



**COMMENTS**

**FROM THE**

**MEDICAL INDUSTRY ASSOCIATION  
OF AUSTRALIA Inc**

**ON THE**

**Productivity Commission Progress Report**

**Impacts of medical technology in Australia,  
April 2005**

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## INTRODUCTION

The Productivity Commission Progress Report “*Impacts of medical technology in Australia*” (April 2005) sought public input on its contents.

The Medical Industry Association of Australia (MIAA) is pleased to have the opportunity to comment on the progress Report. MIAA members, while welcoming the broad directions of the Report in its recognition of the benefits of medical technology, have concerns about certain aspects of the Report.

In this commentary, we do not dwell on the many positive aspects of the Report, including its review of the benefits of many technologies (a factor often ignored in earlier analyses of the impact of medical technology on expenditure) and its realistic review of the limitations of the MSAC regulatory process. Rather, we focus our attention on three concerns:

- (1) the imbalanced treatment and extensive duplication of the Report’s comments on the drug-eluting stent (DES), and the imbalanced treatment of pacemakers and implantable cardioverter defibrillators (ICDs) (**Section 1**);
- (2) the nature and limitations of the economic modelling contained in Chapters 3 and 4 (**Section 2**); and
- (4) inconsistencies or gaps in evidence that might be repaired by further review by the Commission (**Section 3**).

### 1. THE COMMISSION’S REVIEW OF DEVICES USED IN HEART DISEASE

Here we focus our attention on two interventions using medical devices mentioned in the progress Report: the drug-eluting stent and the implantable cardioverter defibrillator.

#### 1.1 The drug-eluting stent

There are over twenty separate groups of references to DES through most chapters of the Progress Report (see pages xxxviii, 35, 61, 64, 70, 80, 81, 102, 113, 127, 128, 183, 201, 203 and Appendix B-4).

MIAA makes the following observations.

1. The plethora of references to DES are repetitive, with different paragraphs seemingly the work of different authors. At the very least, tighter editing might help the reader to feel less burdened by the resulting overlaps and inconsistencies.

(2) The general negative thrust of Appendix B-4 portrays the DES as a cost-inducing device that costs more than the bare metal stent, and it also suggests that the DES is used excessively in private hospitals. The Report seems to rely unduly on the BUPA submission (particularly the quotes in

Appendix B-4, p. B-39 where the Victorian Dept of Human Services data seem to be at odds with the BUPA data on the public/private hospital mix, and where there is no mention of the effects of the Victorian grants system for new technology). The impact of inadequate hospital budgets on use rates in the public hospital system is not assessed. It would be instructive if the final Report of the Commission reflected on the lack of transparency of the MSAC process which

- made no recommendations in its final Report for additional public sector funding of DES, and
- then sent a separate letter to the States/Territories recommending such funding (see **ANNEX 1** to this commentary).

(3) One section of the Report (p 64: “there do not appear to be offsetting unit costs”) seems to contradict another (Appendix B - page 43: “DES have a lower rate of restenosis than BMS...”). Most of the analysis understates the impact of DES on the volume of brachytherapy, CABG, repeat procedures (except Appendix B-4, p. 42) or on other cardiac events downstream.

(4) MIAA has serious concerns about the completeness of the data on the relative cost-effectiveness of DES in Table 6.1 (p. 127), particularly if later cost-effectiveness studies are available (see **ANNEX 1**) or if DES is more cost-effective in population subgroups.

(5) MIAA queries the relevance of the Report’s comments on the absence of long-term data on cost-effectiveness (p. 128) when DES is a relatively new technology.

(6) Overall, MIAA believes that in its treatment of DES, the Report exhibits an inordinate focus on its costs without providing balancing data on the benefits (the end of the first paragraph of p. xxxvii contains a particularly inapt choice of words). In this respect, the Report’s disparate comments on DES are, sadly, a replica of the same cost fears expressed about both CABG in the 1980’s and angioplasty in the 1990’s. The many achievements of interventional cardiology across these two decades, particularly their health benefits, could and should be presented in a more even-handed fashion.

**ANNEX 1** of this commentary includes MIAA reflections on the available evidence on DES, and on recent MSAC decisions affecting the funding of DES. It also includes comments on a new study released in late May 2005 comparing CABG with stenting, noting the weaknesses of this study that render the results irrelevant to clinical practice using DES.

## **1.2 Pacemakers and implantable cardioverter defibrillators**

In two sections of the Report, comments are made on the cost-effectiveness of dual chamber versus single chamber pacemakers (pages 122-123) and implantable cardioverter defibrillators (page 127).

**Pacemakers:** The first reference to pacemakers reflects on the UK NICE assessment of the two types of pacemaker, and then goes on to note how the cost-effectiveness ratio is influenced by many factors, including the patient’s

condition, the price of the device, and the duration of the benefits caused by the devices. These are parameters that should be tested in any economic assessment, but the Report then goes on to discuss the subjectivity of benefits, making the following assertion:

*“QALYs or life-years saved are unlikely to capture fully people’s preferences about medical treatment in different circumstances (e.g., whether the)...technology is used according to the characteristics of the recipient (for example, their age) and whether it is a life-saving intervention or alternative treatments exist....Thus, the measure of benefits should also reflect the main objective of the intervention”.*

Pacemakers are a life-saving intervention, alternative treatments exist, age should not be a consideration in the doctor’s decision if a clinical benefit is likely to accrue, and measuring the quality of life of a patient with or without a pacemaker should not be beyond the ken of a designer of a healthcare technology assessment. Given the rapid pace of change in pacemaker technology and their constant evolution, it is highly unlikely that the benefits of today’s pacemakers will be the same as the pacemakers available in 10 years. MIAA hopes that in its final Report, the Commission’s prescriptions for practical estimates of the duration of future benefits of technologies will not embrace theoretical concepts that take economic appraisal in directions that are inappropriate for rapidly-evolving medical devices.

**Implantable cardioverter defibrillators:** Emphasising this latter concern, if the Commission’s Report is to be authoritative it should accurately reflect the fast-moving pace of medical device innovation. In its comments on the ICD, the Commission summarises the results of one cost-effectiveness study, and it also makes the following assertion about the clinical benefits of statins and ICDs:

*“...the size of these benefits is dependent on whether they are used to treat or prevent an episode of illness... The cost per life saved for ICDs likewise ranges from US\$54,000 for those who have experienced heart failure to US\$120,000-\$153,000 for primary prevention....”*

We make three observations on the Commission’s opinions on ICDs. First, the minimalist comment on page 127 leaves the reader with the view that the ICD is a costly technology that may have benefits. The Commission’s final Report will hopefully identify the rapid and continuing evolution of the ICD since the 1980s. In 1980, we had large devices in an abdominal site (with fewer than 1000 patients and many complications), and today we have small devices in a pectoral site (with over 100,000 implants a year, shorter hospital stays and fewer complications). Future technology will have enhanced automation and reduced device size, allowing enhanced diagnostics, smaller lead technology and patient modifications that reduce clinic visits. There is no recognition of these benefits in the commentary on ICDs.

Second, the final Report will hopefully reflect the large number of clinical studies that have reported the clinical benefits of the ICD, including the newer versions that combine a defibrillator with a biventricular pacemaker (cardiac

resynchronisation therapy-defibrillators or CRT-D). New evidence<sup>1</sup> on the CRT-D was reported in *NEJM* in April 2005, based on an 82-hospital study in Europe funded by Medtronic Inc. It concluded that, compared with drugs, CRT on its own confers a 36% mortality reduction over an average of 29 months of treatment of heart failure, and that the defibrillator add-on is perhaps less important and more costly. While the study was not sufficiently powered statistically to show the impact of CRT versus CRT-D, the two device arms (CRT alone and CRT+ICD) performed better than the drug treatment arm.

Third, the Commission has focused exclusively on the Hlatky (2005) study of cost-effectiveness of the ICD, reporting its very large estimates of US\$1.54-2.20 million per QALY. The new European study<sup>2</sup> of CRT finds that the incremental cost-effectiveness ratio is below US\$50,000 per QALY, and that this result is fairly robust to variations in other parameters. In **ANNEX 2**, we have summarised other economic studies not mentioned by the Commission.

**ANNEX 2** of this commentary is a review of the available evidence on ICDs and CRT-D, updating material that MIAA originally included in its submission in January 2005.

## **2. THE COMMISSION'S MODELLING OF THE IMPACT OF MEDICAL TECHNOLOGY ON HEALTHCARE EXPENDITURES**

MIAA believes that the modelling methods and results deserve further scrutiny within the Commission since the results are likely to influence health policy following the Commission's final Report. MIAA summarises below its major concerns about the data and models.

While we have not had the time or resources to invest in alternative modelling assumptions or statistical techniques, we believe the Report's dependence on simple linear models is at odds with most other alternative approaches, many of which we identified in our original submission.

### **2.1 Dated references**

Many references used in the Report are from two decades ago. While MIAA has not documented their net effect on all the arguments raised in the Report, with the conspicuous exception of Chapter 5 these dated references are unlikely to reflect the true impact of medical devices when the evidence on benefits is more accurately recorded in recent years. For example:

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<sup>1</sup> Cleland JG, Daubert J-C, Erdmann E et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *New England Journal of Medicine* 2005 7 March (published at [www.nejm.org](http://www.nejm.org) (10.1056/NEJMoa050496), 7 March 2005, downloaded 8 March 2005). An earlier meta-analysis by the US Agency for Healthcare Research and Quality (AHRQ) concluded that CRT is associated with a 24% relative reduction in all-cause mortality, driven largely by a 42% reduction in progressive heart failure deaths-see: AHRQ. Cardiac resynchronization therapy for congestive heart failure. Evidence Report/Technology Assessment Number 106 (downloaded 19 May 2005 from <http://www.ahrq.gov/clinic/epcsu/sums/resynsum.htm>)

<sup>2</sup> Banz K. Cardiac resynchronization therapy (CRT) in heart failure- a model to assess the economic value of this medical technology. *Value in Health* 2005; 8 (2): 128-139.

- \* Pages 28-36 draw references from 1984 (p. 36) and the mid-1990s (pp. 29-31) when describing the determinants of technological change in health care. Table 2.2 draws on Victor Fuchs' 1995 paper.
- \* Three of the studies of the "residuals methods" shown in Table 3.1 (p. 42) are from the period 1979-1992. The time period is not trivial when we are trying to estimate the impact of a wider range of medical technology in 2005.
- \* The income elasticity of demand is important in future forecasting of healthcare expenditures. Yet, the Report (p. 44) seems to be suggesting a lower bound estimate based in part on two studies in the 1970s, and the model results generate a very high estimate of 1.8-see **Section 2.3** below.

## 2.2 Choice of measure of medical technology

The full details of the model appeared on the Commission's website as an Appendix E after a brief mention on page 51 of the Report. MIAA is concerned that the Commission's model relies solely on one measure- US Health R&D Expenditures- as a proxy for technological change without any comparison with other measures.

- The rationale provided by the Commission for this choice oversimplifies the challenges of (1) representing technological change, and (2) capturing the relevant dimensions - direct and indirect - of the impact of any single medical technology.
- The weaknesses of using R&D indicators, patents and time indices have been identified by Kleinknecht et al (2002),<sup>3</sup> and are barely touched upon in Appendix E or in the text of the progress Report. Patents may be a better measure than R&D expenditure if US companies hold about 70% of total patents and dominate the publication citation count, and if most innovations are patented in the USA. R&D measures such as R&D expenditures (and extent of industry collaboration) provide no information about the output side of the innovation process. There is some support for the view that, while not all innovations are patented, in the medical device industry the number of patents might better approximate the returns from device product and process innovation.<sup>4</sup>
- MIAA believes that for completeness of literature search alone, the Commission's final Report might benefit from a review of the draft report<sup>5</sup> of a parallel EU study of medical devices, particularly its detailed

<sup>3</sup> Kleinknecht A, van Montfort K, Brouwner E. The non-trivial choice between innovation indicators. *Economics of Innovation and Technology* 2002; 11 (2): 109-121

<sup>4</sup> The 1994 Carnegie Mellon Survey results are summarised in Cohen, Nelson and Walsh (2000), quoted in : Pammolli F, Riccaboni M, Oglialoro et al . *Medical devices : competitiveness and impact on public health expenditure*. Report prepared for the Enterprise Directorate General of the European Commission, DRAFT February 2005, p. 119.

<sup>5</sup> Pammolli F, Riccaboni M, Oglialoro et al . *Medical devices : competitiveness and impact on public health expenditure*. Report prepared for the Enterprise Directorate General of the European Commission, DRAFT February 2005, particularly Chapter 3, page 19 et seq.

assessment of the limitations of R&D measures as proxies for “technological change”,<sup>6</sup> its thorough literature review for the period 1990-2004,<sup>7</sup> and its detailed overview of the relationships between R&D activity and innovation in healthcare.<sup>8</sup>

## 2.3 Selection of independent variables and modelling technique

Five matters concern MIAA. First, on page 51 the Commission does not present a defensible justification of its selection of five sets of variables to model real *per capita* healthcare expenditures.

Second, while the technical nature of the modelling techniques is appropriate for discussion in a technical appendix, the technically trained reader would still have great difficulty assessing the sensitivity of the results summarised in Table E.7. Some judicious editing might reduce the complexity while improving the transparency of the Commission’s core model.

Third, the Report’s explanations of the unexpected findings (e.g., the very high income elasticity of 1.8 on page E.17) and the choice of lags (page E.18) weaken the Commission’s arguments. It is virtually impossible to assess what is the lag period for R&D expenditures and whether the Commission’s final paragraph on page E.18 is valid, viz., “*the lags of these two variables (i.e., private insurance and R&D expenditures) provide useful information in predicting health expenditures*”. The US drug approval system reduces the average patent protection for drugs by 10-15 years, and the FDA regulatory process takes a few years off the patent protection period for devices. Thus the lag between an expenditure on R&D and the use of a drug or device that leads to healthcare expenditures should reflect those 3-15 year delays, affording any statistician no comfort in defending shorter lag periods. It is then very disconcerting to read on page E.16 that “*...using lag exclusion tests, a lag length of two was found to be optimal*”. The search for statistical rigour may have ignored these realities in the choice of “appropriate” lag lengths when measures such as US R&D expenditures are used to predict Australian healthcare expenditures.

Fourth, the Report makes no reference to the Jones (2004) model<sup>9</sup> which MIAA used as a benchmark model to show the positive long-term impacts of medical technology in reducing the real per capita costs of some diseases. It ignores the Hall-Jones model (2004) findings incorporating the effects of rising income and consumer willingness to pay, both non-trivial matters when firstly, Australia’s growth rates of out-of-pocket payments are among the highest in the industrialised world, and secondly, the demand for future medical

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<sup>6</sup> Ibid Chapter 7 is particularly insightful about the limitations of different R&D measures.

<sup>7</sup> Ibid, Table 5 is a particularly useful, thorough and up-to-date summary of many studies of technological innovation in healthcare and their use of many measures of “technological change”.

<sup>8</sup> Ibid, Chapter 7, page 114 et seq. This analysis also provides some insights on the need to split the patent measures by health sector sub-categories to take into account the generality and originality indices that differ across drugs, biotechnology, surgery and medical instruments, and miscellaneous drugs and medicines-see *ibid*, Table 3, page 121. The intensity of R&D also varies across these different submarkets- see *ibid*, pages 126-132.

<sup>9</sup> Submission by the Medical Industry Association of Australia to the Productivity Commission Study into “The impact of advances in medical technology on healthcare expenditures in Australia”, page 101.

technology will be conditioned by ability and willingness to pay. In our view, the Commission's review of defensible models is incomplete while these two models are neglected. The one-line mention of the Hall-Jones model on page 45 of the Report resembles an after-thought rather than a systematic review of its findings.

## 2.4 Reconciling the modelling in two Commission Reports

It is impossible to tell what biases or understatements of the role of medical technology might result from the model's basic assumptions. The net result of the two sets of models embedded in the Commission's reports on Economic Implications of an Ageing Australia (March 2005) and this Impacts of Medical Technology Report is that the strong assertions of the first report (viz., ageing is the major issue in *government expenditure*) are partly offset by the findings of the Appendix E modelling of the impact of medical technology (viz., technology contributed 47% of the growth in *total health expenditure* over the last decade, and ageing a mere 13%).

These are not trivial differences, and the Commission's discussion of why ageing is not statistically significant on page E-16 and in Chapter 3 does not give us any assurance about the Commission's conclusion that 47% of the growth in healthcare expenditures is associated with medical technology.

## 3. OTHER MATTERS WHERE BALANCE IS ESSENTIAL

The following paragraphs summarise other MIAA concerns that might be resolved by judicious editing or by the inclusion of balancing points of view.

### 3.1 Errors

The relative severity of admissions to public and private hospitals is mentioned in a footnote on p. 59. The comment ignores other evidence by AHIA and APHA that over 50% of some major procedures are now being done in private hospitals, and it ignores the possibility that public hospitals may indeed be less efficient than private hospitals.

Recently, Professor Brian McCaughan (Royal Prince Alfred Hospital, Sydney) has given another explanation for the slow take-up of same-day surgery in public hospitals compared with private hospitals: "*there are many surgeons still operating in public hospitals who have not yet embraced same-day surgery*".<sup>10</sup> A more recent report on NSW public hospitals<sup>11</sup> provides another possible explanation: cancelled elective procedures may be restricting the efficiency of use of theatres in public hospitals, thereby limiting access to time-saving technology.

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<sup>10</sup> Source: Quoted in R Pollard. "Day-Only Surgery To Speed Up Hospitals". *Sydney Morning Herald* 22 December 2004, 1

<sup>11</sup> A Stafford. "Cancelled surgery avoidable". *Australian Financial Review* 20 June 2005, 6. This article summarises a new academic study in NSW hospitals. It suggests that such delays would never occur in private hospitals.

### **3.2 Selective discussion of evidence**

The summary comments on the cost-effectiveness of some classes of technology seem to damn with faint praise. The most egregious example is the box on page 125, where Lichtenberg's studies of the impact of modern drugs are criticised for their exclusion of outliers or variations in the sample (an opinion lacking any supporting evidence, particularly given the widespread quotation and endorsement of the Lichtenberg models since the end of the 1990s).

There are numerous examples through the Report of quotations from submissions that weaken the case for higher investment in medical technology. The worst cases are the quoted opinions (but with no evidence) of the Australian Nursing Federation (p. 85: "research on the benefits of technological advances in health care is still in its infancy"), the BUPA submission and the Goldstein submission (see the conclusions drawn from their submissions in Appendix B-1, page 10).

### **3.3 The relative prices of prostheses to public and private hospitals**

On pages 18-19, the Report focuses on the imbalances in supply of prosthesis benefits. The assertions of the BUPA and VDHS submissions (submissions 28 and 24, respectively and Appendix B-4) seem to flow into the conclusions reached on page 19 (that the funds "pay significantly more for the same devices and prosthesis than do public hospitals"). TABLE 4.3 on page 81 does not present any estimates of the range of device prices in public and private hospitals, and the BUPA data deserve closer scrutiny by the Commission. For instance:

- Do these BUPA prices represent the sale of a few stents per hospitals or the price of a large volume of stents to a hospital group?
- Do the BUPA data come solely from Victorian hospitals, and are they representative of other state/territory government prices paid for stents?

The fourth paragraph on page 35 reflects on the same pricing differences, and adds patent protection as a possible cause. In our first submission, MIAA drew the attention of the Commission to the differences in patent protection between drugs and devices, noting that patents do not usually protect the prices for devices when the average market life is so short.

MIAA summarises here some major reasons why prices differ in different device markets.

1. At a theoretical level, there is significant agreement that different prices in different markets worldwide may represent an efficient pricing system. There is no sound theoretical rationale for striking a single "global" price for all devices in a single category.
2. In individual markets for different devices, prices sometimes vary because of price discounts for large volumes. The nature of such contracts is straightforward: in return for a guaranteed volume of

devices from the buyer, the seller agrees to offer a price below the price that would be paid if the order was for a few devices. The price so agreed may benefit buyer and seller if the volume-based price enables the seller to predict inventories, minimise delivery costs, or avoid the risks of foreign exchange hedging that may be required when products are sourced from abroad. These arrangements are common because there are benefits to both parties, and they are an accepted part of the commercial process and of competitive markets. They are usually commercial-in-confidence contracts for this latter reason.

3. Stock nearing expiry may be priced lower to minimise wastage and write-offs if there is a sudden demand for the product that can be used before the expiry date.
4. New devices may be offered to the large teaching hospitals at lower introductory prices to enable clinicians to evaluate the product. This is particularly relevant for new technologies that require up-skilling of hospital staff.

### **3.4 Indirect costs in technology pricing decisions**

On page 92, the Report directs that indirect costs should not be included in the economic appraisal of technology. Outside the advisory apparatus to the Pharmaceutical Benefits Scheme, there is increasing evidence that experts in healthcare technology assessment are moving to the view that indirect costs should be considered in any economic evaluation as well as in pricing negotiations for prostheses and other devices.

The UK NICE, widely endorsed by the Commission all through the Report, allows estimates of such costs to be included. We hope that the Commission's final Report will identify the impact of omitted indirect costs on the prices paid for products used in treatments of particular diseases where the potential indirect cost savings from reduced disability may exceed the direct cost savings.

### **3.5 Inputs to further work of the Commission**

On page 245, the Report indicates its ongoing research is not yet completed. We realise that the Commission is concerned about the lack of detailed case studies in the areas of diagnostics and minimally invasive surgery, other technologies, and the benefit-cost tradeoffs.

MIAA included several case studies in its original submission, particularly case studies of new diagnostic devices that seem likely to change the future patterns of care. The potential role of the diagnostics industry has not been recognised in the progress Report. The forthcoming EU report on medical devices includes a study of devices used in Diabetes type II. At this late stage, we are unable to add others, but we have updated our original case studies for DES and defibrillators in **ANNEXES 1 and 2**, and we are prepared to elaborate further on the other case studies included in our original submission.

## **ANNEX 1: REVIEW OF COMMISSION OPINION ON THE DRUG-ELUTING STENT**

The Commission's discussion on drug eluting stents (DES) describes the technology and the timing of its introduction to the Australian health care system.

The Commission notes that conversion of procedural treatment with DES for coronary artery disease (CAD) has been rapid since its introduction to the Australian market. A significant limitation of the progress Report is that its commentary predominantly focuses on the costs of DES and the private healthcare system experience. A further concern to MIAA members is that while the progress Report details the many limitations of the MSAC process with great accuracy, the end-stage of the MSAC process on DES was not fully reported by the Commission.

### **1. Estimating the cost impact of DES**

With 43% of Australia's population privately insured and the Commission's obligation to identify the overall cost of technology on Australia's healthcare, this progress Report lacks significant commentary on the impact DES will have on the treatment of CAD in Australia.

The Report's reliance on Australian private sector data provided by the Australian Health Insurance Association (AHIA) results in a skewed cost impact distribution. Whilst the DES and bare metal stent (BMS) procedure numbers referred to in this document can only account for 42% of private patients in 2002/03 and 49% in 2003/04, the national cost of DES is not available. To more accurately assess the impact of DES expenditure over the next five to ten years, the distribution of costs between both public and private needs to be sought from a wider data source.

The *Cardiac Society of Australia* and the individual cardiac catheter laboratories in Australian hospitals all collate data specifically related to DES use, and in some cases, respective patient history is also collated. With statistically significant clinical trial outcomes available for interpretation, the Commission should assess all data, including post-marketing registries, to further substantiate the cost-effectiveness of DES technology.

Since some states in Australia implement specific requirements for DES use, it is more appropriate to compare each of the NSW, QLD and SA guidelines to assess similarities. It would also be appropriate for the Commission to note that WA has fully adopted the technology based on the scientific evidence available.

The allocation of a Medicare number in the USA prior to FDA approval of DES allowed US healthcare technology assessment (HTA) processes to collate relevant data post commercialisation. In the absence of similar data, Australia will constantly have to refer to overseas data to compare the cost effectiveness of BMS and DES. As the Commission's Report correctly

highlights, it will likely be 2008 before an appropriate data collation process is in place in Australia to facilitate incremental funding of DES.

## **2. Public versus Private Sector Access to DES**

The progress Report highlights the gaps in the current mechanism for reimbursement of prostheses and the limitations of the newly implemented Schedule 5 process. The Commission has made an accurate assessment of the protracted review and negotiation processes and their impact on patient access to new technologies, and it has also accurately pinpointed the inefficiencies and cross-communication between multiple approval bodies all under the auspices of the Department of Health and Ageing. The latest manifestation of delays is the two-month delay in the “with-effect” date for the August 2005 implementation of Schedule 5.

Despite the high quality of clinical and economic evidence supporting the safety, efficacy and cost-effectiveness of DES technology, the access of public patients to this new technology has been restricted due to the time frames for HTA as a result of the well referenced “silo” approach to assessment of technologies in Australia. The Commission’s assumption that there are insufficient data to support the cost of DES technology will not increase access of Australian patients and clinicians to a technology that has been subjected to rigorous clinical trials.

## **3. The inadequacies in reporting of the MSAC review of DES**

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers’ Advisory Council (AHMAC) and report its findings to AHMAC.

In December 2003, following a reference by AHMAC to undertake an assessment of DES, MSAC commenced a systematic review of the literature on drug-eluting stents (CYPHER<sup>TM</sup> and TAXUS) - MSAC Reference 30. More than a year and a half later following TGA approval of the first DES available on the Australian market, MSAC published its report in April 2005.

The following Ministerial recommendation and MSAC clinical and economic evaluation is based on the results of this review provided in ‘Drug-Eluting

stents, MSAC Reference 30, Report November 2004'. This recommendation was accepted by the Minister for Health on 2 March 2005 and has been disseminated to all states and territories, the Ministry of Health in New Zealand and ASERNIP-s.

**Ministerial recommendation:** At its November 2004 meeting, MSAC came to the following conclusion:

'MSAC found that on the strength of current evidence regarding drug-eluting stents:

- The technology is as safe as bare metal stents for the treatment of *de novo* atherosclerotic lesions of the coronary arteries at up to one year post-procedure;
- The technology is more effective than bare metal stents in reducing the rates of revascularisation procedures at up to one year;
- There is insufficient evidence at this time to demonstrate a difference in the rates of myocardial infarction, coronary artery bypass grafting or mortality in patients receiving this technology compared to those receiving bare metal stents;
- There is some evidence that the technology is more effective than bare metal stents in reducing the rates of revascularisation at up to one year in patients with diabetes, long lesions greater than 18mm and small vessels less than 2.5mm. However, there is insufficient evidence at this time to demonstrate any additional benefit in these and other subgroups of patients at high risk of stent restenosis;
- Cost-effectiveness is based on single *de novo* lesions; and
- On the basis of trial data alone, the technology is cost-effective if a cost of \$3,700 to \$6,200 is considered acceptable to avoid a target lesion revascularisation. However a sensitivity analysis to estimate the cost-effectiveness in Australian clinical practice indicates that the cost per target lesion revascularisation avoided may be higher than this figure. Australian clinical practice data is required to resolve this uncertainty.'

**Clinical effectiveness:** The MSAC Evaluation concluded that, based on a systematic review of 7 high quality RCTs (Level 1 evidence):

- No statistically significant difference in MI or death between CYPHER™ and TAXUS compared with BMS (likely to be the result of insufficient power);
- Both CYPHER™ and TAXUS are more effective in reducing TLR and MACE than BMS (**Table 1**).

**Table 1: Absolute reduction in TLR and MACE at 12 months for CYPHER™ and TAXUS vs BMS**

	TLR		MACE	
	CYPHER™	TAXUS	CYPHER™	TAXUS
<b>Total pooled</b>	<b>16.5%</b>	<b>10.3%</b>	<b>15.7%</b>	<b>9.6%</b>
<b>Individual trials</b>				
RAVEL (sirolimus)	22.8%		22.9%	
SIRIUS (sirolimus)	15.1%		14.0%	
TAXUS (paclitaxel)		10.0%		10.0%
TAXUS II SR (paclitaxel)		8.2%		11.2%
TAXUS IV (paclitaxel)		10.8%		9.3%

Source: Table 21-22 Drug Eluting Stents MSAC Evaluation November 2004, p 48 & 49.

**Safety:** The MSAC Evaluation concluded that:

- Results from the 7 trials indicate the risk of in-stent thrombosis following CYPHER™ and TAXUS stent placement is no worse than following BMS at up to 1 year post procedure (Level I evidence). (Drug Eluting Stents MSAC Evaluation November 2004, p 58).
- Large US case series reported incidence of 1.1% in stent thrombosis up to a median of 100 days post procedure (Level IV evidence). This is comparable to rates reported in studies of BMS. (Drug Eluting Stents MSAC Evaluation November 2004, p 58).
- No adverse events related to overlapping stents.
- Increased incomplete stent apposition with CYPHER™ in the short term, although not associated with any clinically significant adverse events. This was not measured in the TAXUS trials.

**Economic evaluation:** The economic evaluation conducted as part of the MSAC evaluation was limited to short term outcome and cost data (12 months after index procedure) and did not attempt to model the efficiency of drug-eluting stents beyond the trial time horizon. For the clinical outcome of TLR avoided at 12 months, the ICER ranges from \$3,746 for CYPHER™ to \$6,117 for TAXUS if both the cost and number of stents is the same (**Table 2**). For the clinical outcome of MACE avoided at 12 months, the ICER ranges from \$3,955 for CYPHER™ to \$6,583 for TAXUS.

**Table 2: Cost-effectiveness – base case cost/TLR avoided and cost/MACE avoided**

Cost	CYPHER™			TAXUS		
	CYPHER™	BMS	Difference	TAXUS	BMS	Difference
<b>TLR</b>						
Total costs at 12 months	\$10,959	\$10,339	\$620	\$10,887	\$10,255	\$632
TLR rates at 12 months	26/653	132/643	16.5%	34/798	116/795	10.3%
ICER <sup>a</sup> : Cost per TLR avoided at 12 months	<b>\$3,746/TLR avoided</b>			<b>\$6,117/TLR avoided</b>		
<b>MACE</b>						
Total costs at 12 months	\$10,959	\$10,339	\$620	\$10,887	\$10,255	\$632
TLR rates at 12 months	51/653	151/643	15.7%	84/798	160/795	9.6%
ICER <sup>a</sup> : Cost per TLR avoided at 12 months	<b>\$3,955/MACE avoided</b>			<b>\$6,583/MACE avoided</b>		

<sup>a</sup> ICER = (cost of CYPHER/TAXUS – cost BMS)/(benefit of CYPHER/TAXUS – benefit BMS).

Source: Drug Eluting Stents MSAC Evaluation November 2004, p 54.

**MIAA comment on MSAC review of DES:** Despite the high quality of evidence supporting the use of DES for the treatment of CHD, MSAC did not make any recommendation for funding of this new technology.

The three inconsistencies of particular concern (listed below) render this particular MSAC review less useful, while offering some insights into the lack of objectivity in MSAC decision-making.

First, MSAC reported that *'There is insufficient evidence at this time to demonstrate a difference in the rates of myocardial infarction, coronary artery bypass grafting or mortality in patients receiving this technology compared to those receiving bare metal stents'*.

MSAC's conclusion is puzzling, to say the least. Most Australian cardiologists are acutely aware that due to the nature of IHD and the characteristics of restenosis and the controlled setting of clinical trials, evidence for significant differences in myocardial infarction and mortality is not available even when patients in large trials (such as the SIRIUS Sirolimus-eluting stent trial) are followed up for many years.

Second, in all five cardiac interventions considered by MSAC, none showed a significant reduction in myocardial infarction and mortality in clinical trials (see **Table 3**). MSAC recommended three of these for funding (OPACB, MIDCAB, and IVB) and one for funding in limited indications (PTCRA).

**Table 3. MSAC precedents in cardiac revascularisation procedures 2001-2004**

<b>Procedure</b>	<b>OPCAB</b>	<b>MIDCAB</b>	<b>IVUS</b>	<b>PTCRA</b>	<b>IVB</b>	<b>DES</b>
Description	Off-pump CABG + stabilisers	Minimally invasive OPCAB + stabilizers	Intravascular ultrasound as an adjunct to PCI	Rotational atherectomy as an adjunct to PCI	Beta IVB* + PCI ± adjuncts	PCI with DES
MSAC report	September 2001	September 2001	December 2001	May 2002	August 2002	November 2004
Evaluator	ASERNIP-S	ASERNIP-S	NHMRC	Monash IHSR	NHMRC	NHMRC
MSAC decision	Recommended for funding	Recommended for funding	Not recommended for funding	Recommended for funding in limited indications	Recommended for interim funding	<b>No funding recommendation</b>
<b>Clinical evidence</b>						
Comparator	Conventional CABG	Conventional CABG	PCI ± stenting without IVUS	PCI ± adjuncts without PTCRA	PCI ± adjuncts without IVB	PCI + bare metal stent
NHMRC level	Level II (7 trials)	Level II (4 trials)	Level I (pooled 4 trials)	Level II (12 trials)	Level I (pooled 4 trials)	Level II (2 trials)
N	200 (OPCAB =109)	411 (MIDCAB =215)	2,116 (IVUS =1,058)	3,885 (PTCRA =1,718)	934 (IVB = 501)	3,659
Clinically driven TLR measurement	Peri and postoperative to ~ 3 months.	Peri operative in 3 trials, 1 trial (POEM 2001) at 6 months	9-12 months.	NA, only angiographic restenosis reported at 6 months in 3 trials	8-12 months	12 months
Clinically driven TLR outcome	Paucity of data, but no apparent difference	POEM 2001 no significant difference at 6 months.	Significant difference	NA, difference in angiographic restenosis not significant	Significant difference	Significant difference
Myocardial infarction	No significant difference	No significant Difference	No significant Difference	No significant difference at 6 months	No significant difference	No significant difference
Death	No significant difference	No significant Difference	No significant Difference	No significant Difference	No significant difference	No significant difference
Maximum follow-up	13.4 months (in 1 trial)	6 months (in 1 trial)	24 months (in 1 trial)	12 months (in 2 trials)	36 months (1 trial, subgroup only)	24 months (in 1 trial)
TLR outcome at follow-up	NA	NA	TLR difference maintained at 24 months.	NA	Greater late increase in TLR in IVB group than comparator group	TLR difference maintained at 24 months.

\* Gamma IVB was considered by MSAC as a secondary procedure as it is not currently available in Australia.

NA=not available, CABG = coronary artery bypass graft, OPCAB = off pump coronary artery bypass graft, MIDCAB = minimally invasive off pump coronary artery bypass graft, IVUS = intravascular ultrasound, PTCRA = percutaneous transluminal coronary rotational atherectomy, IVB = intravascular brachytherapy, ASERNIP-S = Australian Safety and Efficacy Register of New Interventional Procedures -Surgical, NHMRC = National Health and Medical Research Council, IHSR = Institute of Health Services Research, MSAC = Medical Services Advisory Committee, PCI = percutaneous coronary intervention, TLR = target lesion revascularisation.

**Table3. MSAC precedents in cardiac revascularisation procedures 2001-2004 (cont)**

<b>Procedure</b>	<b>OPCAB</b>	<b>MIDCAB</b>	<b>IVUS</b>	<b>PTCRA</b>	<b>IVB</b>	<b>DES</b>
<b>Economic evaluation</b>						
Undertaken	<b>No, insufficient evidence</b>	No, insufficient evidence	Yes	No, could not calculate a single cost-effectiveness ratio, so a cost analysis was undertaken instead.	<b>Yes</b>	Yes
Type	NA	NA	Decision analytic model	Cost analysis	Decision analytic model	Trial-based model
Effectiveness	NA	NA	Clinically driven TLR at 9-12 months	NA	Clinically driven TLR at 8-12 months	Clinically driven TLR at 9 and 12 months
Incremental difference in effectiveness	NA	NA	-4.05%	NA	-13.99%	-16.5% at 12 months (CYPHER™) -10.3% at 12 months (TAXUS)
<b>Device cost source</b>	NA	NA	Average present market price provided by applicant (Boston Scientific)	Single large centre in Victoria (Monash) so representative of market price	Incremental procedure cost provided by applicant (Guidant)	Average selling price (MSAC state survey)
Incremental difference in procedure \$	NA	NA	\$1,360	\$4,266	\$6,024	\$2,317 (CYPHER™) \$2,317 (TAXUS)
Incremental difference in follow-up \$	NA	NA	-\$307	NA	-\$1,615	\$1,697 (CYPHER™) \$1,685 (TAXUS)
Total difference	NA	NA	\$1,053	NA	\$4,409	\$620.13 (CYPHER™) \$632.42 (TAXUS)
Cost/TLR avoided at 12 months	NA	NA	\$26,014	NA	\$31,527	\$3,747 (CYPHER™) \$6,121 (TAXUS)
Range	NA	NA	\$12,076 - \$798,601	NA	\$17,584 - \$48,055	\$3,700-\$15,320 (CYPHER™) \$6,100-\$25,150 (TAXUS)
Estimated utilisation and government budget impact	NA (but budget impact likely to be low or neutral as OPCAB will substitute for CABG).	NA (but budget impact likely to be low or neutral as MIDCAB will substitute for CABG).	11,334 procedures \$15.4m, with \$3.5m offsets, net \$11.9m per year.	370-472 procedures (~2% of all PCIs) and net \$1.5m- \$2.0m per year.	500-1000 procedures net \$2.2-\$4.4m per year	NA

NA=not available, CABG = coronary artery bypass graft, OPCAB = off pump coronary artery bypass graft, MIDCAB = minimally invasive off pump coronary artery bypass graft, IVUS = intravascular ultrasound, PTCRA = percutaneous transluminal coronary rotational atherectomy, IVB = intravascular brachytherapy, ASERNIP-S = Australian Safety and Efficacy Register of New Interventional Procedures -Surgical,

NHMRC = National Health and Medical Research Council, MSAC = Medical Services Advisory Committee, PCI = percutaneous coronary intervention, TLR = target lesion revascularisation.

Having the comparisons in **Table 3** in mind, MIAA notes here the release on 26 May 2005 of a new US study comparing CABG with stenting (Hannan et al 2005). Using data from the New York cardiac registries on patients treated in the period 1 January 1997 to 31 December 2000, it found that risk-adjusted survival rates were significantly higher in the CABG patients on the registries. Unfortunately, the study has significant weaknesses that render its conclusion less instructive to clinical practice involving the DES:

- This study did not include drug-eluting stents.
- This study is retrospective, and thus of less clinical significance than prospective randomized studies.
- The study compares outcomes in patients whose treatment assignment is determined by the treating physician and/or patient, a process which ensures lack of equivalency in baseline characteristics between the two groups, both for measured and unmeasured variables. This likely has a large effect on measured outcomes.
- Different physicians/groups/hospitals would have contributed in an unequal fashion to the two groups, promoting more likelihood of differences in outcomes being apparent.
- CABG has been shown to reduce mortality in 3-vessel disease and left-main coronary artery disease whereas stenting generally does not reduce mortality and is not commonly utilized for these two indications. The editorial article accompanying the NEJM paper by Hannan, describes the theory explaining this difference very clearly (Gersh & Frye, 2005).
- Randomized studies of multi-vessel stenting (e.g., ARTS I) did not show a difference in mortality in patients randomized to multi-vessel stenting vs. CABG. In fact, ARTS II through its statistical comparison with historical data from ARTS I, showed superior outcomes for the composite of death/myocardial infarction/ target lesion revascularisation/target vessel revascularization..

Third, the MSAC review is inconsistent in its recommendations and its conclusions about relative efficacy. MSAC did not make any recommendation for separate funding of DES. The MSAC Guidelines state that MSAC's recommendations generally fall into one of three categories:

- The evidence is strong and supports public funding ;
- The evidence does not support public funding ; or
- The evidence is inconclusive but suggests that the procedure could be safer, more effective, and more cost-effective than comparable procedures listed for public funding. In these circumstances MSAC may recommend interim funding to enable data collection and further evaluation of the procedure.

The wording of MSAC's conclusion resembles language of a decision of the third type. However, without explanation in its report, MSAC did not recommend interim funding for this technology.

**The Commission's comments on DES and CABG:** It is presumptive - and potentially misleading - for the Commission's Report to claim that "DES may still not be the most cost effective option" for the treatment of CAD and that as an example CABG could be a better option. The above critique of the new study by Hannan et al (2005) indicates that there is still no proof that CABG is a better option. Furthermore, the use of DES in PCI procedures is a minimally invasive procedure, whereas CABG is invasive surgery and requires opening the patient's chest and using blood vessel grafts to bypass blockages in the coronary arteries.

If the overall impact of DES on social outcomes was considered, CABG would not be classed as an alternative. The Report makes little reference to the demographics of the population that receives DES and little regard to the community expectation for the provision of DES.

Finally, considering this is a significant change in interventional cardiology procedures, and one that has the perception of high cost, the Commission's final Report will have more relevance if it recommends further assessment of DES diffusion in both public and private hospitals, and its cost-effectiveness in the post-marketing situation.

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## ANNEX 2: IMPLANTABLE CARDIOVERTER DEFIBRILLATION (ICD) THERAPY

### 1 Cardiovascular disease: mortality burden

Cardiovascular disease is a major cause of premature death and disability, and a major contributor to the escalating costs of health care the world over [1] - and Australia is no exception. Cardiovascular disease has been the leading cause of death among Australians for several decades. Cardiovascular disease accounted for 50,294 deaths in 2002, or 38% of all deaths (**Table 1**). In 2002, the greatest proportion of deaths from cardiovascular disease (89%) occurred in people aged 65 years or older [2]. More Australians died from cardiovascular disease in 2002 than from all malignant neoplasms, HIV, chronic obstructive pulmonary disease and road accidents combined (**Table 2**).

**Table 1: Cardiovascular mortality in Australia in 2002 [2]**

Mortality cause	Female deaths	Male deaths	Total mortality (% of all deaths)
All cause mortality	64,822	68,885	133,707 (100%)
Cardiovascular disease	26,306	23,988	50,294 (37.6%)
Coronary heart disease	12,208	13,855	26,063 (19.5%)
Heart failure	1,696	1,033	2,729 (2.0%)

**Table 2: Selected causes of non-cardiovascular mortality in Australia in 2002**

Mortality cause	Female deaths	Male deaths	Total mortality (% of all deaths)
Malignant neoplasms <sup>1</sup>	16,581	21,041	37,622 (28.1%)
HIV disease <sup>1</sup>	10	101	111 (0.1%)
Chronic obstructive pulmonary disease <sup>1</sup>	2,270	3,327	5,597 (4.2%)
Road fatalities <sup>2</sup>	471	1,243	1,714 (1.3%)

1. AIHW: personal communication.

2. Australian Transport Safety Bureau [3]

#### 1.1 Sudden cardiac death

Sudden cardiac death (SCD) is unexpected death preceded by abrupt loss of consciousness within 1 hour after onset of acute symptoms. About 80% of SCD events are caused by ventricular tachyarrhythmia, either ventricular tachycardia

(VT) or ventricular fibrillation (VF) [4]. Coronary heart disease and its major structural consequences, 'active' coronary lesions and acute and healed myocardial infarction (MI), are commonly the structural basis for SCD [5]. Major risk factors for SCD include a previous near-SCD episode, left ventricular ejection fraction (LVEF) < 40%, prior MI, inducible VT or documented episodes of non-sustained VT. The risk of SCD increases as patients acquire each additional risk factor.

It is estimated that SCD accounts for about 50% of all cardiovascular mortality [6], over 25,000 deaths each year in Australia. Therefore SCD represents a significant proportion of the overall mortality burden in Australia (**Table 1**). Additionally, though most patients who suffer an out-of-hospital cardiac arrest do not survive, those who are resuscitated may have severe, long-term cognitive impairment and motor impairment due to delays before a stable rhythm could be restored [7], adding to the morbidity burden and associated healthcare expenditure.

## **1.2 Heart failure**

Heart failure is a complex syndrome, which results from any structural or functional cardiac disorder that reduces the ability of the heart to function as a pump [8]. The condition is characterised by dyspnoea, fatigue, and fluid retention. Patients with mild heart failure may have very few symptoms, but in more severe cases they suffer from chronic tiredness, have limited exercise capacity, frequent need for hospitalisation [9], high rates of mortality and an impaired quality of life. Heart failure can result from a variety of diseases that impair or overload the heart, e.g. hypertension, myocardial infarction, diabetes, but the most common cause in the developed world and Australia is coronary heart disease [10].

Heart failure is primarily a disease of the elderly; approximately 6% to 10% of people older than 65 years have heart failure, and approximately 80% of patients hospitalized with heart failure are more than 65 years old [11]. Despite considerable advances in the management of congestive heart failure, it remains associated with a very poor prognosis, worse than many forms of cancer. In severe heart failure, survival can be less than 50% at one year [12]. Heart failure also has a major impact on the quality of a patient's life, worse than angina or chronic airways disease.

Two major barriers in determining the incidence and prevalence of heart failure in Australia are the lack of a universally agreed definition and difficulties in diagnosis, particularly when the condition is mild. However it is assumed that the epidemiology here is similar to Europe and the USA [13], and based on these overseas findings, it is estimated that at least 300,000 Australians have chronic heart failure (or about 4% of the population aged 45 or more), with 30,000 new cases diagnosed each year [10]. The prevalence of heart failure in Australians over 60 years has been estimated at 13.2% [14]. An ageing population, improved survival from heart attack and the increased prevalence of diabetes and obesity may increase the number of people with heart failure in the future [10].

Heart failure is an important cause of mortality and hospitalisation in Australia. Heart failure accounted for more than 2,700 deaths (2% of all deaths) and over 39,500 hospitalisations in 2001-02 (0.7% of all hospitalisations) [15]. Rates of hospitalisation for heart failure in Australia increase markedly with age (especially among males, who are 28.4% more likely to be hospitalised), with about 70% of hospitalisations in patients over 75 years old [15].

### **1.2.1 Economic burden of heart failure**

The economic burden of heart failure is large and growing [16]. It is estimated that direct health care costs for heart failure amounted to \$600 million in 2000-01 (11% of cardiovascular disease costs), the fourth highest among cardiovascular conditions after coronary heart disease, high blood pressure and stroke. About 40% of these direct health care costs were spent on hospital inpatient care.

## **2 Prevention of sudden cardiac death and treatment of heart failure**

### **2.1 Sudden cardiac death prevention**

Therapeutic strategies for the prevention of SCD may be divided into two general categories: primary prevention and secondary prevention. Primary prevention refers to the prevention of the first life-threatening arrhythmic event such as sustained ventricular tachycardia, ventricular fibrillation, or cardiac arrest. Secondary prevention refers to the prevention of a recurrence of a potentially fatal arrhythmia or cardiac arrest among patients who have had clinical events of that type.

Until recently the standard treatment for ventricular tachyarrhythmia has been pharmacological, with antiarrhythmic drugs (AADs) and vasodilating beta-blockers such as amiodarone and sotalol. But despite using the best appropriate medical treatment, arrhythmia recurrence rates are still 40–50% at five years [17]. Also, although AAD therapy can decrease the number of episodes of ventricular arrhythmia, and thus lower the incidence of SCD, it can do nothing to stop a life-threatening arrhythmia once it has started. The development of ICDs over the last 20 years has offered a new alternative. ICD therapy is the only therapy that can prevent SCD due to a life-threatening arrhythmia.

#### **2.1.1 Implantable cardioverter–defibrillator therapy**

Implantable cardioverter–defibrillators (ICDs) are electronic devices which continuously monitor the heart, detect abnormal rhythms and deliver an appropriate electrical counter shock to the myocardium to restore normal sinus rhythm [7]. These devices have been available and in clinical use since the 1980s, and since then have evolved from a therapy of last resort for patients with recurrent cardiac arrest to a management standard for use in primary prevention in high-risk patients, and secondary prevention in patients who have survived sudden cardiac death or have severe coronary heart disease [7,17-19]. ICD therapy has been shown to be 99% effective in terminating life-threatening arrhythmias and thus aborting SCD.

Originally ICD devices had a single therapy option of defibrillation only; the generator was implanted in the abdomen, and thoracotomy was required for electrode placement. With advances in technology the units have become smaller (current ICDs are little bigger than a pacemaker) and can be implanted pectorally. With improvements in sensing, the latest devices offer a graded therapeutic response to a sensed ventricular arrhythmia. Anti-tachycardia pacing, low-energy synchronised cardioversion, and high-energy defibrillation shocks can be given via a single transvenous lead [17-19].

Implantation of an ICD is now technically very straightforward, and only a little more complicated than pacemaker implantation. In the past, ICD implants were performed under general anaesthesia; however, many centres now implant these devices using a combination of local anaesthesia and intravenous sedation. Before hospital discharge the device is programmed to detect and treat episodes of ventricular tachycardia and fibrillation, the precise programmed values being governed by the patient's clinical history, maximum sinus rate, and rates of any documented ventricular and supraventricular arrhythmias [17-19].

ICD manufacturers have allocated (and continue to provide) significant resources toward developing features and benefits that make modern ICD therapy more effective, more efficient, and more cost-effective, with over \$1,600 million invested in research and development alone, and significant additional investments in clinical trials, and customer education and support. Key development areas include:

Continued reductions in device size: Size is important to patient comfort. Achieving smaller size without sacrificing capability also reduces the potential for certain complications, including erosion of the implant, which is particularly important in slender people or children. Decreases in the size of the ICD have been made possible by reducing the amount of energy required to provide defibrillation therapy to terminate fibrillation. Most devices produced today are <40cc (e.g., the Guidant Corp. *Vitality*<sup>®</sup> family of ICDs are only 30cc in size) allowing for smaller incisions and increased patient comfort.

Enhanced lead technology: Improved reliability has resulted in fewer lead dislodgements or fractures over the past 5 years. Lead-related complications have been decreased to less than 2% of all ICDs with new lead technology in place. The landmark MADIT-II trial reported lead-related complications of about only 1.8% [20].

Extended longevity: Newer devices can last at least 5 years before a replacement is needed (e.g., the Guidant Corp. *Vitality 2 EL*<sup>®</sup> family of ICDs last 7 years, cf., 2-3 years for older models), an important feature for clinical management and patient quality of life, which also makes modern devices cost-effective.

Enhanced diagnostics: In the past few years, arrhythmia detection algorithms have been enhanced to minimize false positives and negatives. Modern ICDs have improved arrhythmia discrimination to differentiate

between atrial and ventricular tachyarrhythmias, and clinicians can programme them more precisely to the patient's needs, leading to a reduction in inappropriate shocks [21].

## **2.2 Heart failure treatment**

The basic aims of heart failure treatment are to relieve symptoms, improve quality of life, slow progression of the disease, prevent hospital admission and reduce mortality. Considerable advances have been made in the drug treatment of heart failure over the past few decades. Current guidelines recommended that angiotensin-converting enzyme (ACE) inhibitors and beta-blockers are first-line agents that should be used for all patients with severe heart failure unless contraindicated or not tolerated; diuretics may be employed where necessary for symptom relief [11].

### **2.2.1 Cardiac resynchronisation therapy**

Conduction system abnormalities are common among patients with heart failure; up to 50% of patients with heart failure may have conduction delays such as first-degree atrial-ventricular block, or intraventricular conduction delays such as left bundle branch block. These conduction delays result in abnormal electrical depolarisation of the heart, and as a result patients with heart failure often have a dyssynchronous contraction of the cardiac chambers [22].

The dyssynchrony may be due to ineffective synchronisation between the atria and ventricles (AV dyssynchrony), or within the two ventricles (ventricular dyssynchrony). Intraventricular and interventricular conduction delays can also cause an inefficient uncoordinated pattern of left ventricular activation with segments contracting at different times [22]. Consequently, there is a shorter diastole and/or overlapping systole/diastole and aggravation of functional mitral regurgitation. Ventricular dyssynchrony is an independent prognostic risk factor for increased mortality in heart failure. The rationale for cardiac resynchronisation therapy (CRT) is to create a more coordinated and efficient systolic contraction and improve the mechanical efficiency of the heart by simultaneously pacing both ventricles [8, 22].

CRT is proposed as a treatment for heart failure in patients already receiving optimal pharmacological therapy (with an ACE inhibitor and a beta-blocker, and usually also a loop diuretic). The procedure involves cardiac catheterisation equipment and techniques, and a specially designed catheter to gain access to the venous system of the left ventricle via the coronary sinus. A specially designed pacing lead is placed in a branch of the coronary sinus and, along with standard pacing leads in the right atrium and ventricle, attached to a CRT device, similar to a conventional pacemaker, with the capability of sensing and pacing in the three chambers. The procedure is usually conducted under local anaesthetic, and may require an overnight stay in hospital.

Cardiac resynchronisation therapy defibrillator (CRT-D) refers to the combination of CRT and ICD into a single device, with the aim of meeting the major goals of heart failure treatment, i.e., to relieve symptoms, improve quality of life, slow

progression of the disease, prevent hospital admission and improve survival, and also protect against life-threatening arrhythmias.

### **2.3 Efficacy and safety of ICD, CRT and CRT-D**

#### **2.3.1 ICD efficacy and safety**

There is a substantial literature on the safety and efficacy of ICD therapy. A number of well-designed studies have shown the effectiveness of ICD therapy in severe heart failure; meta-analyses and health technology assessments [23-25] and guidelines have been published [26-29]. ICDs have consistently shown to be effective in reducing total mortality in patients with life-threatening ventricular tachyarrhythmias as compared to antiarrhythmic drug therapy. Mortality reductions in various trials have been between about 30 and 50%, and the numbers-needed-to-treat (at 3-years follow-up) in the range 3-11 (cf., 20-37 for drug therapy).

The recently published landmark Sudden Cardiac Death in Heart Failure (SCD-HeFT) trial showed conclusively that ICD therapy was also beneficial in patients with NYHA class II or III heart failure, reducing mortality by 23.2% relative to amiodarone, which had no impact on survival [30]. In May 2005 NICE, the technology assessment body which advises the UK NHS, recommended that the use of ICDs be routinely considered for primary and secondary prevention of arrhythmias [31].

#### **2.3.2 CRT and CRT-D efficacy and safety**

There is also a substantial literature on the safety and efficacy of CRT and CRT-D therapy. Several major trials have demonstrated the value of these treatments. The landmark CARE-HF study showed that CRT in addition to standard drug therapy reduced the incidence of complications and the risk of death compared with drug therapy alone [32]. The COMPANION study, another landmark trial, confirmed trends of earlier studies [33, 34], and demonstrated that CRT-D reduces all-cause mortality and hospitalisation [35].

Reviews of the trial data, meta-analyses and consensus and policy statements have been published on both CRT and CRT-D [8, 22, 29, 36-40]. All the major trials report an improvement in functional capacity, exercise tolerance and the quality of life of patients.

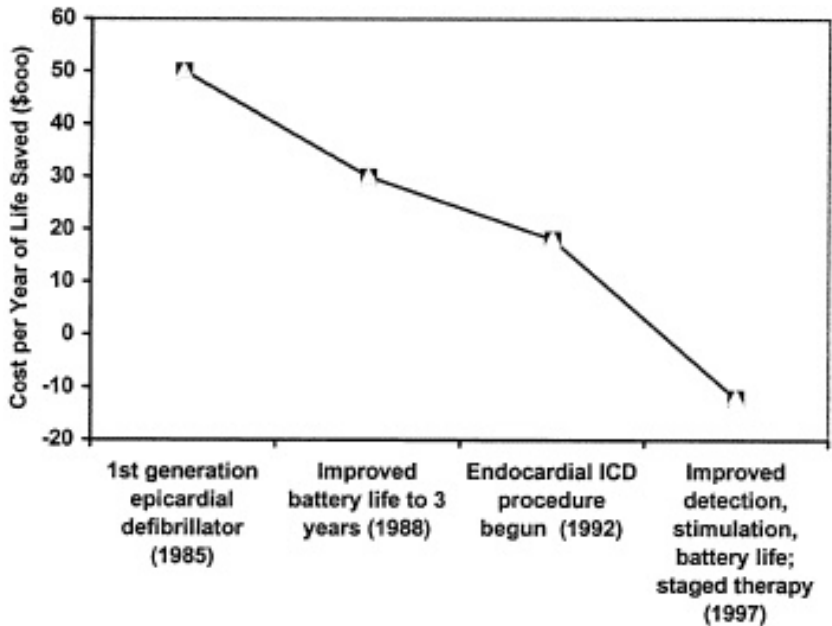
## **3 Economic considerations**

### **3.1 Cost-effectiveness of ICD, CRT and CRT-D therapy**

Treatment for patients at risk of SCD is focused on suppressing or terminating the arrhythmia, and it is well established that the clinical effectiveness of ICDs in addition to standard drug therapy is superior to AAD therapy alone. However the pattern of costs associated with the two treatments differ, in that ICDs have a high initial cost for implantation whereas the often comparably high costs of drug therapy are spread over several years and therefore less visible [41].

Although the costs of devices and implantation are substantial, it may be that the current technologies actually represent cost savings relative to alternative treatments. This cost reduction is the result of continual improvements in efficacy brought about by progressive advances in arrhythmia detection and stimulation algorithms and further extensions of battery life, and also because of the multifunctional capabilities of modern devices that permit them to adapt automatically to changes in the patient’s clinical status (**Figure 1**). These technological advances have markedly reduced expensive hospitalization episodes, as well as improving patients’ quality of life and productivity.

**Figure 1: Impact of technological evolution on cost-effectiveness of ICDs [42]**



The cost-effectiveness of ICDs has been shown in several trial-based economic evaluations and systematic reviews [43, 44].

More recently, a US economic analysis based on the large SCD-HeFT trial [30] found that though ICD therapy was more expensive than amiodarone therapy over a 5-year horizon (US\$61,968 versus US\$49,443), at US\$33,192 per life-year gained it was cost-effective even in NYHA class II or III patients [45].

Similarly, CRT has been shown to be cost-effective in heart failure (**Table 3**), with incremental costs per QALY (relative to drug therapy) similar to other common interventions [50].

**Table 3: CRT cost-effectiveness: a selection of published reports, 2000-2005**

<b>Authors</b>	<b>Study type and analysis</b>	<b>Results</b>
Braunschweig F, et al. (2000) [46]	The aim of this study was to assess total and heart failure related hospital days as well as safety and efficacy of cardiac resynchronization in patients with severe heart failure and delayed intraventricular conduction.	The need for hospital care decreased significantly after CRT. The total number of hospital days reduced by 82% resulting in reduced need for hospital care.
Bentkover JD, et al. (2003) [47]	Economic model to evaluate the components of treating Class III/IV heart failure patients in Canada and the resulting direct medical costs. The model also estimates the potential savings that could result from the introduction of new technology such as CRT that reduces morbidity and mortality.	Potential savings in Canada could reduce the total annual costs for this group of patients by ~10%. The high level of morbidity and mortality in Class III/IV heart failure patients and costs associated with their care are an impetus for the development of new therapies such as CRT.
Curnis A, et al. (2003) [48]	Analysis of hospital costs and clinical effectiveness of cardiac resynchronization in heart failure.	In the 12 months following the implant, overall costs reduced by 24%. Cardiac resynchronization in heart failure patients represents an efficient approach in the hospital perspective and allows a less intensive use of clinical resources.
Lynd L, et al. (2003) [44]	Review of current evidence on the cost-effectiveness of Implantable cardioverter defibrillators	Implantable cardioverter defibrillator therapy may be a cost-effective option in patients at high risk for ventricular tachycardia/fibrillation
Banz K (2005) [49]	Computerized economic model to explore the cost-effectiveness of CRT as compared to optimal pharmacological treatment alone in patients with moderate to severe heart failure and intravenous conduction delay.	CRT appears to be an economically meaningful treatment strategy and it can be expected that cost savings may even increase over time as the beneficial effects of this therapy are reported to be sustained over at least 2 years.

As would be expected from any therapy with heavily ‘front-loaded’ costs, the cost-effectiveness of CRT-D therapy manifests in the few years following implantation. It has been argued that the therapeutic benefits of traditional ICD therapy continue long after the initial period post-implantation, providing continued protection in the face of ongoing event risk; this would also be true for CRT-D.

It should be noted that the US Centers for Medicare & Medicaid Services (CMS), a governmental entity not easily given to funding new healthcare technology, has recognised that CRT is an important development in the treatment of the failing heart, and in January 2003 introduced specific Physician Billing Codes and DRGs to facilitate the uptake and use of this technology.

On 28 January 2005 CMS, in response to the published results of the SCD-HeFT trial [30], further expanded the reimbursement of ICDs to include patients with heart failure and poor left ventricular function [51, 52]. The Administrator of CMS was quoted as follows:

*“Our expanded coverage for devices to prevent sudden death in people with heart disease will save thousands of lives each year and improve the quality of life for America’s seniors. By increasing the use of defibrillators we are striking a blow against the leading cause of death among older Americans. This coverage decision demonstrates our determination to save lives by making prompt coverage decisions using new medical evidence, and to improve the evidence available to doctors and patients to help them get the greatest benefits while avoiding unnecessary risks and costs.” [52]*

The expansion will increase the number of US Medicare beneficiaries eligible for an ICD by one-third, to nearly 500,000. CMS expects to provide ICD therapy to at least 25,000 additional patients in the first year of coverage.

#### **4 Conclusions**

The major goals of heart failure treatment are to improve the length and quality of a patient's life. ICDs provide substantial mortality benefits by preventing sudden cardiac death in patients with heart failure who have ischaemia, poor ejection fraction and a history of ventricular arrhythmias, but do not improve functional outcomes. On the other hand, CRT clearly improves quality of life by improving many of the pathophysiological changes seen in patients with advanced heart failure. The combination of ICD and CRT in one device therefore makes CRT-D a powerful therapy, with the capability of protecting patients at risk from life-threatening arrhythmias as well as improving their quality of life and clinical outcomes. The therapeutic benefits of ICD and CRT-D continue long after the initial period post-implantation, providing continued protection in the face of ongoing event risk.

As the benefits of ICD and CRT-D therapy become more evident, an increase in their use in Australia can be expected. Healthcare funders have expressed concern that increased use of ICDs and CRT-Ds could disproportionately increase the total healthcare expenditure in Australia. However, these concerns must be addressed within the context of total health services expenditure, considering also the benefits over an appropriate time period. The analyses in the peer-reviewed literature suggest that ICD and CRT-D therapies have acceptable cost-effectiveness ratios for therapies for serious life-threatening conditions, and that they should be funded. MSAC's ongoing review of ICD and CRT-D should take notice of the many prior evaluations of these technologies, which have demonstrated their cost-effectiveness, and recognise that these devices have diffused rapidly because of their benefits to patients.

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### ANNEX 3 : GLOSSARY

AAD	antiarrhythmic drug
ACA	Australian Consumers Association
ACE inhibitors	angiotensin converting enzyme inhibitors
AHIA	Australian Health Insurance Association
AIDS	acquired immune deficiency syndrome
AMI	acute myocardial infarction
ARTG	Australian Register of Therapeutic Goods
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures – Surgical
BMS	bare metal stents
CABG	coronary artery bypass graft
CAD	coronary artery disease
CAG	Clinical Advisory Group (Prostheses)
CAKR	computer-assisted knee replacement
CAOS	computer-assisted orthopaedic surgery
CAS	computer-assisted surgery
CGMS	continuous glucose monitoring system
CHD	coronary heart disease
CHF	congestive heart failure
CMS	Centers for Medicare & Medicaid Services (US)
CRT	cardiac resynchronization therapy
CRT-D	cardiac resynchronization therapy - defibrillators
CSSI	continuous subcutaneous insulin infusion
CT	computed tomography
CTC	Clinical Trials Centre (of NH&MRC)
DCCT	Diabetes Control and Complications Trial
DES	drug-eluting stent
DOHA	Department of Health and Ageing
DRG	diagnosis related group
EDIC	Epidemiology of Diabetes Interventions and Complications Research Group
ET	energy transfer
FDA	Food & Drug Administration (US)
GDP	gross domestic product
HbA1C	glycosolated haemoglobin
HealthPACT	Health Policy Advisory Committee on Technology
HTA	health technology assessment
ICD	implantable cardioverter-defibrillator
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IDDM	insulin-dependent diabetes mellitus
IgM	immunoglobulin M
IHD	ischaemic heart disease
ISR	in-stent restenosis
IVB	intravascular brachytherapy
IVUS	intravascular ultrasound
LOS	length of (hospital) stay
LVEF	left ventricular ejection fraction

MACE	major adverse cardiac events
MBS	Medical Benefits Schedule
MDI	multiple daily injection
MI	myocardial infarction
MIAA	Medical Industry Association of Australia
MIDCAB	minimally invasive off pump coronary artery bypass graft
MIS	minimally invasive surgery
MRA	Mutual Recognition Agreement
MSAC	Medical Services Advisory Committee
NAA	nucleic acid amplification
NH&MRC	National Health & Medical Research Council
NHSU	National Horizon Scanning Unit
NICE	National Institute for Clinical Excellence (UK)
NYHA	New York Heart Association
OPACB	off pump coronary artery bypass graft
OTC	over the counter (non-prescription)
PAG	Policy Advisory Group (Prostheses)
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCI	percutaneous coronary interventions
PCR	polymerase chain reaction
PDC	Prostheses & Devices Committee
PET	positron emission tomography
PHI	private health insurance
PTCA	percutaneous coronary intervention with angioplasty alone
PTCRA	percutaneous transluminal coronary rotational atherectomy
QALY	quality-adjusted life year
R&D	research & development
RACS	Royal Australasian College of Surgeons
RCT	Register of Clinical Trials
SCD	sudden cardiac death
SDA	strand displacement amplification
TGA	Therapeutic Goods Administration
TKR	total knee replacement
TLR	target lesion revascularisation
TTA	Trans-Tasman Agency
UKPDS	United Kingdom Prospective Diabetes Study
VDHS	Victorian Department of Human Services
VLU	venous leg ulcer
VF	ventricular fibrillation
VT	ventricular tachycardia