was majority support for this proposal, there is an additional benefit that was not identified in stakeholder interviews. In the case of emerging breast cancer imaging devices, accepting FDA approval would have prevented these devices from entering the Australian market in low-risk categories. In the United States, thermography and electrical impedance devices are classified as Class III, high-risk devices, and can only be accessed via prescription if used for breast cancer screening or diagnosis.\(^{(263)}\)

Extending the pre-approval of advertising to include medical devices was the most favoured option to reform the regulation of therapeutic goods advertising. Participants indicated that this option provided the greatest amount of consumer protection from false or misleading advertising. However, it was acknowledged that this would incur a significant increase in resource allocation and financial costs to both the industry and TGA. Concerns were raised about the capacity of the TGA, or any individual body, to pro-actively screen advertising material for all therapeutic goods prior to broadcast or publication. In short, there was little doubt that this was the best option to improve consumer safety, but there was no clear strategy for how this option could be implemented in practice. Instead of applying a broad-stroke approach to advertising pre-approval, a potential solution may be to limit the pre-approval process to higher-risk devices, significantly reducing the regulatory burden on both government and industry. In contrast, the option to remove the pre-approval process for advertising in favour of active monitoring and industry self-regulation was not viewed favourably. The limitations of industry self-regulation have been highlighted by the rise in complaints raised against the Australian medical devices industry since 2007.\(^{(116-118, 252)}\)
Given the track record of advertising self-regulation in the CAM industry, and increasing evidence of deficient self-regulation in the medical devices industry, participants did not have confidence that this arrangement would be effective at preventing misleading advertising claims.

The second aim of this study was to determine the views of stakeholders on how emerging breast imaging devices and their advertising material might be assessed outside of the reform options, thus highlighting any limitations or gaps in the TGA’s reform process. There was a notable difference between stakeholder views on the characteristics of imaging devices that should be assessed prior to ARTG approval, compared to the current level of assessment required of devices. While stakeholders viewed the efficacy and effectiveness of a device as essential requirements for pre-approval, this type of evidence is not considered in the TGA’s pre-market approval process for non-invasive medical imaging devices. Manufacturers of designated Class IIa devices are only required to provide substantial evidence to justify the safety of a device for an intended purpose. The TGA may request technical documentation supporting a Class IIa device, but does not assess how well it can achieve its intended purpose in terms of clinical efficacy or effectiveness.

Along with the themes of efficacy and effectiveness, stakeholders also valued the consideration of comparative evidence during pre-market approval; specifically, the comparative safety, efficacy, and benefit of a new device compared to an existing technology. These factors are of relevance to the case of breast cancer imaging devices, as these devices are often advertised directly towards consumers as a suitable replacement or alternative to conventional breast imaging modalities. These comparator devices - conventional X-ray mammography, magnetic resonance imaging, and B-mode ultrasonography - have all been approved for Medicare Benefits Schedule (MBS) funding in Australia for the purposes of breast cancer screening and diagnosis in specific populations, and as such have undergone a full HTA. As many stakeholders highlighted, the omission of a rigorously-assessed and widely adopted device in favour of a low-risk device that was not assessed for efficacy or effectiveness prior to market registration poses safety risks for consumers who choose to use unproven devices.

The principle behind the use of comparative evidence to assess new health technology is a major component of the pre-market approval process in the United States. In a similar manner to Australia, medical devices being considered for market approval in the United States of America (USA) are subject to a risk-based assessment process, based on the perceived harms a device may pose to a patient. Moderate-risk devices in the USA are assessed for market approval through the 510(k) process, in which they are required to prove substantial equivalence to an existing product in order to gain
market approval.\textsuperscript{(265, 266)} However, the failure of implantable prostheses has highlighted significant problems with the use of substantial equivalence to regulate new medical devices, as devices use as comparators may not have been assessed for efficacy prior to market.\textsuperscript{(3, 267)} In this regard, Australian regulatory policy could benefit from the consideration of comparative evidence for premarket approval, but under the strict caveat that the comparator device has been assessed for efficacy and safety appropriately, and that the appropriate level of comparative evidence for new devices is presented. However, reforming the premarket approval process in this manner will not ensure patient safety if the present system for risk-classification is retained.

The risk-classification that determines the level of pre-market evaluation a medical device faces during conformity assessment is determined by the manufacturer of the device when applying for ARTG certification.\textsuperscript{(140)} However, the intended use of a listed device on the ARTG is often different from the practical application of the device. For example, the intended use of one alternative breast imaging device currently listed on the ARTG, as defined by the sponsor, states that the device:

“… is intended to document lesions as identified during a clinical breast exam by producing an accumulated image for each of the areas that contain a lesion. The device should not be used for clinical decision-making.”(ARTG entry number141616)

However, on the manufacturer’s website it states that the device:

“… is a unique digital sensing device that assists a physician or other trained healthcare professional in screening for breast cancer during routine exams”.\textsuperscript{(268)}

This particular example is less explicit than advertising material presented in the past, as the manufacturer altered online claims due to a complaint raised to the CRP in 2010.\textsuperscript{(118)} However, this is merely one example of an issue that has been identified throughout the industry, and may be occurring with an unknown number of other classes of products. A broader review of the industry, similar to that conducted within the CAM industry by Harvey and colleagues may fuel the necessary debate around regulatory change to this area that was not covered in the TGA’s public consultation process.\textsuperscript{(31)}

5.5.1 Limitations

The present study aimed to collect informed perspectives on regulatory reform from stakeholders with working knowledge of breast cancer research, patient advocacy and screening. In order to achieve this goal, national, not-for-profit organisations working within these key areas were approached to gauge in-principle interest. During the initial stage of the recruitment process the response rate from organisations was only 50 per cent (n = 5/10),
potentially introducing self-selection sampling bias into the study results.\(^{(269)}\) Four of the organisations that declined to participate stated a lack of expertise in the field, and one did not respond to the initial invitation. However, of the organisations that agreed to participate (n = 5/10), the response rate from nominated individuals was very high (n = 16/18). In this regard, the self-limiting nature of the sampling strategy ensured that information-rich participants were selected. Finally, although interviews were conducted with a standardised interview schedule, the semi-structured and open-ended nature of the questions may have affected the type and depth of information collected from different participants.

### 5.5.2 Conclusions and policy considerations

The Australian process for the pre-market approval of medical devices and medical device advertising is undergoing a detailed series of public reforms. The results of this study have identified a number of strengths, weaknesses and considerations in the reform options presented by the TGA. As such, stakeholder recommendations on the proposed options for reform have been compiled, and submitted directly to the TGA in two official submissions (Appendix E, Appendix F). These submissions have contributed to the TGA’s official stakeholder consultation process, and are to be considered when the TGA makes its final determinations about policy reform. Based on stakeholder views, there are a number of key factors or recommendations that need to be taken into account, that were not included in the TGA’s proposed options for reform:

- **Recommendation 1:** The risk-classification system does not account for the efficacy of diagnostic medical devices. The assessment of efficacy, not just safety, should be required for lower risk devices with a testing function.
- **Recommendation 2:** Self-registration into risk classification classes should be revised or overseen, in order to ensure that a device is registered correctly.
- **Recommendation 3:** Robust post-market monitoring is needed to ensure that the use of a device in public is aligned with its approved use on the ARTG.
- **Recommendation 4:** Regulatory reform for the pre-approval of therapeutic goods advertising should include medical device advertising, but may necessarily be limited to high-risk devices to reduce the regulatory burden.

The challenge moving forward is in implementing changes to the current model of medical device regulation, which align high-level regulatory principles with real-world practical application and resource limitations. It is a balance between the ideal and what can be reasonably implemented.
CHAPTER 6

Discussion and conclusions
6.1 Introduction

The primary aims of this thesis were to determine whether the regulatory framework for medical devices in Australia ensures that emerging breast cancer imaging devices have sufficient evidence of safety and effectiveness to support their use, and whether the advertising material for these devices is supported by evidence. Following the demonstrated limitations with the current regulations, the evidence collected in this thesis was used to explore ways in which medical device regulation in Australia may be improved. In this chapter, the implications of the results presented in each primary chapter will be addressed, the general limitations of the thesis will be discussed, and recommendations for future research and policy changes will be made.

6.2 Key findings and implications

6.2.1 What is the available evidence of safety, effectiveness and diagnostic accuracy of digital infrared thermal imaging (DITI), electrical impedance scanning (EIS) and electronic palpation imaging (EPI) for breast cancer screening and diagnosis?

The first research question presented in this thesis was examined through a comprehensive systematic review and narrative synthesis. During the search phase in the investigation, no outcome measures for diagnostic or screening effectiveness were identified, and the surrogate outcome measure of diagnostic accuracy was used as the primary outcome of importance. After an extensive, systematic and transparent literature search of available diagnostic accuracy studies for DITI, EIS and EPI, it was not possible to continue to meta-analysis due to heterogeneity among included studies. Heterogeneity may be explained by differences in study populations, differences in diagnostic thresholds for positive and negative test results, data collection errors, the type of index test under examination, or study design.\(^{161}\). Given the current divergence of supporting evidence for each device, there is no clear or conclusive evidence to suggest a meaningful range of diagnostic accuracy. Therefore, the only conclusion that could be drawn from the results of this review was that there is currently insufficient evidence to support their use for breast cancer screening and diagnosis.

To date, this review remains the only systematic review conducted on the use of EIS and EPI for breast cancer screening and diagnosis. There have, however, been two additional systematic reviews of DITI, reporting results up to June 2012\(^{229}\) and April 2011 respectively.\(^{230}\) In comparison, the search period for the systematic review presented in this
thesis was up to March 2011. The primary difference between the current review and the review conducted by Brennan and Houssami was the inclusion criteria relating to the type of thermography device under review. The present review was strictly limited to DITI devices, as older liquid-crystal contact thermography devices are less likely to be used in clinical practice since the development of DITI. In contrast, the Brennan review was inclusive of older contact thermography devices, or studies in which the device type was not clearly specified. As a result, the Brennan review included three additional studies published in 1980, and one study published in 1990 from asymptomatic screening populations that used older devices. Likewise, the review also included five additional diagnostic accuracy studies which utilised older technology, but failed to include two studies identified in the present review that investigate up-to-date DITI devices. In contrast, the review by Fitzgerald and Berenton-Shaw included the same evidence for diagnostic accuracy as the present review. Like the present review, neither were able to meta-analyse the included studies due to either the presence of significant heterogeneity among included studies, or a lack of available evidence from primary studies. Despite some differences in study inclusion criteria listed above, the additional published systematic reviews of DITI reached the same conclusions as the present review, lending validation to the results of the present review.

Given the low-level, poor quality evidence identified for DITI, EIS and EPI, the results of this review have significant implications for the current pathway to market for these devices. Under the present risk classification system these devices are registered as Class IIa medical devices, as they are active medical devices used for the diagnosis of vital physiological processes that do not emit ionising radiation. Class IIa devices are not required to submit evidence of efficacy or effectiveness during the pre-market conformity assessment process, and instead need only self-certify that they meet the Essential Principles for quality assurance. As the sensitivity and specificity of these emerging breast imaging devices were found to be as low as 25 per cent and 8 per cent respectively, women who use these devices for breast imaging have a high probability of being adversely affected by either potentially treatable disease being missed, or needless invasive follow-up testing. The potential for these harms to occur may be elevated further if women chose to undergo DITI, EIS or EPI in lieu of a conventional screening test such as mammography.

The sponsors of these devices have accurately registered these devices as Class IIa within the current regulatory guidelines. The issue, therefore, seems to be with the Class IIa risk category itself, which does not subject diagnostic tests to a review of their efficacy prior to market. Although there is potential for harm to occur in the present case study due to the poor accuracy of these devices, the current state of the Class IIa regulations also have
implications for diagnostic imaging in Australia more broadly. Perhaps the most significant limitation in the current system identified in this thesis is that the disease or indication for which the diagnostic test is applied is not incorporated into the risk classification of devices included on the Australian Register of Therapeutic Goods (ARTG). As a result, diagnostic imaging devices for serious diseases such as breast cancer (for example, ARTG ID 141616) are placed in the same category as thermometers used to measure eardrum and forehead temperature (for example, ARTG ID 221258). Until the medical device risk classifications are updated to better reflect the breadth of safety implications posed by these devices, devices with poor diagnostic accuracy will remain unimpeded by current regulations.

6.2.2 What is the nature and frequency of advertising claims made on Australian websites for DITI, EIS and EPI? To what extent are claims made on websites for these devices supported by evidence?

Three systematic reviews of DITI (including the review in this thesis) were conducted by independent research groups from Australia and New Zealand within a 15 month time period, reflecting the level of concern that these devices are raising amongst the local research community. The promotion of these devices has also drawn the attention of Australian regulators, government bodies and not-for-profit organisations, including:

- The National Health and Medical Research Council\(^{(227)}\)
- The Therapeutic Goods Administration (TGA)\(^{(127)}\)
- The Australian Competition and Consumer Commission (ACCC)\(^{(270)}\)
- BreastScreen Australia\(^{(271)}\)
- Breast Screen South Australia\(^{(272)}\)
- BreastScreen Western Australia\(^{(138)}\)
- Cancer Australia\(^{(273)}\)
- Cancer Council of Western Australia\(^{(138)}\)
- The Royal Australian and New Zealand College of Radiologists\(^{(274)}\)
- Breast Cancer Network Australia\(^{(275)}\)

In addition to local concern, international researchers\(^{(221)}\) and regulatory bodies in the United States\(^{(276)}\) and Canada\(^{(277)}\) have also raised issue with the promotion of these devices. Despite the concern directed towards the direct-to-consumer advertising (DtCA) of these devices, no studies investigating their advertising claims had been conducted prior to this thesis. Research questions two and three aimed to address this gap in the current evidence base, by investigating the claims being made by companies promoting DITI, EPI
and EIS devices in Australia, and comparing the findings with the results from the systematic review. Such an investigation has not been conducted for any other type of medical device on the Australian market.

Websites that advertised these devices for breast cancer imaging were collected in order to determine the indications, populations, and with what level of supporting evidence the devices are advertised. In order to achieve this goal, content analysis was carried out with two independent coders in addition to the thesis candidate. Coding was conducted by at least two coders, in order to ensure that the coded data were reliable and accurately reflected the content of the websites under analysis. The results of the content analysis were then compared narratively with the diagnostic accuracy and safety results presented in Chapter 3. This comparison identified that these devices are currently advertised to populations, and for indications that are not supported by evidence. Of key importance, the content analysis identified that these devices are actively promoted as a suitable alternative to mammographic imaging, and are targeted towards younger women and children who are not indicated for breast cancer screening due to their low risk of developing the disease. (65) These results appear in contrast to the evidence identified in the systematic review, whereby no evidence was found to support their use for screening or diagnosis, and at least one study found evidence that they not be used for breast cancer screening. (98)

As described in the policy commentary in Chapter 2, the reason that devices can be advertised in this manner is clear. Under the current system, medical device advertising is not actively regulated in Australia, and is instead subject to a complaints-based system for identifying companies that do not comply with relevant regulations. This retroactive system for regulating medical device advertising has proven to be ineffective at ensuring that the advertising material for breast cancer imaging devices is supported by evidence, as demonstrated by the results of the systematic review and content analysis in this thesis. While results suggest that an independent regulatory body with the capacity to monitor advertising claims made in the medical device industry may be needed, recent litigation (described below) against two companies promoting DITI and EIS devices for breast cancer screening and diagnosis suggest some degree of impact of the current system.

In March 2014, Safe Breast Imaging and BreastCheck were found guilty of misleading conduct in the Australian Federal Court, after the ACCC raised concerns regarding the promotion of EIS and DITI devices for breast cancer screening and diagnosis. (228, 278) It was claimed in advertisements that these devices could assess whether a customer may be at risk of breast cancer, and whether or not they have breast cancer. These claims were found to be deliberately false, misleading and deceptive.
representations.\(^{(228, 278)}\) Following the successful hearing it was posited by Mr Rod Sims, the ACCC’s Chairman, that:

\[
\text{“This judgment and the decision last week in the ACCC proceedings against Breast Check are a clear warning to the medical services industry that claims about medical services must be accurate and supported by credible scientific evidence,”}^{(228)}
\]

While the court action in this instance represents a success for consumer protection, the results of the content analysis suggest that there are at least 37 other companies that have promoted the same or similar devices since 2011, for similar indications. The successful prosecution of Safe Breast Imaging and BreastCheck may provide a deterrent to other medical device manufacturers who chose to advertise their products in a false or misleading manner. However, the longitudinal analysis of advertising claims made on websites for DITI, EPI and EIS presented in Chapter 4 demonstrate that only one third of companies amended their advertising material between March 2011 and March 2012, following the first set of complaints and regulatory action taken against companies promoting similar devices.\(^{(116-119, 127)}\) It may be that the effect of the court action is limited to an isolated case of a potentially much larger problem. The extent of this issue for breast cancer devices been clearly outlined in the content analysis, but is unknown in the broader medical device industry. As an addendum to this debate, it is unknown how many women were adversely affected by these devices in the time between their introduction onto the market prior to 2010, and the final court hearing handed down in March 2014. It is also unknown how many women continue to utilise these services.

### 6.2.3 What are the strengths and weaknesses of the TGA’s proposed reforms to the pre-market assessment of medical devices and their advertising material in Australia? Which characteristics of medical devices and their advertising should be assessed by an independent regulator?

Given the limitations of the current regulatory system described in the first four chapters of this thesis, Chapter 5 sought to engage with stakeholders from the breast cancer community around options to reform the current regulations for medical devices and their advertising. In this study, the results of the policy commentary, systematic review and content analysis were synthesised, and discussed in detail with members of the breast cancer community. This material provided context for the changes necessary to improve the policy framework for regulating breast cancer imaging devices and their advertising material in Australia. The interview schedule was based around the TGA’s proposed options for reform to the pre-market assessment of medical devices, and regulation of medical device...
advertising.\textsuperscript{131, 132} Through focusing on the TGA's options for reform rather than a set of options specific to breast cancer devices, findings from this study are more directly relevant to the policy reform process. By framing the stakeholder engagement around the TGA's options, it was possible to submit the results from the study directly to the TGA (see Appendix E and F) in an open and transparent manner, while providing guidance on how the proposed changes would likely impact emerging breast cancer imaging devices.

Chapter 5 also addressed the fifth research question, whereby participants recommended criteria that should be used to regulate breast cancer imaging devices and their advertising material in Australia. A set of criteria were generated from a thematic analysis of stakeholders' responses, following their consideration of the TGA's proposed options for reform. In addition to test accuracy and safety, participants favoured comparative evidence as a minimum criterion that should be required for pre-market approval of these devices. Although test accuracy was viewed to be of primary importance to stakeholders, this is not a requirement for Class IIa devices.\textsuperscript{13}

Resource limitations faced by the TGA caused stakeholders to doubt whether the proposed reforms will improve medical device regulation. The TGA is currently funded on a cost-recovery basis, through fees and charges paid by the therapeutic goods industry.\textsuperscript{12} This contrasts with the Food and Drug Administration (FDA), which is funded by government and industry contributions.\textsuperscript{279} Although the stakeholder engagement was focussed on the TGA's proposed options for reform, the role of the ACCC is of key importance to the case study of emerging breast imaging devices. Unlike the TGA, the ACCC is funded by the Government and has demonstrated the regulatory impetus to penalise companies that promote breast imaging devices in a false or misleading manner.\textsuperscript{228, 270, 278, 280} While this thesis has highlighted the need to regulate medical device advertising, the combined responsibilities of the ACCC and TGA for this role are questionable. An alternative model could involve collaboration between the two agencies, with better defined roles and less duplication of responsibility: a more rigorous pre-market evaluation of medical devices by the TGA, and active monitoring of medical device advertising by the ACCC.

It is unknown whether the TGA's options to reform the regulation of medical device advertising will have a significant impact on the misleading representation of devices documented in this case study. The TGA's initiatives may lend some degree of quality assurance to medical device advertising, but this is dependent upon the course of action that it decides to take. For example, stakeholders suggested the option to remove advertising pre-assessment in favour of active monitoring will provide the least amount of confidence in promotional material for devices, as there will be less impetus for the TGA to conduct monitoring retrospectively.\textsuperscript{31} Alternatively, expanding the current pre-approval system for
therapeutic goods advertising to include medical devices would offer the best level of quality assurance, however, it would require considerable resources. As discussed in Appendix F, a more suitable approach may be to expand the current pre-market assessment process for therapeutic goods advertising to include medical devices, but to limit this assessment to high-risk devices. For this approach to be effective for the case study, these breast imaging devices would need to be classified into a higher risk category.

6.3 Thesis limitations and recommendations for future research

The limitations of each piece of empirical work presented in this thesis have been discussed in the relevant chapters. Therefore, this discussion will focus on the limitations of the thesis as a whole. The ability to address the overall aim of this thesis is limited by the scope of investigation, the timeliness of the investigations, and the validity of the recommendations for regulatory reform.

Scope of investigation: The information and recommendations for regulatory change presented in Chapter 5 were delivered from the perspective of not-for-profit stakeholders involved in breast cancer research, patient advocacy and screening. While the views and opinions of this group are relevant to the case study examined in this thesis, the review of the TGA’s regulatory processes was open to input from a broader array of stakeholders, including medical technology and pharmaceutical industry members, consumer advocacy groups, professional associations, and interested individuals. A broader, industry-wide focus may have allowed more robust recommendations to have been developed in this thesis. However, this would have required a different methodology. The scope of work required to undertake an industry-wide review of regulatory processes is beyond the remit of a PhD thesis, and may be better suited to governmental review.

Given the regulatory limitations identified in the present case study, a review of the broader industry would allow future researchers to better demonstrate the effectiveness of the current regulations on the industry as a whole. This thesis also highlighted significant limitations in the risk-based classification system for medical devices. An evidence-based review of the risk classification system for diagnostic devices would inform the level of pre-market assessment that these devices require, including a consideration of the severity of disease under investigation.

Timelines of investigation: Challenges were presented by the conduct of research on a regulatory issue undergoing constant change during the course of this thesis. The regulatory framework for these devices entered a state of reform shortly after the commencement of the research agenda. It became necessary to alter the research
program mid-way through the project, following the release of the TGA’s blueprint for reforms to the regulatory framework for medical devices.\(^{253}\) The release of this document rendered a planned Delphi study obsolete. This study aimed to develop a range of reform criteria specific to the breast imaging case study, but was deemed less relevant to policy following the release of the TGA’s reform options. The research program was altered to ensure that the results of the thesis could contribute to the TGA’s reform process. Although the TGA released updated reform options after the data collection for Chapter 5 had been completed, the results of this study were still relevant to the ongoing debate.\(^{281, 282}\)

**Validity of recommendations:** Several companies faced legal action from the TGA and ACCC during the course of the thesis, which affected their ability to promote their devices.\(^{127, 270}\) The regulatory action against companies offering EITI, EIS and EPI for breast cancer screening and diagnosis may contradict the need for regulatory reform proposed by this body of work. While this may appear to indicate that the current system is effective at ensuring that devices are safe, effective, and advertised in accordance with evidence, three arguments can be made against this case:

First, regulatory action taken against companies promoting breast imaging devices was due to consumer advocacy initiatives from not-for-profit organisations and interested individuals. There is a history of consumer advocacy within breast cancer, which was also demonstrated in this case study. However, it is unknown how many other classes of devices used to treat or diagnose disease with lower public profiles than breast cancer currently exist on the market without a demonstrated evidence base. A broader review of the advertising standards within the industry in general would help to determine the extent to which these problems occur elsewhere in the medical device market in Australia.

Second, these devices remain on the ARTG under a ‘low risk’ classification, under which their efficacy and safety (in terms of their diagnostic performance) are not assessed by an independent regulator. It is also not known how many other DtCA diagnostic devices which pose similar harms to consumers are currently included on the ARTG under this risk classification.

Finally, it is not possible to determine how many women may have already been adversely affected by the use of these tests, either by way of a false positive or false negative test result, the unnecessary referral for an invasive breast biopsy, or through the omission of an established test such as mammography. A system of regulation which relies on the retrospective assessment of medical technologies, raised at the discretion of public concern, will invariably expose the wider public to harm which may have otherwise been avoided if an effective pre-market assessment system was in place.
6.4 Conclusion

The purpose of medical device regulation is to ensure that safe and effective medical devices are made available to the general public in a timely manner, so that technical innovations are able to benefit patients as soon as possible. In practice, marrying the goals of regulation with resource constraints presents a significant challenge to regulators in Australia as the demand for new medical devices increases. In this thesis it has been demonstrated that the current regulations in place to govern the pre-market approval of DITI, EIS and EPI do not offer a guarantee that these devices are adequately supported by evidence. Despite this lack of evidence, it has been established that these devices are marketed directly towards Australian consumers for use in breast cancer screening and diagnosis, often in direct comparison to conventional imaging practices. The disconnect between the research evidence and advertising material highlights the need to reform the current model of regulation for medical device advertising in Australia.

Although the reform options proposed by the TGA will begin to address this disconnect, they represent broader regulatory changes that will not address all of the limitations identified in the case study. Under the proposed options for reform, breast cancer imaging devices will not be assessed for efficacy prior to market due to their classification as Class IIa or IIb low-risk devices. Similarly, there are currently no established plans to ensure that the advertising material for these devices is aligned with evidence. This does not suggest that the TGA’s reform processed failed to meet the intended objectives, rather, that the consultations had a broader focus that did not detect issues relevant to breast cancer imaging devices.

Several solutions to reduce the divide between advertising claims and research evidence, beyond those offered by the TGA, are recommended in this thesis. Firstly, raising the risk classification of diagnostic devices for serious disease will require them to be assessed for efficacy, as well as safety, prior to market. Secondly, monitoring the use of a device in practice compared to its approved use on the ARTG will prevent healthcare providers from using devices for indications that are not approved. Finally, extending the current regulations for advertising pre-approval to include high-risk medical devices will determine whether advertising claims are supported by evidence before they are broadcast to consumers. When combined, these initiatives will lessen the gap between the DtCA and evidence for emerging breast imaging devices promoted in Australia.
APPENDIX A

Peer-reviewed publications
arising from this thesis
Pre-market approval and post-market direct-to-consumer advertising of medical devices in Australia: a case study of breast cancer screening and diagnostic devices

T. D. Vreugdenberg, 1 C. D. Willis, 2 L. Mundy 1 and J. E. Hiller 3

1Adelaide Health Technology Assessment (AHTA), Discipline of Public Health, 2School of Population Health and Clinical Practice, The University of Adelaide, South Australia and 3Faculty of Health Sciences, Australian Catholic University, Victoria, Australia

Key words
direct-to-consumer advertising, breast cancer, Australian health policy, medical devices.

Correspondence
Email: thomas.vreugdenburg@adelaide.edu.au

Received 9 May 2011; accepted 26 September 2011.


Abstract
While research investigating direct-to-consumer advertising of therapeutic goods in Australia has historically focused on prescription medicines, recent action taken by regulators against companies promoting medical devices has placed the industry into the spotlight. Despite the need to effectively regulate direct-to-consumer advertising of medical devices due to its potential harms, inadequacies in the current regulatory system have been noted. Under the present system, devices with a questionable evidence base may enter the Australian marketplace without an evaluation of their effectiveness, and regulators are reliant on industry self-regulation and consumer complaints to draw attention to cases of advertising misconduct. Although some successes in the present system have been observed, we argue that the outlined inadequacies continue to enable the promotion of medical devices to consumers without thorough or sufficient examination of evidence.

Introduction
Research on direct-to-consumer advertising (DiCA) of therapeutic goods in Australia and overseas has historically focused on prescription pharmaceuticals. In contrast, DiCA in the rapidly expanding medical devices industry has received relatively little attention, with the exception of the burgeoning area of genetic testing. However, a recent succession of complaints raised against several companies marketing medical devices in Australia has recently turned the spotlight on to DiCA of these products, as well as the wider medical devices industry.

The merits of DiCA for the promotion of therapeutic goods have been extensively debated. Proponents argue that DiCA educates members of the public about health conditions and available treatment options, and empowers individuals to engage in informed discussions with healthcare providers. Opponents suggest, however, that the ability of DiCA to function as an educational and empowering tool is often adversely affected by poor quality, biased and unbalanced information presented in advertisements. For medical screening and diagnostic devices specifically, DiCA may carry significant risks relating to both safety, through misdiagnosis of disease presence or absence, and confidentiality, as test results may impact the future acquisition of employment, healthcare or life insurance. DiCA of screening and diagnostic devices also carries financial implications for both the patient and the wider healthcare system, as while a test using a device may be funded out of pocket, the results of the test can lead to further investigation in the public system.

Owing to the potential risks associated with DiCA of diagnostic and screening devices, there is a need for an effective regulatory framework governing this practice. Recent action taken by the Therapeutic Goods Administration (TGA), the Complaints Resolution Panel (CRP) and the Australian Competition and Consumer Commission (ACCC) against several diagnostic/screening device suppliers for presenting false or misleading...
A systematic review of elastography, electrical impedance scanning, and digital infrared thermography for breast cancer screening and diagnosis

Thomas D. Vreugdenburg · Cameron D. Willis · Linda Mundy · Janet E. Hiller

Received: 13 July 2012 / Accepted: 17 December 2012 / Published online: 4 January 2013
© Springer Science+Business Media New York 2013

Abstract The objective of this study aimed to systematically identify and evaluate all the available evidence of safety, effectiveness and diagnostic accuracy for three emerging classes of technology promoted for breast cancer screening and diagnosis: Digital infrared thermal imaging (DITI), electrical impedance scanning (EIS) and elastography. A systematic search of seven biomedical databases (EMBASE, PubMed, Web of Science, CRD, CINAHL, Cochrane Library, Current Contents Connect) was conducted through March 2011, along with a manual search of reference lists from relevant studies. The principal outcome measures were safety, effectiveness, and diagnostic accuracy. Data were extracted using a standardised form, and validated for accuracy by the secondary authors. Study quality was appraised using the quality assessment of diagnostic accuracy studies tool, while heterogeneity was assessed using forest plots, Cook’s distance and standardised residual scatter plots, and I² statistics. From 6,808 search results, 267 full-text articles were assessed, of which 60 satisfied the inclusion criteria. No effectiveness studies were identified. Only one EIS screening accuracy study was identified, while all other studies involved symptomatic populations. Significant heterogeneity was present among all device classes, limiting the potential for meta-analyses. Sensitivity and specificity varied greatly for DITI (Sens 0.25–0.97, Spec 0.12–0.85), EIS (Sens 0.26–0.98, Spec 0.08–0.81) and ultrasound elastography (Sens 0.35–1.00, Spec 0.21–0.99). It is concluded that there is currently insufficient evidence to recommend the use of these technologies for breast cancer screening. Moreover, the high level of heterogeneity among studies of symptomatic women limits inferences that may be drawn regarding their use as diagnostic tools. Future research employing standardised imaging, research and reporting methods is required.

Keywords Breast cancer · Diagnostic accuracy · Screening · Systematic review

NOTE:
This publication is included on page 122 in the print copy of the thesis held in the University of Adelaide Library.

It is also available online to authorised users at:

APPENDIX B

Supplementary material for the systematic review
### eTable 1  Systematic review search strategy

<table>
<thead>
<tr>
<th>Query</th>
<th>Search Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>breast neoplasms[MH] OR breast neoplasm*[all fields] OR breast*[all fields] OR mammary*[all fields]</td>
</tr>
<tr>
<td>#2</td>
<td>(thermography[mh]) OR (thermal imag*[tiab]) OR (infrared imag*[tiab]) OR (infra-red imag*[tiab]) OR (thermology[tiab]) OR (thermometry[tiab]) OR (thermograph[tiab])</td>
</tr>
<tr>
<td>#3</td>
<td>(electrical impedance[mh]) OR (electrical impedance[tiab]) OR (electromagnetic imag*[tiab]) OR (bioelectric* impedance[tiab]) OR (electric impedance[tiab])</td>
</tr>
<tr>
<td>#4</td>
<td>(Elasticity Imaging Technique*[MH]) OR (computerised imag*[tiab]) OR (computerized imag*[tiab]) OR (mechanical imag*[tiab]) OR (tactile imag*[tiab]) OR (soft tissue elastometer*[tiab]) OR (electronic palpation imag*[tiab]) OR (EPI[tiab]) OR (Model-based imaging[tiab]) OR (Force sensor array[tiab])</td>
</tr>
<tr>
<td>#5</td>
<td>#1 AND (#2 OR #3 OR #4)</td>
</tr>
</tbody>
</table>

### eTable 2  Inclusion and exclusion criteria based on PICO criteria

<table>
<thead>
<tr>
<th></th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Human participants</td>
<td>Animal participants</td>
</tr>
<tr>
<td></td>
<td>Symptomatic women (diagnostic)</td>
<td>Simulated/prosthetic samples</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic women (screening)</td>
<td>Excised tissue samples</td>
</tr>
<tr>
<td>Intervention</td>
<td>Screening and/or diagnosis of breast cancer</td>
<td>Other interventions</td>
</tr>
<tr>
<td></td>
<td>- Other interventions</td>
<td>- Not breast cancer</td>
</tr>
<tr>
<td>Index Test</td>
<td>Elasticity imaging</td>
<td>Contact thermography</td>
</tr>
<tr>
<td></td>
<td>Electrical impedance imaging</td>
<td>Device not defined/identified</td>
</tr>
<tr>
<td></td>
<td>Digital infrared thermal imaging</td>
<td></td>
</tr>
<tr>
<td>Outcome - Effectiveness</td>
<td>Survival rates/reduction in mortality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quality of life</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interval cancers (surrogate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cancer detection rates (surrogate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumor size/stage (surrogate)</td>
<td></td>
</tr>
<tr>
<td>Outcome - Accuracy</td>
<td>Sensitivity/Specificity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>False positive/negative rates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive/negative predictive values</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive/negative likelihood ratios</td>
<td></td>
</tr>
<tr>
<td>Outcome - Safety</td>
<td>Physical harm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>False positive/negative rates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Physical harm</td>
<td></td>
</tr>
<tr>
<td>Publication Type</td>
<td>Peer-reviewed journal articles</td>
<td>Letter to the editor</td>
</tr>
<tr>
<td></td>
<td>- Conference abstract or poster</td>
<td>- Narrative review</td>
</tr>
<tr>
<td></td>
<td>- Editorial</td>
<td></td>
</tr>
<tr>
<td>Year of Publication</td>
<td>1981 till March 2011</td>
<td>1980 or earlier</td>
</tr>
</tbody>
</table>
### eTable 3  NHMRC hierarchy of evidence according to research question

<table>
<thead>
<tr>
<th>Level</th>
<th>Intervention 1</th>
<th>Diagnostic accuracy 2</th>
<th>Screening Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
</tr>
<tr>
<td>II</td>
<td>A randomised controlled trial</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation</td>
<td>A randomised controlled trial</td>
</tr>
<tr>
<td>III-1</td>
<td>A pseudorandomised controlled trial (i.e. alternate allocation or some other method)</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation</td>
<td>A pseudorandomised controlled trial (i.e. alternate allocation or some other method)</td>
</tr>
</tbody>
</table>
| III-2 | A comparative study with concurrent controls:  
- Non-randomised, experimental trial 7  
- Cohort study  
- Case-control study  
- Interrupted time series with a control group | A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence | A comparative study with concurrent controls:  
- Non-randomised, experimental trial  
- Cohort study  
- Case-control study |
| III-3 | A comparative study without concurrent controls:  
- Historical control study  
- Two or more single arm study 8  
- Interrupted time series without a parallel control group | Diagnostic case-control study 6 | A comparative study without concurrent controls:  
- Historical control study  
- Two or more single arm study |
| IV    | Case series with either post-test or pre-test/post-test outcomes | Study of diagnostic yield (no reference standard) | Case series |

1 Definitions of these study designs are provided on pages 7-8 How to use the evidence: assessment and application of scientific evidence (NHMRC 2000b).

2 The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

3 If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the ‘Intervention’ hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the ‘Aetiology’ hierarchy of evidence should be utilised.

4 A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

5 The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

6 Well-designed population based case-control studies (eg. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfill the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

7 This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).

8 Comparing single arm studies ie. case series from two studies. This would also include unadjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).
## Diagnostic accuracy results of included studies

<table>
<thead>
<tr>
<th>Device name</th>
<th>Test name</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-0</td>
<td>0</td>
<td>86.7%</td>
<td>74.2%</td>
<td>0.69%</td>
<td>0.71%</td>
</tr>
<tr>
<td>M-1</td>
<td>1</td>
<td>81.7%</td>
<td>81.7%</td>
<td>0.78%</td>
<td>0.66%</td>
</tr>
<tr>
<td>M-2</td>
<td>3</td>
<td>54.5%</td>
<td>92.6%</td>
<td>0.72%</td>
<td>0.51%</td>
</tr>
</tbody>
</table>

### eTable 4

<table>
<thead>
<tr>
<th>Device name</th>
<th>Test name</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-0</td>
<td>0</td>
<td>86.7%</td>
<td>74.2%</td>
<td>0.69%</td>
<td>0.71%</td>
</tr>
<tr>
<td>M-1</td>
<td>1</td>
<td>81.7%</td>
<td>81.7%</td>
<td>0.78%</td>
<td>0.66%</td>
</tr>
<tr>
<td>M-2</td>
<td>3</td>
<td>54.5%</td>
<td>92.6%</td>
<td>0.72%</td>
<td>0.51%</td>
</tr>
</tbody>
</table>

### Appendix B

*Systematic Review Supplement*

Page 126
<table>
<thead>
<tr>
<th>Citation</th>
<th>Device name</th>
<th>Index test</th>
<th>Measurement scale</th>
<th>Cut-off score for benign/malignant</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho et al 2008</td>
<td>EUB-8500</td>
<td>USE</td>
<td>5 point Itoh et al scale</td>
<td>B = 1.2 M = 3.5</td>
<td>82%</td>
<td>84%</td>
<td>52%</td>
<td>96%</td>
</tr>
<tr>
<td>Cho et al 2010</td>
<td>EUB-8500</td>
<td>USE</td>
<td>Strain ratio (fat/mass)</td>
<td>B ≤ 2.2 M &gt; 2.2</td>
<td>95%</td>
<td>75%</td>
<td>48%</td>
<td>98%</td>
</tr>
<tr>
<td>Chung et al 2010</td>
<td>EUB-8500</td>
<td>USE</td>
<td>5 point Itoh et al scale</td>
<td>B = 1.3 M = 4.5</td>
<td>58.0%</td>
<td>92.9%</td>
<td>84.8%</td>
<td>75.0%</td>
</tr>
<tr>
<td>Chung et al 2010</td>
<td>EUB-8500</td>
<td>USE</td>
<td>Strain ratio</td>
<td>B &lt; 2.1 B &gt; 2.1</td>
<td>88%</td>
<td>78.6%</td>
<td>74.6%</td>
<td>90.2%</td>
</tr>
<tr>
<td>Evans et al 2010</td>
<td>Explorer</td>
<td>USE</td>
<td>Mean elasticity score (kPa)</td>
<td>B ≤ 50 M &gt; 50</td>
<td>97%</td>
<td>83%</td>
<td>88%</td>
<td>95%</td>
</tr>
<tr>
<td>Fleury et al 2009</td>
<td>Sonix SP</td>
<td>USE</td>
<td>4 point scale</td>
<td>B = 1.3 M = 4</td>
<td>86.7%</td>
<td>96.0%</td>
<td>76.5%</td>
<td>97.9%</td>
</tr>
<tr>
<td>Garra et al 1997</td>
<td>Spectra</td>
<td>USE</td>
<td>Width differences + brightness score differences</td>
<td>NR NR</td>
<td>100%</td>
<td>58%</td>
<td>63.2%</td>
<td>100%</td>
</tr>
<tr>
<td>Giuseppetti et al 2005</td>
<td>EUB-8500</td>
<td>USE</td>
<td>5 point Itoh et al scale</td>
<td>B = 1.2 M = 3.5</td>
<td>79%</td>
<td>89%</td>
<td>94.4%</td>
<td>64.9%</td>
</tr>
<tr>
<td>Itoh et al 2006</td>
<td>EUB-8500</td>
<td>USE</td>
<td>5 point Itoh et al scale</td>
<td>B = 1.3 M = 4.5</td>
<td>86.5%</td>
<td>89.8%</td>
<td>88.2%</td>
<td>88.3%</td>
</tr>
<tr>
<td>Ko et al 2011</td>
<td>EUB-7500</td>
<td>USE</td>
<td>5 point Itoh et al scale</td>
<td>B = 1.3 M = 4.5</td>
<td>65.4%</td>
<td>90.4%</td>
<td>72.3%</td>
<td>85.8%</td>
</tr>
<tr>
<td>Kumm et al 2010</td>
<td>Hi Vision 900</td>
<td>USE</td>
<td>Strain ratio</td>
<td>B &gt; 4.5 M &lt; 45</td>
<td>79%</td>
<td>76%</td>
<td>57%</td>
<td>90.0%</td>
</tr>
<tr>
<td>Kumm et al 2010</td>
<td>Hi Vision 900</td>
<td>USE</td>
<td>Strain ratio</td>
<td>B = 1.2 M = 3.5</td>
<td>76%</td>
<td>81%</td>
<td>60%</td>
<td>90.0%</td>
</tr>
<tr>
<td>Lee et al 2011</td>
<td>EUB-8500</td>
<td>USE</td>
<td>5 point Itoh et al scale</td>
<td>B = 1.3 M = 4.5</td>
<td>35.4%</td>
<td>99.8%</td>
<td>85%</td>
<td>89.5%</td>
</tr>
<tr>
<td>Lee et al 2011</td>
<td>EUB-8500</td>
<td>USE</td>
<td>Strain ratio</td>
<td>B = 2 M = 2</td>
<td>68.8%</td>
<td>64.8%</td>
<td>26%</td>
<td>92%</td>
</tr>
<tr>
<td>Leong et al 2010</td>
<td>Antares</td>
<td>USE</td>
<td>Length ratio</td>
<td>B ≤ 1.1 M &gt; 1</td>
<td>100%</td>
<td>73.8%</td>
<td>54.2%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Moon et al 2005</td>
<td>Voluson 530</td>
<td>USE</td>
<td>Support vector machine</td>
<td>Automatic classification</td>
<td>75%</td>
<td>83%</td>
<td>75%</td>
<td>83%</td>
</tr>
<tr>
<td>Moon et al 2009</td>
<td>EUB-8500</td>
<td>USE</td>
<td>Artificial Neural Network</td>
<td>B = 0.5 M = 0.5</td>
<td>83.3%</td>
<td>87.5%</td>
<td>80.3%</td>
<td>90.0%</td>
</tr>
<tr>
<td>Moon et al 2010</td>
<td>EUB-8500</td>
<td>USE</td>
<td>Artificial Neural network</td>
<td>B = 0.5 M = 0.5</td>
<td>92%</td>
<td>74%</td>
<td>58%</td>
<td>96%</td>
</tr>
<tr>
<td>Moon et al 2010</td>
<td>EUB-8500</td>
<td>USE</td>
<td>5 point Itoh et al scale</td>
<td>B = 1.3 M = 4.5</td>
<td>54%</td>
<td>91%</td>
<td>70%</td>
<td>84%</td>
</tr>
<tr>
<td>Navarro et al 2011</td>
<td>Antares</td>
<td>USE</td>
<td>5 point Itoh et al scale</td>
<td>B = 1.3 M = 4.5</td>
<td>69.5%</td>
<td>83.1%</td>
<td>78.9%</td>
<td>75.0%</td>
</tr>
<tr>
<td>Parajuly et al 2010</td>
<td>Antares</td>
<td>USE</td>
<td>5 point Itoh et al scale</td>
<td>B = 1.2 M = 3.5</td>
<td>95.7%</td>
<td>96%</td>
<td>94.3%</td>
<td>96.6%</td>
</tr>
<tr>
<td>Roza et al 2010</td>
<td>EUB-8500</td>
<td>USE</td>
<td>5 point Itoh et al scale</td>
<td>B = 1.3 M = 4.5</td>
<td>83.6%</td>
<td>87.4%</td>
<td>76.1%</td>
<td>91.7%</td>
</tr>
<tr>
<td>Regni et al 2010</td>
<td>EUB-8500</td>
<td>USE</td>
<td>Modified 5 point Itoh et al scale</td>
<td>B = 1.2 M = 3.5</td>
<td>86.5%</td>
<td>92.7%</td>
<td>86.1%</td>
<td>94.1%</td>
</tr>
<tr>
<td>Regner et al 2006</td>
<td>Elegra</td>
<td>USE</td>
<td>Width ratio of USE versus B-mode US</td>
<td>B ≤ 1.0 M ≥ 1.0</td>
<td>96%</td>
<td>21%</td>
<td>62.0%</td>
<td>80.0%</td>
</tr>
<tr>
<td>Regner et al 2006</td>
<td>Elegra</td>
<td>USE</td>
<td>Area ratio of USE versus B-mode US</td>
<td>B ≤ 1.1 M ≥ 1.1</td>
<td>96%</td>
<td>24%</td>
<td>62.8%</td>
<td>81.3%</td>
</tr>
<tr>
<td>Satake et al 2011</td>
<td>EUB-8500</td>
<td>USE</td>
<td>5 point Itoh et al scale</td>
<td>B = 1.3 M = 4.5</td>
<td>81.8%</td>
<td>70.4%</td>
<td>90.0%</td>
<td>54.3%</td>
</tr>
<tr>
<td>Scaparrotta et al 2008</td>
<td>Hi Vision</td>
<td>USE</td>
<td>Modified 5 point Itoh et al scale</td>
<td>B = 1.3 M = 4.5</td>
<td>80.0%</td>
<td>81.0%</td>
<td>71.5%</td>
<td>87.1%</td>
</tr>
<tr>
<td>Citation</td>
<td>Device name</td>
<td>Index test</td>
<td>Measurement scale</td>
<td>Cut-off score for benign/malignant</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>PPV</td>
<td>NPV</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
<td>-------------------</td>
<td>-----------------------------------</td>
<td>------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Schaefer et al 2009</td>
<td>EUB-8500</td>
<td>USE</td>
<td>5 point ltoh et al scale</td>
<td>B = 1-3 M = 4-5</td>
<td>96.9%</td>
<td>76.0%</td>
<td>66.7%</td>
<td>98.0%</td>
</tr>
<tr>
<td>Sohn et al 2009</td>
<td>Antares</td>
<td>USE</td>
<td>5 point ltoh et al scale</td>
<td>B = 1-3 M = 4-5</td>
<td>65.5%</td>
<td>79.0%</td>
<td>45.8%</td>
<td>89.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>USE</td>
<td>Length ratio</td>
<td>B ≤ 0.6 M &gt; 0.6</td>
<td>87.7%</td>
<td>54.7%</td>
<td>35.2%</td>
<td>94.1%</td>
</tr>
<tr>
<td>Tan et al 2008</td>
<td>EUB-8500</td>
<td>USE</td>
<td>5 point ltoh et al scale</td>
<td>B = 1-3 M = 4-5</td>
<td>78.0%</td>
<td>98.5%</td>
<td>93.9%</td>
<td>94.2%</td>
</tr>
<tr>
<td>Thomas et al 2006</td>
<td>EUB-8500</td>
<td>USE</td>
<td>5 point ltoh et al scale</td>
<td>B = 1-3 M = 4-5</td>
<td>77.6%</td>
<td>88.1%</td>
<td>84.4%</td>
<td>82.5%</td>
</tr>
<tr>
<td>Thomas et al 2007</td>
<td>Apollo90</td>
<td>USE</td>
<td>5 point ltoh et al scale</td>
<td>B = 1-3 M = 4-5</td>
<td>96%</td>
<td>80%</td>
<td>82.8%</td>
<td>95.2%</td>
</tr>
<tr>
<td>Thomas et al 2010</td>
<td>Hi Vision</td>
<td>USE</td>
<td>5 point ltoh et al scale</td>
<td>B ≤ 1.3 M ≥ 4.5</td>
<td>81%</td>
<td>85%</td>
<td>84%</td>
<td>82.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>USE</td>
<td>Strain ratio</td>
<td>B &lt; 2.5 M ≥ 2.5</td>
<td>90%</td>
<td>89%</td>
<td>89%</td>
<td>90.2%</td>
</tr>
<tr>
<td>Wojcik et al 2010</td>
<td>EUB-8500</td>
<td>USE</td>
<td>5 point ltoh et al scale</td>
<td>B = 1-3 M = 4-5</td>
<td>81.2%</td>
<td>89.5%</td>
<td>86.8%</td>
<td>84.8%</td>
</tr>
<tr>
<td>Yerli et al 2011</td>
<td>EUB-7000</td>
<td>USE</td>
<td>Modified 5 point ltoh et al scale</td>
<td>B = 1-3 M = 4-5</td>
<td>95%</td>
<td>80%</td>
<td>84%</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>USE</td>
<td>Strain ratio</td>
<td>B ≤ 3.5 M &gt; 3.5</td>
<td>93%</td>
<td>80%</td>
<td>80%</td>
<td>93%</td>
</tr>
<tr>
<td>Yoon et al 2011</td>
<td>EUB-7500</td>
<td>USE + US</td>
<td>Combined methods</td>
<td>Combined methods</td>
<td>98.5%</td>
<td>33.3%</td>
<td>45.1%</td>
<td>97.9%</td>
</tr>
<tr>
<td>Zhi et al 2007</td>
<td>EUB-8500</td>
<td>USE</td>
<td>5 point ltoh et al scale</td>
<td>B = 1-3 M = 4-5</td>
<td>70.1%</td>
<td>95.7%</td>
<td>87.1%</td>
<td>88.5%</td>
</tr>
<tr>
<td>Zhi et al 2010</td>
<td>EUB-8500</td>
<td>USE</td>
<td>5 point ltoh et al scale</td>
<td>B = 1-3 M = 4-5</td>
<td>70.1%</td>
<td>93.0%</td>
<td>77.7%</td>
<td>90.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>USE</td>
<td>Strain ratio</td>
<td>B ≤ 3.1 M &gt; 3.1</td>
<td>92.5%</td>
<td>91.1%</td>
<td>78.2%</td>
<td>97.2%</td>
</tr>
<tr>
<td>Zhu et al 2008</td>
<td>EUB-8500</td>
<td>USE</td>
<td>5 point ltoh et al scale</td>
<td>B = 1-4 M = 5</td>
<td>85.5%</td>
<td>86.9%</td>
<td>88.1%</td>
<td>96.1%</td>
</tr>
</tbody>
</table>

**Table:** Digital Infrared Thermal Imaging, MG: Mammography, N/A: Not Applicable, NPV: Negative Predictive Value, NR: Not Reported, PPV: Positive Predictive Value, US: B-Mode Ultrasound.

*Calculated by corresponding author with extracted data, not reported in the original article.
### eTable 5  Investigation of heterogeneity in subgroup likelihood ratios

<table>
<thead>
<tr>
<th>Device class and subgroups</th>
<th>Studies (n)</th>
<th>I2 (95% CI)</th>
<th>Q (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measure - Bright white spot</td>
<td>6</td>
<td>92 (84-99)</td>
<td>24.78 (p = 0.000)</td>
</tr>
<tr>
<td>Measure - Level of suspicion</td>
<td>4</td>
<td>0 (0-100)</td>
<td>0.79 (p = 0.337)</td>
</tr>
<tr>
<td>Non-blinded index test</td>
<td>4</td>
<td>93 (88-99)</td>
<td>30.51 (p = 0.000)</td>
</tr>
<tr>
<td>Mean age 50-69</td>
<td>4</td>
<td>91 (81-100)</td>
<td>21.34 (p = 0.000)</td>
</tr>
<tr>
<td><strong>DITI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All studies</td>
<td>7</td>
<td>99 (99-100)</td>
<td>241.95 (p = 0.000)</td>
</tr>
<tr>
<td>Prospective design</td>
<td>6</td>
<td>100 (99-100)</td>
<td>410.33 (p = 0.000)</td>
</tr>
<tr>
<td><strong>USE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measure - Elasticity score</td>
<td>26</td>
<td>99 (98-99)</td>
<td>143.31 (p = 0.000)</td>
</tr>
<tr>
<td>Elasticity Score - Exclusions</td>
<td>21</td>
<td>94 (89-99)</td>
<td>34.38 (p = 0.000)</td>
</tr>
<tr>
<td>Measure - Strain ratio</td>
<td>7</td>
<td>0 (0-100)</td>
<td>0.44 (p = 0.401)</td>
</tr>
<tr>
<td>Measure - Size ratio</td>
<td>6</td>
<td>75 (45-100)</td>
<td>8.05 (p = 0.009)</td>
</tr>
<tr>
<td>Measure - Neural network</td>
<td>4</td>
<td>67 (26-100)</td>
<td>6.10 (p = 0.024)</td>
</tr>
<tr>
<td>USE + B-mode</td>
<td>8</td>
<td>97 (94-99)</td>
<td>61.42 (p = 0.000)</td>
</tr>
<tr>
<td>Blinded index test</td>
<td>20</td>
<td>99 (98-99)</td>
<td>139.66 (p = 0.000)</td>
</tr>
<tr>
<td>Level II diagnostic evidence</td>
<td>13</td>
<td>98 (96-99)</td>
<td>90.53 (p = 0.000)</td>
</tr>
<tr>
<td>Level III-2 diagnostic evidence</td>
<td>24</td>
<td>99 (99-100)</td>
<td>261.67 (p = 0.000)</td>
</tr>
<tr>
<td>Prospective design</td>
<td>19</td>
<td>99 (98-99)</td>
<td>177.72 (p = 0.000)</td>
</tr>
<tr>
<td>Retrospective design</td>
<td>7</td>
<td>97 (95-99)</td>
<td>67.29 (p = 0.000)</td>
</tr>
<tr>
<td>Mean age &lt; 50</td>
<td>23</td>
<td>99 (99-100)</td>
<td>243.43 (p = 0.000)</td>
</tr>
<tr>
<td>Mean age 50-69</td>
<td>11</td>
<td>97 (95-99)</td>
<td>71.44 (p = 0.000)</td>
</tr>
<tr>
<td>Device: EUB-8500</td>
<td>20</td>
<td>99 (98-99)</td>
<td>154.23 (p = 0.000)</td>
</tr>
<tr>
<td>Device: Elegra/Antares</td>
<td>6</td>
<td>98 (96-99)</td>
<td>93.06 (p = 0.000)</td>
</tr>
</tbody>
</table>

eTable 6  **Explanation of the QUADAS quality appraisal tool, as adapted for the systematic review**

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>How to Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Was the spectrum of patients representative of the patients who will receive the test in practice?</td>
<td>This item will usually be scored as ‘yes’, as these tests are being advertised for use in women of all ages, with all spectrum of disease. Score this item as ‘no’ if the sample includes males, disease severity is limited (eg BI-RADS IV or higher), or a narrow age range is selected (eg 20 years). If age range is not reported, score it ‘unsure’.</td>
</tr>
<tr>
<td>2</td>
<td>Were selection criteria clearly described?</td>
<td>If inclusion/exclusion criteria are described, score it ‘yes’. If neither inclusion nor exclusion criteria are presented, score it ‘no’. If inclusion criteria are presented but exclusion criteria are not, score it ‘unsure’.</td>
</tr>
<tr>
<td>3</td>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>If histopathology (any type of sampling method) was used as the reference, score it ‘yes’. If biopsy was not used as the reference, or no reference was used, score it ‘no’. If unclear, score it ‘unsure’.</td>
</tr>
<tr>
<td>4</td>
<td>Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?</td>
<td>If time between the index test and reference standard is stated as &lt; 12 months, or the study recruitment took place over &lt; 12 months, score it ‘yes’. If the reported time between tests is &gt; 12 months, score it ‘no’. If time between tests is not stated, and the study recruitment was longer than 12 months, score it ‘unsure’.</td>
</tr>
<tr>
<td>5</td>
<td>Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?</td>
<td>If the whole sample or random selection of the sample received the reference, score it ‘yes’. If the sample was non-random, score it ‘no’. If it is not clear whether the sample was random, score it ‘unsure’.</td>
</tr>
<tr>
<td>6</td>
<td>Did patients receive the same reference standard regardless of the index test results?</td>
<td>If all patients received the same reference standard (all forms of biopsy are classified as ‘biopsy’, and treated as the same reference type), score it ‘yes’. If patients received different reference standards based on index test results, score it ‘no’. If not clear, score ‘unsure’.</td>
</tr>
<tr>
<td>7</td>
<td>Was the reference standard independent of the index test? (i.e. the index test did not form part of the reference standard?)</td>
<td>If the index test did not form part of the reference standard applied, score it ‘yes’. If no reference standard was used, score it ‘no’. If not clear, score ‘unsure’.</td>
</tr>
<tr>
<td>8</td>
<td>Was the execution of the index test described in sufficient detail to permit replication of the test?</td>
<td>If the execution of the index test is described in detail, score it ‘yes’. If there is limited information available on the execution of the index test, score it ‘no’. If not clear, score ‘unsure’.</td>
</tr>
<tr>
<td>9</td>
<td>Was the execution of the reference standard described in sufficient detail to permit its replication?</td>
<td>If specific method(s) of biopsy/histopathology are described, score it ‘yes’. If another reference standard is used, and described in detail, score it ‘yes’. If the method of biopsy is not described, or another reference standard is used and not described in detail, score it ‘no’.</td>
</tr>
<tr>
<td>10</td>
<td>Were the index test results interpreted without knowledge or the results of the reference test?</td>
<td>If it is clearly stated that test results were interpreted blind to the reference standard results, score it ‘yes’. If it is stated to the contrary, score it ‘no’. If blinding status is not reported, score it ‘unsure’.</td>
</tr>
<tr>
<td>11</td>
<td>Were the reference standard results interpreted without knowledge of the results of the index test?</td>
<td>If it is clearly stated that reference results were interpreted blind to the index test results, score it ‘yes’. If it is stated to the contrary, score it ‘no’. If blinding status is not reported, score it ‘unsure’.</td>
</tr>
<tr>
<td>12</td>
<td>Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?</td>
<td>If an automatic tool is used to interpret test results, score it ‘yes’ (as there is no risk of bias from automatic subjective interpretation). If reference standard results are used to interpret index test results, score it ‘no’. In all other cases score it ‘yes’.</td>
</tr>
<tr>
<td>13</td>
<td>Were uninterpretable/intermediate test results reported?</td>
<td>If uninterpretable results are presented, or there were no uninterpretable results, score it ‘yes’. If uninterpretable results are present, but not reported, score it ‘no’. If unclear, score ‘unsure’.</td>
</tr>
<tr>
<td>14</td>
<td>Were withdrawals from the study explained?</td>
<td>If it is clear what happened to all participants who entered the study, score it ‘yes’. If participants who entered the study but did not complete were unaccounted for, score it ‘no’. If it is not clear what happened to all participants, score it ‘unsure’.</td>
</tr>
</tbody>
</table>
eFigure 1  Percentage of all studies fulfilling individual QUADAS criteria

- Withdrawals explained
- Uninterpretable results
- Clinical data
- Blinded reference
- Blinded index
- Reference description
- Index description
- Independent reference
- Consistent reference
- Full verification
- No Time Lag
- Appropriate reference
- Selection criteria
- Representative spectrum

<table>
<thead>
<tr>
<th>YES</th>
<th>UNCLEAR</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Percentage of Studies

eFigure 2  Individual study estimates of sensitivity and specificity for USE using artificial neural networks

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Sensitivity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moon (2005)</td>
<td>0.85 [0.70 - 0.94]</td>
</tr>
<tr>
<td>Moon (2009)</td>
<td>0.84 [0.73 - 0.92]</td>
</tr>
<tr>
<td>Moon (2010)</td>
<td>0.92 [0.79 - 0.98]</td>
</tr>
<tr>
<td>Chen (2006)</td>
<td>0.85 [0.70 - 0.94]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moon (2005)</td>
<td>0.68 [0.57 - 0.79]</td>
</tr>
<tr>
<td>Moon (2009)</td>
<td>0.80 [0.65 - 0.93]</td>
</tr>
<tr>
<td>Moon (2010)</td>
<td>0.74 [0.60 - 0.82]</td>
</tr>
<tr>
<td>Chen (2006)</td>
<td>0.95 [0.86 - 0.99]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>I2 = 10.09 [0.00 - 100.00]</th>
</tr>
</thead>
</table>

eFigure 3  Individual study estimates of sensitivity and specificity for USE using length ratio

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Sensitivity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sohn (2009)</td>
<td>0.88 [0.77 - 0.95]</td>
</tr>
<tr>
<td>Regnar (2010)</td>
<td>0.96 [0.87 - 1.00]</td>
</tr>
<tr>
<td>Leong (2010)</td>
<td>1.00 [0.87 - 1.00]</td>
</tr>
<tr>
<td>Garra (1997)</td>
<td>0.98 [0.89 - 1.00]</td>
</tr>
<tr>
<td>Burns (2007)</td>
<td>0.99 [0.91 - 0.99]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sohn (2009)</td>
<td>0.55 [0.48 - 0.61]</td>
</tr>
<tr>
<td>Regnar (2010)</td>
<td>0.71 [0.60 - 0.83]</td>
</tr>
<tr>
<td>Leong (2010)</td>
<td>0.74 [0.63 - 0.83]</td>
</tr>
<tr>
<td>Garra (1997)</td>
<td>0.56 [0.40 - 0.76]</td>
</tr>
<tr>
<td>Burns (2007)</td>
<td>0.25 [0.14 - 0.40]</td>
</tr>
<tr>
<td>Barr (2010)</td>
<td>0.95 [0.91 - 0.99]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>I2 = 83.52 [71.35 - 96.68]</th>
</tr>
</thead>
</table>

| I2 = 96.82 [95.36 - 98.26] |
eFigure 4 Individual study estimates of sensitivity and specificity for USE using strain ratio
APPENDIX C

Supplementary material for the content analysis
## Content Analysis Codebook Definitions

### Code Category 1: Test Performance – How good is the test at breast cancer imaging?

<table>
<thead>
<tr>
<th>Code</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>The ability of the test to correctly identify breast cancer, has to have a value, i.e. 80% sensitive. If a value is not listed, code to Technical-Technology sensitivity.</td>
<td>80% sensitive</td>
</tr>
<tr>
<td>Specificity</td>
<td>The ability of the test to correctly identify healthy or benign tissue, has to have a value.</td>
<td>95% specific</td>
</tr>
<tr>
<td>Reliability</td>
<td>The test can reproduce similar results when repeated multiple times, “reproducible”, “reliable”, “repeatable”.</td>
<td>Reproducible</td>
</tr>
<tr>
<td>Accuracy</td>
<td>Any statement which explicitly refers to the degree of accuracy of the test, e.g. “highly accurate”.</td>
<td>Highly accurate</td>
</tr>
<tr>
<td>Risk factor for cancer</td>
<td>The ability of the test results to predict the risk of cancer development following a positive test result, e.g. “A positive test places women at 4 times greater risk than family history of breast cancer.”</td>
<td>Increased risk</td>
</tr>
<tr>
<td>General</td>
<td>A statement about the performance of the test that does not fit into another category.</td>
<td>Test is easy to perform</td>
</tr>
</tbody>
</table>

### Code Category 2: Test Benefits – What benefits does the test have?

<table>
<thead>
<tr>
<th>Code</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pain</td>
<td>The test does not inflict physical pain on patients.</td>
<td>Pain-free procedure</td>
</tr>
<tr>
<td>No compression</td>
<td>The test does not physically compress or squeeze the breast, nor come into contact with the skin.</td>
<td>Non-compressive</td>
</tr>
<tr>
<td>Non-invasive</td>
<td>An explicit statement that refers to the test as being non-invasive.</td>
<td>Non-invasive technology</td>
</tr>
<tr>
<td>No risk</td>
<td>An explicit statement that the test provides no risk to the patients in any way.</td>
<td>Risk-free</td>
</tr>
<tr>
<td>Financial benefits-savings</td>
<td>The test is well priced compared to other available methods of breast imaging, and can save patients money.</td>
<td>Cost-effective</td>
</tr>
<tr>
<td>No doctors referral</td>
<td>A referral from a healthcare practitioner is not required in order to undergo the test.</td>
<td>No referral needed</td>
</tr>
<tr>
<td>General</td>
<td>A statement about the benefits of the test that does not fit into another category.</td>
<td>Cost savings</td>
</tr>
</tbody>
</table>

### Code Category 3: Test Limitations – What are the limitations of the test?

<table>
<thead>
<tr>
<th>Code</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical limitations</td>
<td>A description of the technical limitations of the test, e.g. what it is incapable of, or should not be used for due to its limitations, or whether it is susceptible to error if it deviates from recommended guidelines of use.</td>
<td>Not suitable for patients with implants</td>
</tr>
<tr>
<td>Research limitations</td>
<td>A description of shortcomings in the evidence base supporting the use of the test for breast cancer imaging, e.g. poorly designed research, lack of evidence for an application of the device.</td>
<td>Lack of evidence for effectiveness</td>
</tr>
<tr>
<td>General</td>
<td>A statement about the limitations of the test that does not fit into another category.</td>
<td>Limited accuracy in dense breast tissue</td>
</tr>
</tbody>
</table>

### Code Category 4: Comparators – How does the test compare with established imaging tests (e.g. mammography)?

<table>
<thead>
<tr>
<th>Code</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct comparison with comparator</td>
<td>The test is directly compared to another established breast imaging test e.g. “this test is for any woman who does not want to undergo the discomfort of a mammogram”; “earlier detection than a mammogram”.</td>
<td>Better detection than mammography</td>
</tr>
<tr>
<td>Indirect comparison with comparator</td>
<td>A statement which implies the test may be better than a conventional breast test, in which the comparator is not named, e.g. “Filling the gap in breast health”; “earlier detection that other imaging methods”.</td>
<td>Early detection compared to other tests</td>
</tr>
<tr>
<td>Performance with comparator</td>
<td>The results of the test when used in combination with another breast imaging test, e.g. “the test sensitivity was 95% when used in combination with mammography.”</td>
<td>Improved sensitivity in combination with mammography</td>
</tr>
<tr>
<td>Limitations of comparator</td>
<td>A description of the current limitations of the comparator, e.g. “exposes women to radiation”; “the comparator is uncomfortable”.</td>
<td>Limited in high-risk populations</td>
</tr>
<tr>
<td>Benefits of comparator</td>
<td>A description of the current benefits of the comparator test, e.g. “high sensitivity, effective at detecting early breast cancer”.</td>
<td>Improved detection in dense breast tissue</td>
</tr>
</tbody>
</table>
Technological basis for comparator  The justification for how the comparator works, i.e. the mechanism by which it distinguished between benign and malignant breast tissue, e.g. “an anatomical test which detects regions of suspicious.

General  A statement about a comparator test that does not fit into another category.

**Code Category 5: Technical – How good is the technology used to carry out the test? How does it work?**

<table>
<thead>
<tr>
<th>Advanced technology</th>
<th>A statement which describes the test as cutting edge, advanced, state-of-the-art, etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technology sensitivity</td>
<td>The analytical sensitivity of the test, not the diagnostic sensitivity, i.e. the test is able to measure breast characteristics to a level of precision, e.g. “the test is sensitive to 0.01 degrees”.</td>
</tr>
<tr>
<td>Technological basis for test</td>
<td>The justification for how the device works, i.e. the mechanism by which it distinguished between benign and malignant breast tissue. E.g. for thermography, the phrase “physiological test” indicates the mechanism by which the test operates.</td>
</tr>
<tr>
<td>General</td>
<td>A statement about the technical aspects of the test that does not fit into another category.</td>
</tr>
</tbody>
</table>

**Code Category 6: Effectiveness – Does the test reduce breast cancer related mortality?**

| Survival Rates | Reported statistics of cancer survival as a direct result of breast imaging with the test. |
| General | Any statement that refers explicitly to the effectiveness of the test in plain terms, or its ability to reduce breast cancer mortality. |

**Code Category 7: Safety – Is the test safe?**

| No Radiation | The test does not emit ionizing radiation. |
| Toxicity | Device described as non-toxic. |
| General | Any general/generic remark relating explicitly to the “safety” of the test, e.g. “This test is 100% safe” |

**Code Category 8: Supporting Evidence (or statement of endorsement) – How do they suggest the test is legitimate?**

| Accreditation | A statement that the test or clinic has received accreditation by an official or governing body, e.g. “the clinic is fully accredited by the ACCT” |
| Case study | A sample case study is referenced or presented as evidence of how the test is able to detect breast cancer, typically involving pictures of “healthy” and “diseased” test results. |
| Conference abstract | A conference abstract is referenced or presented as evidence to support the use of the test for breast cancer imaging. |
| Conference poster | A newspaper article is referenced or presented as evidence to support the use of the test for breast cancer imaging. |
| Peer reviewed literature | Peer reviewed journal articles are referenced or presented as evidence to support the use of the test for breast cancer imaging, e.g. “recent studies show”, “a recent clinical trial has proven.” |
| FDA approval | The test has received approval for use for breast imaging by the FDA, the regulator of therapeutic goods in the US, e.g. “FDA approved”, “regulatory approval in the US” |
| TGA approval | The test has received approval for use for breast imaging by the TGA, the regulator of therapeutic goods in Australia, e.g. “TGA approved”, “regulatory approval in AUS” |
| Newspaper article | A newspaper article is presented as evidence to support the use of the test for breast cancer imaging. |
| Staff qualifications | A claim which explicitly states the qualifications and level of training that staff receive, or implicitly states that the staff received training by giving their employment position, e.g. “our tests are carried out by imaging technicians” implies the staff have been technically trained. |
| Author identified | The author of the content provided on the website has been identified by name and/or qualifications, e.g. |
“report by Dr John Smith, MBBS etc”

General
A statement endorsing the test or suggesting that the test is legitimate that does not fit into another category.

**Code Category 9: Target Population – Who is the test used on?**

<table>
<thead>
<tr>
<th>Target Population</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>The test is advertised explicitly for use as a breast cancer imaging tool suitable for all women, “women of all ages”, “every woman’s responsibility”, “all breast types”</td>
</tr>
<tr>
<td>Young women</td>
<td>The test is advertised for breast cancer imaging in “young women” i.e. under 50 years.</td>
</tr>
<tr>
<td>Children</td>
<td>The test is advertised for breast cancer imaging in “children”, i.e. under 18 years.</td>
</tr>
<tr>
<td>Breast size</td>
<td>The test is advertised for breast cancer imaging in women with breasts of any size.</td>
</tr>
<tr>
<td>Breast implants</td>
<td>The test is advertised for breast cancer imaging in women with breast implants.</td>
</tr>
<tr>
<td>Breast shape</td>
<td>The test is advertised for breast cancer imaging in women with breasts of all shapes.</td>
</tr>
<tr>
<td>Breast density</td>
<td>The test is advertised for breast cancer imaging in women with dense breasts.</td>
</tr>
<tr>
<td>Men</td>
<td>The test is advertised for breast cancer imaging in men.</td>
</tr>
<tr>
<td>Increased risk of breast cancer</td>
<td>The test is advertised for breast cancer imaging in women with an increased risk, e.g. due to family history, BRCA1/2 status, hormone replacement therapy etc.</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>The test is advertised for breast cancer imaging in pregnant women.</td>
</tr>
<tr>
<td>General</td>
<td>A statement about the target population for the test that does not fit into another category.</td>
</tr>
</tbody>
</table>

**Code Category 10: Testimonials (Direct quotes from third parties) – What are third parties saying about the test?**

**Patients**

- Comparator: The patient makes explicitly or implicit comparisons between the test and an existing imaging test such as a mammogram.
- Doctor recommended: The patient purchased the test on the recommendation of a healthcare provider.
- Family recommended: The patient purchased the test on the recommendation of a family member.
- Recommend to others: The patient indicated that they would recommend the test to others.
- Empowerment: The patient states that the test empowered them, or helped them be more proactive in their breast health.
- Peace of mind: The patient states that the test gave them peace of mind regarding their breast health.
- Safety: The patient refers to the safety of the test, as outlined in the safety node.
- Service delivery: Any statement made by the patient about the quality of the service delivery at the test clinic.
- Technical: The patient refers to the technical aspects of the test, as outlined in the technical node.
- Test benefits: The patient refers to the benefits of the test, as outlined in the test benefits node.
- Test performance: The patient refers to the test performance, as outlined in the test performance node.
- Target population: The patient refers to the target population for use of the test, as outlined in the target population node.
- Uses of technology: The patient suggests that the test does not emit any radiation.

**Healthcare practitioner**

- Comparator: The clinician makes explicit or implicit comparisons between the test and an existing imaging test such as a mammogram.
<table>
<thead>
<tr>
<th>Code Category 11: Uses of Technology – What is the test used for?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening</strong></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
</tr>
<tr>
<td><strong>Detection – non-specific</strong></td>
</tr>
<tr>
<td><strong>Adjunct screening</strong></td>
</tr>
<tr>
<td><strong>Adjunct diagnosis</strong></td>
</tr>
<tr>
<td><strong>Adjunct detection – non-specific</strong></td>
</tr>
<tr>
<td><strong>Prevention of disease</strong></td>
</tr>
<tr>
<td><strong>Risk factor for disease</strong></td>
</tr>
<tr>
<td><strong>Not an alternative to comparator</strong></td>
</tr>
<tr>
<td><strong>Monitoring current treatment</strong></td>
</tr>
<tr>
<td><strong>Monitor breast health</strong></td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
</tr>
<tr>
<td><strong>General</strong></td>
</tr>
</tbody>
</table>
### Code Category 12: Perception of test by healthcare professionals (indirect quotes, different to testimonials)

<table>
<thead>
<tr>
<th>Supportive</th>
<th>A statement that suggests the test is accepted and endorsed by healthcare professionals, but is not a first-hand testimonial from a clinician, e.g. &quot;used extensively in human medicine, accepted by clinicians, recommended by doctors.&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dismissive</td>
<td>A statement that suggests the test is neither accepted nor endorsed by healthcare professionals, e.g. &quot;not widely accepted by the medical community&quot;, &quot;hesitation to adopt the test.&quot;</td>
</tr>
</tbody>
</table>

### Code Category 13: Reasons for lack of uptake of test in mainstream medicine

<table>
<thead>
<tr>
<th>Reasons for lack of uptake</th>
<th>A justification for why the test is not accepted or widely adopted in mainstream medicine currently.</th>
</tr>
</thead>
</table>

### Code Category 14: Response to criticism, policy intervention, or negative media attention posted on website

<table>
<thead>
<tr>
<th>Response to criticism</th>
<th>An official statement or article on the website which is written in response to negative media attention, specific criticisms from individuals/institutions, or in response to a policy injunction placed on the company by a regulator such as the Therapeutic Goods Complaints Resolution Panel.</th>
</tr>
</thead>
</table>
APPENDIX D

Supplementary material for the stakeholder engagement
12 November 2012

Associate Professor C Laurence
General Practice

Dear Associate Professor Laurence

PROJECT NO: H-2012-146  
*Exploring stakeholder perspectives on the regulation of direct-to-consumer diagnostic and screening devices for breast cancer*

I write to advise you that the Human Research Ethics Committee has approved the above project. Please refer to the enclosed endorsement sheet for further details and conditions that may be applicable to this approval. Ethics approval is granted for a period of three years subject to satisfactory annual progress reporting. Ethics approval may be extended subject to submission of a satisfactory ethics renewal report prior to expiry.

**The ethics expiry date for this project is: 31 October 2015**

Where possible, participants taking part in the study should be given a copy of the Information Sheet and the signed Consent Form to retain.

Please note that any changes to the project which might affect its continued ethical acceptability will invalidate the project’s approval. In such cases an amended protocol must be submitted to the Committee for further approval. It is a condition of approval that you immediately report anything which might warrant review of ethical approval including (a) serious or unexpected adverse effects on participants (b) proposed changes in the protocol; and (c) unforeseen events that might affect continued ethical acceptability of the project. It is also a condition of approval that you inform the Committee, giving reasons, if the project is discontinued before the expected date of completion.


Yours sincerely

[Signature]

Dr John Semmler
Acting Convenor
Human Research Ethics Committee
Applicant: Associate Professor C Laurence

School: General Practice

Project Title: Exploring stakeholder perspectives on the regulation of direct-to-consumer diagnostic and screening devices for breast cancer

THE UNIVERSITY OF ADELAIDE HUMAN RESEARCH ETHICS COMMITTEE

Project No: H-2012-146 RM No: 0000014248

APPROVED for the period until: 31 October 2015

It is noted that this study will involve Thomas Vreugdenburg, PhD candidate.

Refer also to the accompanying letter setting out requirements applying to approval.

Dr John Semmler
Acting Convenor
Human Research Ethics Committee

Date: 10 OCT 2012
The University of Adelaide
Human Research Ethics Committee (HREC)

CONTACTS FOR INFORMATION ON PROJECT AND INDEPENDENT COMPLAINTS PROCEDURE

The following study has been reviewed and approved by the University of Adelaide Human Research Ethics Committee:

<table>
<thead>
<tr>
<th>Project Title:</th>
<th>Exploring stakeholder perspectives on the regulation of direct-to-consumer diagnostic and screening devices for breast cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Number:</td>
<td>H-2012-146</td>
</tr>
</tbody>
</table>

The Human Research Ethics Committee monitors all the research projects which it has approved. The committee considers it important that people participating in approved projects have an independent and confidential reporting mechanism which they can use if they have any worries or complaints about that research.

This research project will be conducted according to the NHMRC National Statement on Ethical Conduct in Human Research (see http://www.nhmrc.gov.au/publications/synopses/e72syn.htm)

1. 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 project co-ordinator:

<table>
<thead>
<tr>
<th>Name:</th>
<th>1) Prof Janet Hiller</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2) Dr Caroline Laurence</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phone:</th>
<th>1) 03 9953 3566</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2) 08 8313 4951</td>
</tr>
</tbody>
</table>

2. If you wish to discuss with an independent person matters related to:
   • making a complaint, or
   • raising concerns on the conduct of the project, or
   • the University policy on research involving human participants, or
   • your rights as a participant,

contact the Human Research Ethics Committee’s Secretariat on phone (08) 8313 6028 or by email to hrec@adelaide.edu.au
The University of Adelaide  
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:

<table>
<thead>
<tr>
<th>Title:</th>
<th>Exploring stakeholder perspectives on the regulation of direct-to-consumer diagnostic and screening devices for breast cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethics Approval Number:</td>
<td>H-2012-146</td>
</tr>
</tbody>
</table>

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. Although I understand the purpose of the research project it has also been explained that involvement may not be of any benefit to me.

4. 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.

5. I understand that I am free to withdraw from the project at any time.

6. I agree to the interview being audio/video recorded. Yes ☐ No ☐

7. 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: __________
Invitation to Participate in a Stakeholder Engagement on the Regulation of Emerging Breast Cancer Imaging Devices

We would like to invite your organisation to participate in a stakeholder engagement on the regulation of emerging breast cancer imaging devices.

In recent years, a number of emerging devices used for breast cancer screening and diagnosis have entered the Australian market. These devices, including digital infrared thermography, have recently garnered considerable attention from regulators due to their questionable advertising material aimed directly towards consumers.

In this study, we are conducting semi-structured interviews with stakeholder organisations involved in breast cancer research, prevention, practice, and policy. Our goal is to engage with prominent members within the breast cancer community around the manner in which these emerging devices and their advertising material is regulated in Australia.

Your organisation has been identified as part of a peak, national organisation which provides support to the breast cancer community. We are seeking up to two representatives from your organisation with some knowledge of breast cancer imaging practice, policy, or research to participate in our engagement.

The interviews will last no longer than 60 minutes, and will discuss the strengths and weaknesses in the current regulatory system for these new devices, as well as potential options for reform. Further information about the project and the nature of the interviews is available in the attached document.

As the Therapeutic Goods Administration is currently in the process of developing options for reform within this area, this engagement presents a unique opportunity for the breast cancer community to provide input into the manner in which new breast imaging devices are regulated in Australia.

At this stage we simply ask that you respond to this email, indicating whether or not your organisation has in-principal interest in participating in this discussion. If so, a member of our research team will be in contact to discuss potential participants from within your organisation in the near future.

Sincerely,

Prof. Janet Hiller
Associate Dean (Research)
Professor of Public Health
Australian Catholic University
janet.hiller@acu.edu.au

Dr Caroline Laurence
Associate Professor of General Practice
The University of Adelaide
caroline.laurence@adelaide.edu.au

Dr Cameron Willis
Senior Research Fellow
The University of Adelaide
cameron.willis@adelaide.edu.au

Ms Linda Mundy
Senior Research Officer
Queensland Health
linda_mundy@health.qld.gov.au

Mr Thomas Vreugdenburg
PhD Candidate
The University of Adelaide
thomas.vreugdenburg@adelaide.edu.au
Participant information sheet

Exploring stakeholder perspectives on the regulation of direct-to-consumer diagnostic and screening devices for breast cancer

What we would like you to do

As a member of a peak organisation invested in breast cancer prevention, we would like to invite you to participate in a stakeholder engagement aimed at investigating the regulation of emerging breast cancer imaging devices in Australia.

We would like to invite you to take part in one semi-structured interview lasting approximately 60 minutes. In the interview we will discuss the strengths and weaknesses of the current system of regulation for breast imaging devices and their related advertising material, the characteristics of a new device that should be considered before it is made available as a screening or diagnostic tool, and the pros and cons of the options for reform to this system that were recently outlined by the Therapeutic Goods Administration (TGA). The results of this study will contribute towards a doctoral thesis, be published in a peer-reviewed journal article, and will be submitted as an advisory report to the Regulatory and Technical Consultative Forum for medical devices (RegTech Forum).

The interviews will be conducted by Mr Thomas Vreugdenburg and will take place in-person where possible, or otherwise via telephone/video conference. The time and location of interviews will be organised at your convenience. To aid in the accurate analysis of interviews, we will be asking permission to record interviews, following which we will provide you with a verbatim interview transcript that you can amend where necessary.

Participation in this study is entirely voluntary, and you may withdraw from the study at any time without prejudice. In the unlikely event that a problem arises during the interview process, the contact details of the research team are available in the Independent Complaints Form attached to this form. The names and contact details of individual participants will remain anonymous in any published work that results from this study, and will only be available to members of the research team.

Background Information

In recent years, a number of new and emerging technologies used for breast cancer screening and diagnosis have entered the Australian market, including electrical impedance scanning (EIS), digital infrared thermal imaging (DITI), and electronic palpation imaging (EPI). These devices are funded out-of-pocket, do not require a referral from a doctor, and are promoted directly towards consumers as safe and effective solutions for breast cancer screening and diagnosis. In response to these advertising claims, the devices have drawn considerable attention from various interest groups that have questioned their safety and performance.

This stakeholder engagement makes up the third and final phase in a case study investigating the regulatory framework for breast cancer screening and diagnostic devices in Australia. The first phase of this study involved a systematic review of the safety and diagnostic accuracy of these devices. In the second phase, online advertising claims for these devices were assessed and compared with the evidence of safety and performance collected in the review. The results of these studies highlighted two important features of the current regulatory system for breast cancer devices:
1. Firstly, breast cancer devices advertised directly towards consumers on the Australian can have highly variable evidence base to support their safety and performance.

2. Secondly, reported claims in advertising material for these technologies are not supported by the available evidence.

Certain characteristics of the current system of regulation may have contributed to this situation. Firstly, breast imaging devices are currently regulated using a risk-based approach that accounts for the potential for physical harm caused by a device, but which overlooks the harms related to the accuracy of non-invasive diagnostic and screening devices (i.e. incorrectly classifying someone as either positive or negative). These devices are consequently classified as ‘low risk’, and are not required to provide evidence supporting their safety and performance prior to market approval. Secondly, regulators are reliant upon industry self-regulation and consumer complaints to draw attention to cases of advertising misconduct, as there is currently no independent body funded or resourced to assess advertisements for breast imaging devices prior to dissemination, nor to carry out active monitoring of existing advertising content. In recognition of these problems, Australia’s therapeutic goods regulator – the TGA - initiated a series of public consultations during 2010, which aimed to review the current regulatory framework for both medical devices and therapeutic goods advertising.

The Medical Devices Regulatory Consultation
Involving primarily industry, the consultation highlighted four key areas for reform, including: reclassifying joint implants as high risk devices, increasing the level of scrutiny required for the pre-market approval of implantable devices, improving the transparency of medical devices that are included on the Australian Register of Therapeutic Goods (ARTG), and publishing product information about devices on the TGA website.[1] While the consultation covered these topics in great detail, it did not address the issues relating to the pre-approval of breast cancer diagnostic devices. Consequently, the current pathway onto the Australian marketplace continues to allow ‘low risk’ breast imaging devices to be marketed without a review of their performance or performance-related safety.

The Therapeutic Goods Advertising Consultation
The therapeutic goods advertising consultation elicited submissions from a broad range of industry, professional, and consumer stakeholder groups.[2] It was agreed in-principle that medical devices (including breast cancer imaging devices) be included into the existing pre-approval process for advertising, which currently includes prescription and non-prescription medicines. However, the current approvals process has been shown to be ineffective, with a large number of pre-approved advertisements found to be in breach of relevant regulations in 2009-2010. [3] Furthermore, the extent to which devices would be included into the pre-approval framework was also not made clear, i.e. whether ‘high risk’, ‘low risk’, or all devices would be required to comply with pre-approval requirements. Following the consultation, three options for reform in regulation of therapeutic goods advertising were proposed:

- **Option 1**: Strengthen the current pre-approval system
- **Option 2**: Remove the pre-approval system in favour of active monitoring
- **Option 3**: Develop a new regulatory system, involving a database of therapeutic goods advertising

While these consultations were open for submissions from the wider public, the breast cancer community was not represented. There are a number of issues highlighted in our previous studies, as well as the TGA’s consultations, which directly affect the marketing and availability of emerging breast imaging technologies in Australia. As the TGA is currently in the process of developing options for reform within this area, this engagement presents a unique
opportunity for the breast cancer community to provide input into the manner in which new breast imaging devices are regulated in Australia.

Thank you for your consideration, and we look forward to your contribution.

Sincerely,

Prof. Janet Hiller  
Associate Dean (Research)  
Professor of Public Health  
Australian Catholic University  
janet.hiller@acu.edu.au

Dr Caroline Laurence  
Associate Professor of General Practice  
The University of Adelaide  
caroline.laurence@adelaide.edu.au

Mr Thomas Vreugdenburg  
PhD Candidate  
The University of Adelaide  
thomas.vreugdenburg@adelaide.edu.au

Dr Cameron Willis  
Senior Research Fellow  
The University of Adelaide  
cameron.willis@adelaide.edu.au

Ms Linda Mundy  
Senior Research Officer  
Queensland Health  
linda_mundy@health.qld.gov.au

References

Proposed Changes to the Regulation of Medical Devices and Therapeutic Goods Advertising in Australia

Medical Devices Regulatory Reforms

Proposal 1 will allow Australian companies that manufacture low-risk devices to be certified by a third party, e.g. a European regulator, instead of the TGA. This option would also involve a process of certifying third party assessment bodies (within AUS and overseas) for competency.

Proposal 2 will amend the way in which medical devices are registered on the Australian Register of Therapeutic Goods (ARTG) – a requirement for the supply of medical devices in AUS – by requiring every model or variation of a device to be listed under the same ARTG entry.

Proposal 3 will require devices that have been approved by the TGA for sale in Australia to identify their ARTG entry number on the information that accompanies the device.

Proposal 4 will extend the product information published about devices on the TGA website, which is currently limited to the name of the device, the name of the sponsor and manufacturer, its intended purpose, and any special conditions relevant to its use.

Therapeutic Goods Advertising Reforms

Option 1: The current pre-market approval process for advertisements (which is currently limited to non-prescription medicines) will be extended to include medical devices and internet websites. This would require sponsors of devices, and all internet advertisements, to be submitted to the TGA prior to being approved for promotion in AUS.

Option 2: Remove the current pre-market approval system in favour of an efficient monitoring system, coupled with increased sanctions and penalties to act as a deterrent against breaching advertising regulations.

Option 3: An alternative, risk-based approach to the current pre-approvals process, in which only “repeat offenders” will be required to submit their ads for approval prior to promotion in AUS. Under this system, all advertisements will be entered onto a central database, and an audit of the database would identify companies that repeatedly breached advertising regulations. These companies would then need to have all of their future advertisements pre-approved.
Interview Schedule

Project Title: Exploring stakeholder perspectives on the regulation of direct-to-consumer diagnostic and screening devices for breast cancer.

Pre-Market Regulation of Medical Devices

1) What is your general understanding about how a medical device (or healthcare product) makes its way onto the Australian market?

2) Given what you know about how a device makes it onto the market, what is your view on the main strengths and weaknesses in the current system? (contingent upon previous response)

3) What aspects or characteristics of a device do you believe should be assessed before the device is allowed onto the Australian marketplace?
   a. For example, as a member of the public who is considering purchasing a cancer test, what kind of evaluations do you think that product should have had to pass before becoming available to you?

4) What kind/type/level of evidence do you think would be sufficient to support these assessments?

5) The TGA has recently come up with a range of proposals to change the way in which medical devices are made available on the market. Each proposal has been raised as a potential option, all of which can be considered, not just one or the other. What do you see as the potential advantages or disadvantages of the following proposals?
   a. **Proposal 1:** The first proposal will allow Australian companies that manufacture devices to be certified by a third party assessment body, for example, a European regulator, instead of the TGA. This option would also involve a process of certifying third party assessment bodies (within Aus and overseas) for competency.
   b. **Proposal 2:** Amend the way in which a kind of medical device is included in the ARTG, by requiring the identification of all devices and/or models that are supplied under the same ARTG entry.
c. **Proposal 3:** Devices that have been approved by the TGA for sale in Australia will be required to identify their ARTG entry number on the information that accompanies the device.

d. **Proposal 4:** In this proposal, the TGA is planning to extend the product information published about devices on its website, which is currently limited to the name of the device, who the sponsor and manufacturer are, its intended purpose, and any special conditions applied.

i. The TGA is specifically looking to publish information about the basis upon why a device is allowed onto the market or not, as well as the amount of evidence that was considered in reaching this decision. What do you see as the potential advantages and disadvantages of this proposal?

ii. Do you think this type of information published for:
   
a. Only high-risk devices, i.e. not including non-invasive breast imaging tests, or
   
b. All devices, or
   
c. Only high-risk devices and “interesting” low-risk devices, including new and innovative technology, or
   
d. Only devices applying for inclusion on the ARTG (without conformity assessment decisions), or
   
e. Only devices successfully listed on the ARTG (without publication of rejections)

iii. Should we publish information about applications that are rejected? And the reasons for rejection?

iv. Is there any additional information would you want to be published about the device, and if so, how in-depth would you expect that information to be?

v. Who do you think should be responsible for authoring and updating the information?

6) Along with these proposals, the TGA has also proposed to increase the level of pre-market scrutiny for high-risk medical devices, in order to provide a more rigorous review of their safety and performance; however, the current pathway onto market for diagnostic medical products remains unchanged. Under the current pre-market arrangements, diagnostic medical devices are not assessed for their performance or efficacy prior to market, nor once they are on the market, unless a specific audit is ordered.
a. Do you think diagnostic devices should be assessed for efficacy prior to market, or retroactively once they are on the market?
b. If so, who should be in charge of collecting and assessing the evidence of efficacy?

Regulation of Medical Devices Advertising

1) What is your general understanding about the way in which medical devices (or healthcare products) are advertised in Australia?

2) Given your current understanding about the advertising arrangements for therapeutic goods, what is your view on the main strengths and weaknesses in the current system?

3) Do you think the advertising content for breast imaging devices should be assessed or monitored before being promoted towards Australian consumers?

4) If so, what type of information or claims should be assessed?
   a. For example, as a member of the public who is considering purchasing a cancer test, what kind of evaluations do you think the advertising material for a product should have had to pass before being presented to you?

7) What kind/type/level of evidence do you think would be sufficient to support these assessments?

5) The TGA is also currently looking into different strategies to change the way they regulate therapeutic goods advertising, including the advertising for medical devices. They have proposed three main options to change the way that advertising material is regulated for accuracy. I’m going to read all of the options, and then we will discuss the advantages and disadvantages of each option individually.
   a. In the first option, the current approvals process for advertisements (which is currently limited to non-prescription medicines) will be extended to include medical devices and internet websites. This would require sponsors of devices, and all internet advertisements, to be submitted to the TGA prior to be approved for promotion.
   b. Option 2 is to remove the current pre-approval system in favour of an efficient monitoring system, coupled with the deterrent of increased sanctions and penalties for companies that breach advertising regulations.
   c. The third and final option involves taking a risk-based approach to the current pre-approvals process, by only requiring “repeat offenders” to submit their ads prior to
promotion. Under the scheme, all advertisements directed towards consumers will be entered onto a central database, and an audit of the database would identify companies that repeatedly breached advertising regulations, who would then need to have all of their future advertisements pre-approved.

6) Given the discussion, which option would you most favour? Or alternatively, can you think of another arrangement which might be appropriate?
APPENDIX E

TGA submission: pre-market assessment of medical devices
Changes to Premarket Assessment Requirements for Medical Devices: Regulatory Impact Statement

June 2013

Mr Thomas Vreugdenburg\textsuperscript{1}, Prof Janet E Hiller\textsuperscript{1,2}, Dr Cameron D Willis\textsuperscript{1,3}, Dr Caroline O Laurence\textsuperscript{1}, Ms Linda Mundy\textsuperscript{1,4}

\textsuperscript{1} School of Population Health, The University of Adelaide, SA, Australia

\textsuperscript{2} Faculty of Health Sciences, Australian Catholic University, VIC, Australia

\textsuperscript{3} Centre for Clinical Epidemiology and Evaluation, The University of British Columbia, BC, Canada

\textsuperscript{4} Health Policy Advisory Committee on Technology, Queensland Government, QLD, Australia
The University of Adelaide

Table of Contents

Background ............................................................................................................................................. 3

Proposal A: Increased scrutiny of conformity assessment as part of mandatory application audits
prior to ARTG inclusion of high risk devices ....................................................................................... 5

Proposal B: Publication of medical device regulatory decisions ........................................................... 6

Proposal C: Abolition of requirement for TGA conformity assessment for Australian manufacturers
of lower Class medical devices (including IVDs). ................................................................................ 9

Final remarks ....................................................................................................................................... 11
Background

For the past four years, the Therapeutic Goods Administration (TGA) has been proactive in reforming many aspects of its function as Australia’s principal regulator of therapeutic goods. These reform consultations have included options to reform the advertising arrangements for therapeutic goods, the premarket approval process for medical devices, and the evaluation of complementary medicines. The emphasis on engaging all aspects of the community around these issues is to be commended, and we welcome the opportunity to comment on the reforms put forward in the present regulation impact statement (RIS) on the preapproval of medical devices.

As recent research and Senate inquiries have indicated, there is a need to improve the regulation of medical devices in Australia.[1, 2] The debate around medical device reforms has focussed primarily on high-risk hip and breast implants, due to the large impact that failed implantable devices have had in both Australia and overseas.[3] However, there are a number of issues which relate to breast cancer imaging devices that are relevant to this discussion of regulatory improvement.

A number of new and emerging technologies used for breast cancer screening and diagnosis have entered the Australian market in recent years, including electrical impedance scanning, digital infrared thermal imaging, and electronic palpation imaging, also referred to as computerised breast imaging. These devices are funded out-of-pocket, do not require a referral from a doctor, and are promoted directly towards consumers as safe and effective solutions for breast cancer screening and diagnosis - applications for which they have not received TGA certification. In response to these advertising claims the devices have drawn considerable attention from various interest groups, including the Australian Competition and Consumer Commission, and the National Health and Medical Research Council, that have questioned their safety and performance as breast imaging tools.[4-10] This situation is known to the TGA, as several devices were removed from the register in 2011, following a series of complaints raised with the Complaints Resolution Panel (CRP).[11]

In 2011, we conducted a systematic review that examined the evidence base to support these devices for breast cancer screening and diagnosis. The findings of our review indicate that there is currently insufficient evidence to recommend the use of these technologies for breast cancer screening, and the high level of variability among studies of symptomatic women limits their utility as diagnostic tools as well.[12] Despite having limited, variable quality evidence for screening and diagnosis, these devices are advertised for these indications in Australia, the United States, Canada, and the United Kingdom.[4, 13-15]
The present consultation presents a unique opportunity for members of the breast cancer community to provide input into the manner in which new breast imaging devices may be regulated in the future. In order to ensure that the breast cancer community is represented in this reform process, we conducted semi-structured interviews with members of national and state-based, not-for-profit organisations involved in breast cancer imaging research (n=4), patient advocacy (n=7), and prevention/screening (n=5) between January and March 2013. In total, we interviewed 16 stakeholders from within the breast cancer community around the TGA’s proposed options for reform to both the premarket approval process for medical devices,[16] as well as the proposed changes to the regulation of therapeutic goods advertising [17]. In this submission, we summarise the responses around the proposed changes to the premarket regulation of medical devices outlined in the RIS.
Proposal A: Increased scrutiny of conformity assessment as part of mandatory application audits prior to ARTG inclusion of high risk devices

Proposal A was not part of our interview process, as emerging breast imaging devices have been registered on the Australian Register of Therapeutic Goods (ARTG) under the low risk category, Medical Device Included Class IIA (ARTG entry numbers 152697, 141616). As such we have no comment from participants on this option for reform. We would, however, like to add general comments on the issue of conformity assessment and risk classification. The risk-category that determines the level of pre-market evaluation a medical device faces during conformity assessment is currently determined by the manufacturer of the device when applying for certification.[18] However, as we have observed in the case of emerging breast imaging devices, the intended use of a listed device on the ARTG is often different from the practical application of the device. For example, the intended use of one imaging device currently listed on the ARTG, as defined by the manufacturer, states that the device:

“... is intended to document lesions as identified during a clinical breast exam by producing an accumulated image for each of the areas that contain a lesion. The device should not be used for clinical decision-making.”(ARTG entry number 141616)

However, on the manufacturer’s website it states that the device:

“... is a unique digital sensing device that assists a physician or other trained healthcare professional in screening for breast cancer during routine exams”. [19]

In this instance, if the device was registered for its practical use, i.e. breast screening, rather than its “intended use” as listed on the ARTG entry, then the device should have been registered in a higher risk category to account for the potential harm the device can cause through false-positive and false-negative test results. This particular example is less explicit than advertising material presented in the past, as the manufacturer altered online claims due to a complaint raised to the CRP in 2010.[9] However, this is merely one example of an issue that has been identified throughout the industry, and may be occurring with an unknown number of other classes of listed products. Furthermore, if the TGA were to accept FDA clearance for low-risk devices, as has been discussed in the recent reform consultations, it would have identified that the thermography and impedance devices from the US received a high-risk, Class III classification for use a breast cancer imaging, and can only be accessed via prescription if used as a standalone breast screening or diagnostic tool.[20] We question whether there needs to be some form of quality assurance to ensure that the risk classification of medical devices, as stated by the device’s manufacturer, is indeed correct and represents the actual use of the device in the community.
Proposal B: Publication of medical device regulatory decisions

Interview participants showed majority support for Proposal B (n=13/16), which aims to publish regulatory decisions for medical devices on the TGA website. As all of the participants were in favour of increasing the amount of information published about ARTG decisions online, we do not recommend the adoption of Option 1 or 3, as outlined in the RIS.

Advantages of Proposal B

The most commonly identified advantage of this proposal was its ability to increase the transparency of TGA regulatory processes and decision making. Participants noted difficulties in accessing information about devices listed on the ARTG, and welcomed any initiatives which would help improve the accessibility of this information and improve transparency of TGA processes. It was also noted, as a consideration, that increasing transparency in this manner may open the TGA to criticism over the quality of evidence considered in the decision making process, but that this should not detract from the additional benefits of improving transparency.

Participants indicated that there is a precedent from within the prescription medicine industry to expand the information presented on regulatory decisions, namely the successful Australian Public Assessment Reports for prescription medicines (AusPAR) initiative. An equivalent initiative, intended to broaden the information provided on registered medical devices, in the same vein as AusPARs would help inform both consumers and clinicians about the best-use for new medical devices, particularly those that are not yet established in practice. However, the ability of the new system to provide this benefit is contingent upon the type of information provided on devices, which at this stage appears to be unclear.

Limitations of Proposal B

The most commonly identified limitation of Proposal B highlighted by participants was the increase in resources required by the TGA, including time, money and staff. However, it does not seem unreasonable, as outlined in Option B, to absorb the cost of this new process through a cost-recovery system. Under this system, the additional cost of $215 for simple decisions and $1197 for complex decisions would be absorbed by manufacturers of medical devices applying for certification. The estimated fees outlined in the RIS were not available at the time of our interviews, so we cannot comment on the ability of industry to absorb this cost. However, it was largely acknowledged that regulatory mechanisms and processes should not stifle innovation and that medical devices that are valuable to patient care should be made available in a fast but safe manner.
The University of Adelaide

Consumer advocates also indicated that the average consumer is unlikely to visit the ARTG website to access this additional information. However, it was noted that this information would be valuable to consumer advocates that act on behalf of consumers, and to employ knowledge translation strategies to make the information about decisions more accessible to consumers where deemed necessary.

Which kinds of devices should decision making information be published for?

Participants indicated a preference to have the additional information approved for all medical devices (n=7/16), however 5 participants had no response. As the majority of medical devices registered in Australia fall within low-risk categories, the estimated time and cost to provide this information would be minimal. In regards to emerging breast imaging devices, such a low-cost initiative would highlight to consumer advocacy bodies and clinicians, that there is little evidence of efficacy or effectiveness considered during the certification process for these devices – a fact that is found to be surprising by the vast majority of the participants. Elucidating the lack of evidence considered during the certification process for these devices will help inform consumers and clinicians when deciding whether to use or recommend one of these devices, either as an adjunct or in lieu of regular breast screening procedures.

Publication of regulatory decisions for devices that are rejected

Participants shared nearly unanimous support for the publication of decisions on devices for which market approval was denied (n=15/16). The most commonly noted benefit of this Proposal was to provide justification for why certain devices that are available internationally are not also available in Australia. This information would be valuable for clinicians and consumer advocacy groups that are regularly faced with queries about devices that are not available in this country. Furthermore, this Proposal would increase the transparency of the TGA’s decision making process, which would have the added benefit of highlighting quality control issues in companies that are repeatedly rejected for certification. Participants also noted that identifying these issues may also be useful for regulatory bodies in neighbouring countries, such as New Zealand.

As with the previous proposal to publish regulatory decisions for devices that receive certification, participants also indicated that publishing rejected applications on the TGA website would require increased resources. However, as the cost of these rejected outcomes has been accounted for in the in the costing for Option 2, we refer to our previous comments on pages 4-5 in regards to the financial cost of this proposal on industry. Similarly, it was noted that regular consumers are unlikely to access the information presented on the ARTG website, however, this Regulation impact statement: Changes to premarket assessment requirements for medical devices
information would be useful for clinicians and consumer advocacy groups that use this information to inform consumers about devices. Finally, participants considered that increasing the transparency of device rejections may also allow companies that have been repeatedly rejected on reasonable grounds to publicly dispute these rejections through various media platforms, increasing time and resources needed.

Recommendation for Proposal B

Based on the responses of participants in our community consultation, we conclude that the most appropriate course of action for Proposal B is Option 2. The development of the AusPAR scheme has been largely praised since its inception, and a move towards a similar system for medical devices is welcomed. However, the benefit of this Proposal for emerging breast imaging devices depends on the type and amount of information published for each device. While there remain issues relating to the risk-classification of these devices, it would be valuable to both consumers and clinicians to understand the level and quality of evidence for safety and efficacy that was considered at certification for use in Australia. Therefore, we recommend that the information provided about medical devices include the evidence that was assessed to determine their utility for an intended purpose, and that this process should be applied retrospectively to devices that are already on the Australian market.
The University of Adelaide

Proposal C: Abolition of requirement for TGA conformity assessment for Australian manufacturers of lower Class medical devices (including IVDs).

Like Proposal B, participants also shared majority in-principle support for Proposal C (n=11/16), which aims to remove conformity assessment requirements for Australian manufacturers of low-risk devices. However, unlike the previous proposal, participants’ support of this arrangement was contingent upon the ability of the TGA to clarify a range of extra conditions.

Conditions and limitations of Proposal C

Firstly, participants showed concern around the lack of Australian context in the conformity assessment process for devices, when certification is received from an international regulator. This issue is particularly relevant for emerging breast cancer imaging devices as they are classified as low risk (Class IIa) in Australia, yet still pose significant risks to consumers through false-positive and false-negative test results. There are a number of variables that can influence conformity assessment procedures, including (but not limited to) variations in health system funding and structure, national mammographic breast screening programs, incidence of breast disease, population demographics, and socioeconomic status. Without an adequate consideration of these factors from an Australian context, the results and requirements for international conformity assessments may substantially differ from Australian standards.

Similarly, participants raised questions over the standards being used to certify international regulatory bodies offering third party conformity assessment for medical devices. A number of participants highlighted concerns with European Commission (CE) certification processes, particularly in the complementary medicines industry, and indicated that similar issues may also exist in the certification of medical devices. Comparatively, participants placed greater trust in the Food and Drug Administration’s (FDA) 510(k) process for certifying medical devices in the United States, however, it was suggested that any international regulator considered in this Proposal, including the FDA, should be required to pass rigorous quality assurance procedures before their conformity assessment rulings should be accepted for these imaging devices.

One participant also raised concerns over whether there is the potential for this Proposal to impede or diminish the value of Proposal B. Specifically, it was questioned how/if external conformity assessment procedures would affect the publication of decision making documents for medical devices (similar to the AusPars), given that the conformity assessment would not be conducted by the TGA. Without clarification on these conditions and limitations, there was not majority support for this Proposal (n=7/16).

Regulation impact statement: Changes to premarket assessment requirements for medical devices
Advantages of Proposal C

Assuming that the above conditions are able to be adequately addressed, participants acknowledged several advantages of Proposal C. Firstly, this Proposal would require less duplication of regulatory processes, i.e. if a device has received adequate certification by the FDA it does not require detailed TGA conformity assessment, and therefore require fewer resources. As outlined in the RIS, this will potentially lead to significant cost savings for the TGA depending on the type and number of conformity assessments they receive each year. Additionally, the reduction in double-handling of regulatory procedures will improve the speed at which new medical devices and services will be made available to the community. An additional benefit of this proposal, as noted earlier, relates to differences between the risk-classification of emerging breast imaging devise between the TGA and the FDA. As the FDA categorises these devices in a higher-risk category than the TGA, it is possible that these devices may be required to pass a more rigorous assessment in order to receive conformity assessment.[20]

Recommendation for Proposal C

Based off of the responses from our participants, we recommended Option B as the most appropriate course of action to take for this proposal. The significant cost savings, coupled with the reduced time to market for new and innovative medical devices, give merit to this proposal. However, consumer advocates, researchers, and clinicians noted concerns around the manner in which external bodies would be certified to operate at Australian standards, as well as the lack of Australian context in regulatory decision making for devices which were not considered to be ‘low risk’, even though they are classified as such.
The University of Adelaide

**Final remarks**

The TGA should be commended for their willingness to engage all sectors within the community during the reform consultations that have taken place over the past four years. We look forward to the opportunity to participate in future discussions around regulatory reform in Australia.

Sincerely,

Mr Thomas Vreugdenburg  
PhD Candidate  
The University of Adelaide  
thomas.vreugdenburg@adelaide.edu.au

Prof. Janet Hiller  
Associate Dean (Research)  
Professor of Public Health  
Australian Catholic University, and Adjunct Professor  
The University of Adelaide  
janet.hiller@acu.edu.au

Dr Caroline Laurence  
Associate Professor of General Practice  
The University of Adelaide  
caroline.laurence@adelaide.edu.au

Dr Cameron Willis  
Senior Research Fellow  
The University of Adelaide  
cameron.willis@adelaide.edu.au

Ms Linda Mundy  
Senior Research Officer  
Queensland Health  
linda_mundy@health.qld.gov.au
The University of Adelaide

References


APPENDIX F

TGA submission: regulation of therapeutic goods advertising
Consultation Regulation Impact Statement: Regulating the Advertising of Therapeutic Goods to the General Public

July 2013

Mr Thomas Vreugdenburg\textsuperscript{1}, Prof Janet E Hiller\textsuperscript{1,2}, Dr Cameron D Willis\textsuperscript{1,3}, Dr Caroline O Laurence\textsuperscript{1}, Ms Linda Mundy\textsuperscript{1,4}

\textsuperscript{1} School of Population Health, The University of Adelaide, SA, Australia

\textsuperscript{2} Faculty of Health Sciences, Australian Catholic University, VIC, Australia

\textsuperscript{3} Centre for Clinical Epidemiology and Evaluation, The University of British Columbia, BC, Canada

\textsuperscript{4} Health Policy Advisory Committee on Technology, Queensland Government, QLD, Australia
The University of Adelaide

Table of Contents

Background .................................................................................................................................................. 3

Proposal 1: Alternatives to the pre-approval scheme ............................................................................. 5

Option 1: Maintain the current system ..................................................................................................... 5

Option 2: Extend the current system to include pre-approval for devices, and cover subscription broadcasting .......................................................................................................................... 6

Option 3: Limit the current pre-approvals scheme to cover only “higher risk” categories of advertisements ............................................................................................................................................. 7

Option 4: Retain pre-approvals (modified or not as per option 2 or 3). .................................................. 9

Option 5: Remove the pre-publication approval scheme. ........................................................................ 9

Summary ...................................................................................................................................................... 11
Appendix F

The University of Adelaide

Background

Previous advertising reform consultations held by the Therapeutic Goods Administration (TGA) have highlighted several areas of the current system that are in need of reform, including the pre-approval of advertising claims, the complaints handling process, and the penalties offered for breaches of the Therapeutic Goods Act 1989. [1, 2] Throughout this process, the TGA have invited submissions on these issues from all members of the community, including industry, academia, and consumer organisations. The emphasis placed on engaging the community around these issues is to be commended, and we welcome the opportunity to comment on the reforms put forward in the present regulation impact statement (RIS) on the advertising of therapeutic goods to the general public.

Our specific research interests have been focussed on a particular aspect of the therapeutic goods market, namely direct-to-consumer breast cancer imaging devices. These new devices, including electrical impedance scanning, digital infrared thermal imaging, and electronic palpation imaging, are funded out-of-pocket, do not require a referral from a doctor, and are promoted directly towards consumers as safe and effective solutions for breast cancer screening and diagnosis - applications for which they have not received Australian Register of Therapeutic Goods (ARTG) certification. Considerable attention has been drawn to these devices since 2010, following a series of complaints raised to the Complaints Resolution Panel (CRP) about inappropriate and misleading advertisements.[3-9] Following these complaints, it was discovered that little was known about the devices’ effectiveness for the indications that they were being advertised for.

In 2011, we conducted a systematic review that aimed to assess the evidence base to support these devices for breast cancer screening and diagnosis. The findings of our review indicated that there is currently insufficient evidence to recommend the use of these technologies for breast cancer screening, and the high level of variability among studies of symptomatic women limits their utility as diagnostic tools as well.[10] Despite having limited, variable quality evidence for screening and diagnosis, these devices are advertised for these indications in Australia, the United States, Canada, and the United Kingdom.[6, 11-13] The main potential harms of such advertising material come from receiving a false-positive or false-negative test results from these devices.

The reforms outlined in the present RIS offer the potential to amend the current system, and provide an increased degree of protection from such inappropriate advertising in the future. This consultation also presents a unique opportunity for members of the breast cancer community to provide input into the manner in which advertising for new breast imaging devices may be regulated in the future. In order to ensure that the breast cancer community is represented in this reform Consultation regulation impact statement: Advertising of therapeutic goods to the general public
The University of Adelaide

process, we conducted semi-structured interviews with members of national and state-based, not-for-profit organisations involved in breast cancer imaging (n=5), consumer advocacy (n=7), and research (n=4) between January and March 2013. In total, we interviewed 16 stakeholders from within the breast cancer community around the TGA’s proposed changes to the regulation of therapeutic goods advertising, as outlined in May 2012 document ‘Advertising regulations for medical devices; options for reform’. [1] Within these options we sought perspectives from stakeholders around the pre-approvals process, specifically targeting the three proposed options:

1. Extend the current pre-approvals process to include medical devices.
2. Remove the pre-approvals process in favour of active monitoring.
3. Only require pre-approval for repeat offenders.

Since holding the stakeholder interviews, the options for reform to the arrangements for therapeutic goods advertising have been updated and refined by the TGA. While the responses we received went into detail around the available options presented above, the key principles guiding the options outlined in Proposal 1 of the present RIS were similar enough that we can offer comment based on their feedback. In this submission, we summarise the responses provided by participants around the proposed changes to the regulation of therapeutic goods advertising outlined in the present RIS.
Proposal 1: Alternatives to the pre-approval scheme

Option 1: Maintain the current system

Option 1 was not part of our interview process, as we focussed around the three proposed changes to system outlined in May 2012. However, throughout the interview process participants stated a range of concerns with the current system, which would preclude option 1 from being recommended as an appropriate course of action. The current lack of pre-approval for medical device advertising has a series of flow-on affects, which have had an impact on the quality of advertising material for emerging breast imaging devices:

1. Firstly, the current system allows devices to be advertised directly towards consumers for indications that they did not receive ARTG certification for.[10] This practice appears in contrast to the stated principles of the Therapeutic Goods Act 1989.

2. Secondly, there has been a history of inefficiency in the current system of self-regulation for Complementary and Alternative Medicine (CAM) advertising,[14] and a steady increase in the number of complaints raised about advertising within the medical devices industry.[1] This option would do nothing to improve the quality of CAM or medical device advertising, as it offers no alternative to industry self-regulation.

3. Thirdly, the inefficiency of industry self-regulation, coupled with the current lack of pre-market approval of medical device advertising, has led to a reliance on the general public and competitor companies to identify inappropriate advertising. Participants suggested that this is an unnecessary impost on the general public, as the purchasers of these products are unlikely to have the skills or resources needed to adequately differentiate between appropriate advertising claims and false or misleading advertising claims.

4. Finally, medical devices are often not limited to use by medical practitioners, and are often accessible to consumers without a referral from a registered healthcare practitioner. In cases where a consumer can access a product without input from a registered practitioner, such as an emerging breast imaging device, consumers are reliant on the accuracy of the information provided in the advertising material which may be unreliable.

Recommendation for Option 1

The current system does not include provisions to pre-approve medical device advertising, and instead relies on industry self-regulation and consumer complaints to ensure the quality of...
The University of Adelaide

advertising claims. Given the highlighted issues with this arrangement, maintaining the status quo is not recommended as a suitable option.

Option 2: Extend the current system to include pre-approval for devices, and cover subscription broadcasting.

Option 2 aims to extend the current pre-approval system to include medical devices, including in-vitro medical devices, and subscription broadcasting. Stakeholders expressed both advantages and disadvantages of option 2, but were largely in favour overall (n=11/16). However, 3 participants needed clarification about the proposal before offering comment, and 2 participants did not support the option.

Advantages of Option 2

Participants indicated a range of advantages for option 2:

1. This proposal would lead to the greatest increase in consumer confidence of advertising claims compared to the other proposed options.
2. This option would provide a standardised process across all advertising of therapeutic goods, and allow for a greater level of consistency to be applied to regulatory decisions.
3. Assuming that this process is effective at adequately approving advertisements for therapeutic goods, it would lead to a degree of cost-recovery by reducing the burden on the complaint handling system.
4. Stakeholders representing consumer advocacy groups also noted that this option places the impetus of discerning the accuracy of advertising claims on the regulator instead of the consumer.
5. Advertisements have less ability to present false or misleading information to the general public.

Disadvantages of Option 2

The main disadvantage of option 2 identified by stakeholders was the increased cost and resource requirements for the expanded pre-approvals process. These associated costs would be born predominantly by the regulated industries, but would also require a significant increase in resources for the TGA in order to carry out the approval process. This would also have a flow-on effect of slowing down the time-to-market for advertisements of new and innovative therapeutic goods, which may slow their uptake within the community. One participant also questioned how the Consultation regulation impact statement: Advertising of therapeutic goods to the general public
The University of Adelaide

pre-approvals process would affect government-funded health services, such as a national screening campaign, which are promoted to the public. A final disadvantage of this option comes in relation to the issue discussed in bullet point 1 of option 1; devices are often advertised for indications that they did not receive ARTG certification for. In this instance, the perpetrators of false or misleading advertising may not be the sponsor or manufacturer of the product, but a local distributor or small business within the community. It may be the case that, as these sole-practitioners may not be members of a regulated industry body, that they may not be aware of their obligation to submit their advertising for pre-approval. Overall, the general consensus towards this approach is summarised succinctly by Participant 1:

“My doubt is not whether this is the best arrangement, my doubt is about the extent to which it can be successfully introduced.”

Recommendation for option 2

In the interest of increasing public safety from false or misleading advertising, option 2 is recommended as the most suitable approach. This option was most favoured by interview participants, and will ensure the highest level of consumer confidence in therapeutic goods advertising from the proposed options. However, serious concerns were raised about the capacity of the TGA and the cost to industry required to carry out this proposal.

Option 3: Limit the current pre-approvals scheme to cover only “higher risk” categories of advertisements.

The option to limit the current pre-approvals scheme to only cover “higher risk” categories of advertisements was not explicitly discussed with participants as an option for reform, however it was highlighted by two participants as a potential alternative to the other options outlined in the May 2012 report.[1] The following views on this option are the result of in-depth discussion between the interview participants and the principal author (TV), and may not be representative of the broader stakeholder community.

Advantages of Option 3

Assuming that option 3 would also be expanded to include advertisements for medical devices, this option has the benefit of being more resource, time and cost-efficient than option 2, as the number of advertisements requiring approval would be significantly fewer, while maintaining a higher level of consumer protection from false or misleading advertising than option 1 or option 5.
The University of Adelaide

Under this arrangement, new and innovative therapeutic goods that pose little risk to public safety can be accessed sooner by consumers, while higher-risk products will receive adequate assessment of their advertising claims.

Disadvantages of Option 3

There are a number of disadvantages and qualifications to be made around this proposal in order for it to be recommended as the most appropriate course of action. Currently, the risk-category that determines the level of pre-market evaluation a medical device faces during conformity assessment is determined by the manufacturer of the device when applying for ARTG certification.[15] However, as we have observed in the case of emerging breast imaging devices, the intended use of a listed device on the ARTG is often different from the practical application of the device. If the TGA plan to use this same risk classification system to determine which products require advertising pre-approval, then emerging breast cancer imaging devices would not be covered under this scheme as they are currently certified by their manufactures as “low risk”. We previously raised the issue of risk-classification for these imaging devices in the TGA consultation for the pre-market assessment of medical devices, and this issue is equally relevant here.

Interview participants did offer comment on the classification of a ‘repeat offender’, as this provision was included under option 3 of the May 2012 options for reform.[1] If an advertisement is to be labelled as ‘high risk’ on the basis of the sponsor having repeatedly breached advertising regulations, three key considerations that need to be taken into account:

1. How many times would a company have to breach regulations before it is labelled as a ‘repeat offender’?
2. This system will be open to exploitation, as smaller companies can re-register under new trading names to void their ‘repeat offender’ status.
3. There is the potential for harm to occur before a company is labelled as a ‘repeat offender’.

Recommendation for option 3

It is the opinion of the authors and two of the interview participants that option 3 could be a suitable alternative to the current system, under the condition that medical devices were included in the pre-approval system, and risk-classification for diagnostic devices were revised accordingly so that they would be covered by the pre-approval system. This approach would be less resource
intensive for both industry and the TGA compared to option 2, and will offer a greater amount of consumer protection from fraudulent advertising than options 1 or 5.

**Option 4: Retain pre-approvals (modified or not as per option 2 or 3) and: maintain current pre-approval delegations to industry associations, such as ASMI and CHC, or: appoint an independent statutory office holder to undertake pre-approval function, or: TGA to undertake the pre-approval function.**

The main benefits and disadvantages of this option are outlined in our response to option 2 and 3. However, the options for reform discussed with participants did not include arrangements for who should be tasked with carrying out the pre-approvals, and as such we have no stakeholder comments to offer to this option.

**Option 5: Remove the pre-publication approval scheme.**

Although we didn’t put this forward as an option exactly as presented in the current RIS, it was similar in principle to the “monitoring system” option discussed during the stakeholder interviews. There was little support (n=3/16) for a proposal that would remove the pre-approval scheme in favour of industry-self regulation, with the majority of participants indicating that they did not support this type of arrangement (n=12/16). One participant did not offer a response on this proposal.

**Advantages of Option 5**

Participants noted three key benefits of this option:

1. This option would reduce the resources required for pre-approval for both the TGA - by removing their responsibility to pre-approve advertisements - and for industry bodies - by removing the fees required for TGA approval.
2. This option would decrease the time-to-market for companies to broadcast their advertising for new therapeutic goods.
3. This option may prove to be an appropriate deterrent against false and misleading advertising if it is coupled with appropriate increases in penalties for misconduct.
The University of Adelaide

Disadvantages of Option 5

In contrast to the proposed benefits, stakeholders highlighted a number of key disadvantages that ultimately diminished their support for this option. The most commonly regarded disadvantage of this proposal was the history of ineffectiveness of industry self-regulation of therapeutic goods advertising in Australia. Participants pointed out examples of deficiencies in the self-regulation of advertising in the CAM industry, as have been highlighted in peer-reviewed literature.[14] The authors would also like to point to the large rise in complaints in the medical devices industry, including complaints targeted towards breast cancer imaging devices,[3-5] raised to the Complaints Resolution Panel as an indication of ineffectiveness of industry self-regulation.[1] Given the track record of advertising self-regulation in the CAM industry, and increasing evidence of deficient self-regulation in the medical devices industry, participants did not have confidence that this arrangement would be effective at preventing misleading advertising claims.

It was also noted that the regulation of therapeutic goods advertising should aim to minimise the potential harm to the general public, by limiting their exposure to false or misleading advertising claims. On this point, it was suggested that by removing the requirement for pre-approval there is less impetus for companies to adhere to the relevant codes of conduct (legislated or industry-nominated), as any breaches and penalties would be administered after profits had been garnered. This would likely lead to three follow-on effects for consumers:

1. It will likely increase consumer exposure to inappropriate advertising due to advertising breaches being detected retroactively.
2. It places a large burden on consumers and health activists to identify and differentiate between inappropriate and appropriate advertising, a task which they likely lack the capacity for as even trained professionals can find this difficult.
3. It requires consumers to identify and complain about inappropriate advertising after a harmful event has occurred that could have otherwise been avoided, such as receiving a false-positive test result from an emerging breast imaging device.

Recommendation for Option 5

Based on the responses from participants, we suggest that the highlighted disadvantages of this option are not justified by the proposed benefits in terms of cost-saving and time-saving. In particular, this option allows for the potential of undue harm to come to the community, which can be otherwise prevented if an efficient pre-approval process was in place. Removing the role of the TGA as the principle regulator of therapeutic goods advertising places the main burden of Consultation regulation impact statement: Advertising of therapeutic goods to the general public 10
monitoring advertising claims on the general public, as industry self-regulation is unlikely to be an effective means for ensuring appropriate advertising. It is therefore recommended that this arrangement not be considered as a worthwhile option for reform.

**Summary**

After consideration of the views of 16 individual participants, option 2 was most favoured by stakeholders from breast cancer imaging, consumer advocacy, and research. Of the options proposed in the present RIS, participants indicated that option 2 provides the greatest amount of consumer protection from false or misleading advertising, however they acknowledged that this option would incur a significant increase in resource allocation and financial costs to both the industry and TGA. Concerns were raised by stakeholders about the capacity of the TGA, or any individual body for that matter, to pro-actively screen advertising material for all therapeutic goods prior to broadcast or publication.

The authors suggest that option 3 should also be considered as a viable option, as it is less resource intensive than option 2, while offering a higher level of consumer protection than option 1 or option 5. However, this option should only be considered under the condition that medical devices be included in the pre-approval process, and that the risk-classification for emerging diagnostic imaging devices be revised to adequately reflect their risk to public health.

We would like to extend our appreciation to the TGA for providing the opportunity to contribute the views of the breast cancer community to the proposed options for reform, as they relate to a contemporary issue of concern. We look forward to the opportunity to participate in future discussions around regulatory reform of therapeutic goods in Australia.

Sincerely,

Mr Thomas Vreugdenburg  
PhD Candidate  
The University of Adelaide  
thomas.vreugdenburg@adelaide.edu.au

Prof. Janet Hiller  
Associate Dean (Research)  
Professor of Public Health  
Australian Catholic University,  
and Adjunct Professor  
The University of Adelaide  
janet.hiller@acu.edu.au

Dr Caroline Laurence  
Associate Professor of General Practice  
The University of Adelaide  
caroline.laurence@adelaide.edu.au

Dr Cameron Willis  
Senior Research Fellow  
The University of Adelaide  
cameron.willis@adelaide.edu.au

Ms Linda Mundy  
Senior Research Officer  
Queensland Health  
linda_mundy@health.qld.gov.au

Consultation regulation impact statement: Advertising of therapeutic goods to the general public
The University of Adelaide

References

3. Complaints Resolution Panel, Complaint 2010-03-038 Thermography Australia, Australia: http://goo.gl/n1XLZ. [Date 08-09-11]
4. Complaints Resolution Panel, Complaint 2010-03-032 Safe Breast Imaging, Australia: http://goo.gl/1JRuC. [Date 08-09-11]
Reference List


8. Merlin T, Weston A, Tooher R (2009) Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence', BMC Med Res Methodol. 9(34);34.


22. Freeman B, Chapman S (2008) Gone viral? Heard the buzz? A guide for public health practitioners and researchers on how Web 2.0 can subvert advertising restrictions and spread health information, J Epidemiol Community Health. 62(9);778-82.


52. Toop L, Richards D, Dowell T, et al. (2003). Direct to consumer advertising of prescription drugs in New Zealand: for health or for profit? Report to the Minister of Health supporting the case for a ban on direct to consumer advertising, New Zealand Departments of General Practice, Christchurch, Dunedin, Wellington and Auckland Schools of Medicine, Available from: URL no longer available.


76. Baum M, Buzdar A, Cuzick J, et al. (2003) Anastrozole alone or in combination with tamoxifent versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: Results of the ATAC (arimidex, tamoxifen alone or in combination) trial efficacy and safety update analyses, Cancer. 98(9);1802-10.


107. Fricke H, Morse A (1926) The electrical capacity of tumors of the breast, J Cancer Res. 1926(10);340-76.


146. Liang BA, Mackey T (2011) Direct-to-consumer advertising with interactive internet media: global regulation and public health issues, JAMA. 305(8);824-5.


163. Deeks JJ, Macaskill P, Irwig L (2005) The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed, *J Clin Epidemiol.* 58(9);882-93.


diagnostic performance by combining the BI-RADS (registered trademark)-US classification system with sonoelastography, *Ultraschall Med.* 31(5);484-91.


