Cardiac ablation catheters for the treatment of atrial fibrillation

Report Part 3:

Extended economic analysis

06 February 2019

Disclaimer:

The economic analysis in this report is an extended version of the economic analysis presented in Report Part 2. The current analysis incorporates specific advice received from MSAC and the Department of Health, but is still largely based on the rapid review of high-level clinical evidence described in Report Part 1 and other assumptions detailed in Report Part 2.

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ABBREVIATIONS

AAD	antiarrhythmic drug
AF	atrial fibrillation
AHRQ	Agency for Healthcare and Research Quality
AR-DRG	Australian Refined Diagnosis Related Group
CA	cardiac/catheter ablation
CAD	coronary artery disease
CADTH	Canadian Agency for Drugs and Technologies in Health
CSANZ	Cardiac Society of Australia and New Zealand
FU	follow up
GP	general practitioner
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
INR	international normalised ratio
ITT	intention to treat
LOS	length of stay
LV	left ventricular
MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee
MT	medical therapy
NHFA	National Heart Foundation of Australia
OAC	oral anticoagulant
PBS	Pharmaceutical Benefits Scheme
PI	Product Information
PL	Prostheses List
PLAC	Prostheses List Advisory Committee
QALY	quality-adjusted life year
RCT	randomised controlled trial
RF	radiofrequency
RMH	Royal Melbourne Hospital
SF-36	36-item Short Form Survey
SR	systematic review

Key findings

At what 'bundled price' are cardiac ablation devices cost-effective?

In response to advice received from the Medical Services Advisory Committee (MSAC) and the Department of Health, the timeframe in the focused economic model described in Report Part 2 was extended from 12 months to 5 years and 10 years. According to advice from the Department, a range of per procedure 'bundled prices' were then applied to the re-structured, re-specified model to explore the impact of the cost of cardiac ablation catheters on the modelled incremental cost-effectiveness ratio (ICER) compared with medical therapy.

The extended model retains many of the inputs and assumptions underpinning the original focused economic analysis, most notably the reliance on 'freedom from AF' as the primary patient-relevant outcome. Differential cardiac hospitalisations have been considered in the model, but no inferences have been made regarding benefit in terms of stroke or mortality in the modelled population (who are assumed to not have heart failure). The key differences relate to assumptions around the probabilities of AF recurrence and cardiac hospitalisation over time, and disutility attributed to serious/major hospitalisation (which are now more reflective of the approach taken by CADTH (Assasi et al. 2010)).

As expected, the extended time horizons capture longer-term benefits of freedom from AF (in terms of health-related quality of life) and this has improved the incremental cost-effectiveness of cardiac catheter ablation relative to medical therapy. As shown in the table below, cardiac ablation is likely to be cost-effective over a ten-year time horizon at a bundled price of **approximately $6,500** (assuming that ICERs below $50,000 per QALY represent acceptable cost-effectiveness).

The limitations of the current analysis (refer to Section 3.3) should be taken into account when interpreting these findings.

Table 1 Indicative cost-effectiveness of cardiac ablation catheters versus medical therapy for the treatment of AF by bundled price and time horizon

Bundled price per ablation[a]	Cost per additional QALY	
	5-year time horizon	10-year time horizon
$1,000	$46,684	-$1,018
$2,000	$62,179	$8,174
$3,000	$77,674	$17,366
$4,000	$93,169	$26,557
$5,000	$108,664	$35,749
$6,000	$124,159	$44,941
$7,000	$139,653	$54,133
$8,000	$155,148	$63,325

Abbreviations: AF, atrial fibrillation; QALY, quality-adjusted life year.

a The 'bundled price' includes all ablation and mapping catheters required for an ablation procedure. The price applies to any type of catheter (radiofrequency or cryoablation).

1 Introduction

On 26 September 2018, the Department of Health engaged a contractor to prepare the following:

- Report Part 1 – A Rapid Review of high-level clinical evidence for cryo- and radiofrequency (RF) cardiac ablation catheters used to treat atrial fibrillation (AF).
- Report Part 2 – A focused economic evaluation to determine whether cardiac catheter ablation is cost-effective at the prices currently being paid in Australia, and a focused analysis of the likely utilisation and budget impact of a decision to list cardiac ablation catheters on the Prostheses List (PL).

The Medical Services Advisory Committee (MSAC) considered both reports on 22 November 2019. MSAC was largely satisfied with the inputs and assumptions underpinning the focused economic analysis; however, a key concern was the short duration of the model (12 months), which does not capture the longer-term benefits that could potentially be attributed to long-term freedom from AF and which might reasonably be expected to affect the incremental cost-effectiveness of the procedure.

On 14 January 2019, the contractor was engaged to revise the economic model according to specified parameters. It was agreed that the extended model should largely retain the inputs and assumptions described in Report Part 2 (as appropriate), most notably the reliance on 'freedom from AF' as the primary patient-relevant outcome, with no inferences made regarding benefit in terms of stroke or other cardiovascular events avoided. The Department requested that the extended analysis should incorporate the following changes:

- extrapolation of the timeframe from 12 months to (a) 5 years and (b) 10 years; and
- use of a range of 'bundled prices' per ablation procedure (irrespective of device type and incorporating all associated device costs) to explore the impact of the cost of the device on the modelled incremental cost-effectiveness ratio (ICER).

The current report documents the revised approach and findings of the extended economic analysis.

2 Development of the focused economic model

The focused economic analysis described in Report Part 2 compared the direct medical costs and outcomes related to cardiac ablation versus medical therapy in patients with AF. The management pathway was informed by the 2018 National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (NHFA/CSANZ) *Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation*, and therefore focuses on patients with symptomatic AF who are refractory or intolerant to at least one Class I or III antiarrhythmic drug (AAD). Given the limitations in the evidence available, and the requirement to develop the model in a short timeframe, a simple short-term model, without extrapolation, was considered appropriate at the time.

The extended analysis described herein extends the modelled time horizon to 10 years, which is well beyond the follow up period reported in the published randomised controlled trials (RCTs) discussed in Report Part 1. A systematic literature search was conducted on 17 January 2019[1] to identify any full-text, peer-reviewed publications from the landmark *Catheter ABlation vs ANtiarrhythmic Drug Therapy in Atrial Fibrillation* (CABANA) trial (N=2,204). Preliminary findings are available from an online conference presentation but no full-text, peer-reviewed publications were identified in the search.[2]

Although interpretation of the findings from CABANA is affected by incomplete blinding and high rates of crossover between arms, the results – when published in full – may nonetheless provide valuable additional evidence to inform the clinical effectiveness and cost-effectiveness of cardiac ablation compared with medical therapy. According to the preliminary results, cardiac ablation was found to be associated with a significant reduction in recurrence of AF compared with "current state-of-the-art pharmacologic therapy" at a median follow up of approximately four years (hazard ratio 0.53; 95% confidence interval 0.46 – 0.61). However, there was no statistically significant difference between arms in the primary endpoint of the trial (the composite of all-cause mortality, disabling stroke, serious bleeding, or cardiac arrest) or the individual components of the primary endpoint using an intention-to-treat (ITT) approach.

Accordingly, the current extended economic analysis relies on 'freedom from AF' as the primary patient-relevant outcome, with consideration of differential cardiac hospitalisations, but with no benefit attributed to a reduction in all-cause mortality, stroke or other cardiovascular events avoided.

Consistent with the previous analysis, the extended economic analysis does not apply to cardiac catheter ablation performed intraoperatively (e.g. during valve replacement surgery) or as an adjunct to surgery (hybrid ablation). These scenarios were explicitly excluded from the evidence review described in Report Part 1. Likewise, the extended economic analysis does not apply to patients with heart failure (albeit with use of some preliminary evidence from the CABANA trial, in which approximately 15% of patients had congestive heart failure at baseline). A review of the clinical evidence for use of cardiac ablation catheters in patients with heart failure was not in scope of Report Part 1.

2.1 MODEL STRUCTURE

The revised decision analytic model (described herein) retains many of the inputs and assumptions underpinning the original focused economic analysis described in Report Part 2. Key probabilities were derived from the findings of the clinical evidence review (Report Part 1), supplemented where appropriate with longer-term data from CABANA, and verified where possible by clinical experts and/or data from Medicare Australia.

[1] Refer to Appendix A for the search strategy.
[2] Preliminary findings from the CABANA trial are available at cabana trial. Accessed 11 October 2018.

The main features of the model structure are detailed in Table 2 below.

Table 2 Description of main extended model components

Component	Description
Type(s) of analysis	Cost-utility analysis
Outcomes	Quality-adjusted life years
Time horizon	5 years and 10 years
Method(s) used to generate results	Hypothetical cohort of 1,000 people aged 61-70 years for each arm. The cohort remains in this age bracket for the duration of the model. A decision tree was used for the first cycle of the ablation arm and a Markov model thereafter. For the medical therapy arm, the cohort is suspended in an assumed 'AF state' for one model cycle, then cycle within a Markov model thereafter. Discounting was applied at 5% to costs and benefits after the first year (i.e. the discount on costs and benefits for the first cycle of Year 2 is equal to that applied to the last cycle in Year 2). No half-cycle correction was applied.
Health states	For the ablation arm, with or without complications of procedure for the first model cycle. Thereafter and for the medical therapy arm, the health states are: 1. AF free 2. AF recurrence 3. Cardiac hospitalisation (separated into minor and major hospitalisation). Considered to be mutually exclusive of State 1 and State 2. 4. Re-ablation (ablation arm only, once only and within 12 months only). Considered to be a subset of State 2. 5. Dead
Cycle length	Monthly
Transition probabilities	Described in Table 3
Software	Microsoft Excel 2011 (Redmond, Washington, United States)

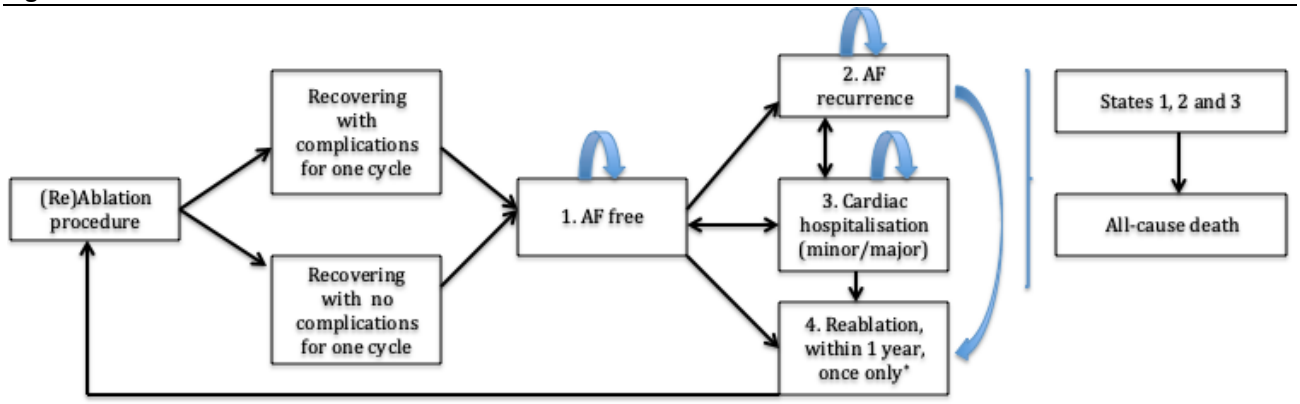
Abbreviations: AF, atrial fibrillation.

Due to the longer time frame for this extended analysis, a Markov model was used. This approach is preferred for longer time horizons compared to decision trees, as time can be accounted for. A hypothetical cohort of 1,000 people for the ablation arm and medical therapy arm was cycled through the model, with their passage described in Figure 1 (ablation arm) and Figure 2 (medical therapy arm). As requested by the Department, the model duration was set to 5 years and 10 years, applied in a step-wise fashion to enable comparison with the findings from the previous focused economic model. Each cycle in the model was one month in duration.

Consistent with the previous model, cardiac ablation is considered to be an alternative to medical therapy and not an add-on. No crossover between arms was allowed. Patients in the model received initial treatment with either cardiac ablation or medical therapy (i.e. amiodarone) after failure of, or intolerance to, a Class I or another III AAD (e.g. flecainide or sotalol). Probabilities were assigned for patients in both arms remaining free from AF (normal sinus rhythm), experiencing a recurrence of arrhythmia, a cardiac hospitalisation (of minor or major complexity), or all-cause death. Patients in the cardiac ablation arm could undergo one repeat ablation (termed 're-ablation'), following which the success rate is assumed to be equal to that following the first procedure. Re-ablation could only occur within the first twelve months of the model, could occur once only, and people receiving an ablation procedure were considered to be a subset of those experiencing an AF recurrence for each model cycle. This decision was made on the basis that only people experiencing a recurrence of AF symptoms would consider a repeat procedure. People admitted for a cardiac hospitalisation were considered to be mutually exclusive of those experiencing an AF recurrence (i.e. no overlap was assumed in the model). In addition, people could transition from recurrence to re-ablation.

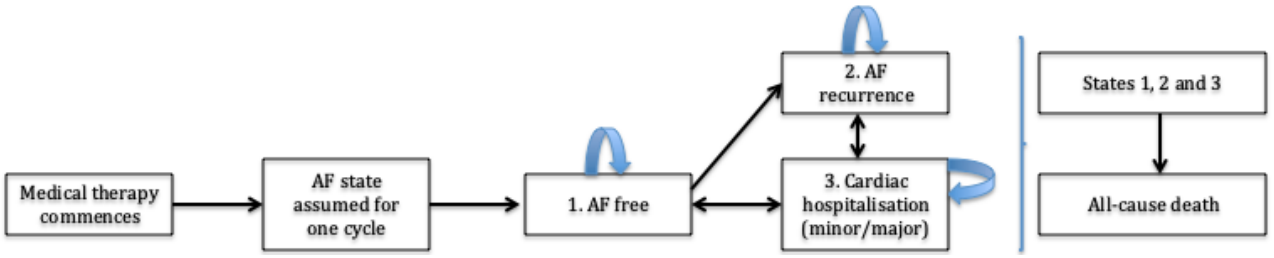
The model assumed that patients with symptoms of AF have reduced health-related quality of life (HRQoL), as do patients who experience major or serious complications associated with the ablation procedure, and patients who experience a cardiac hospitalisation. This reduction in HRQoL is captured in the model by applying a utility decrement from a mean norm utility weight for Australians aged 61-70 years. This age bracket was selected based on Medicare data indicating this is the main demographic group undergoing the ablation procedure. Similarly, all-cause mortality was assigned using the average mortality rate for Australian males and females aged 61-70 years, reported in the 2015-17 Australian life tables[3].

Figure 1 Ablation decision tree and Markov model structure for ablation arm



Note 1: The re-ablation group (Health State 4) is taken to be a subset of the AF recurrent group (Health State 2) to avoid double counting. States 1, 2 and 3 are considered mutually exclusive
Note 2: The probabilities applied to the model were derived from a published systematic review and, for longer timeframes; observational studies rather than an individual study and refer to the entire starting population.

Figure 2 Markov model for medical therapy arm



Note 1: States 1, 2 and 3 are considered mutually exclusive for both arms.
Note 2: The probabilities applied to the model were derived from a published systematic review and, for longer timeframes; observational studies rather than an individual study and refer to the entire starting population.

The model is agnostic to the type of cardiac catheter ablation performed (RF ablation or cryoablation), as there is no reliable evidence supporting the superiority of one device type over the other.

Health resource utilisation was modeled to reflect AF management in Australian clinical practice. Estimated unit costs were applied to the resource use, and the total costs were derived as the sum of the initial treatment and follow up. Discounting of 5% was applied to costs and benefits each year after the first year in the model (i.e. costs and benefits were not discounted within the first year of the model, and then for each subsequent year the discount applied in the first cycle of that year was equal to that applied to the final cycle). Due to the short cycle-length relative to the 5- and 10-year time horizon, and because incremental costs and benefits were the focus of this analysis, no half-cycle correction was applied.

[3] Australian Bureau of Statistics (ABS). Life tables: states, territories and Australia, 2015-17 [Internet]. ABS: Canberra, Australian Capital Territory, Australia; 2018 [cited 21 January 2019]. Available from: Australian Bureau of Statistics

A limited number of sensitivity analyses were performed to account for key uncertainties.

2.2 KEY ASSUMPTIONS

2.2.1 Probabilities

The probabilities applied in the model are shown separately in Table 3 for the cardiac ablation and medical therapy arms. These probabilities are largely the same as those applied to the previous model, except that the longer time horizon meant that assumptions had to be made regarding the probabilities of AF recurrence and cardiac hospitalisation over time.

Changes to AF recurrence probabilities over time

A key concern in modelling the cost-effectiveness of cardiac catheter ablation over a longer time horizon is the paucity of RCT evidence beyond a 12-month timeframe. As a consequence, there is higher uncertainty in the incremental benefit of ablation beyond one year, in contrast to the first twelve months where ablation is clearly superior to medical therapy in terms of maintenance of an 'AF free' state.

In the previous model (see Report Part 2) and the revised model described herein, the probability of recurrence in the first twelve months has been taken from a published systematic review and meta-analysis of 8 RCTs in patients with AF (Khan et al, 2018). Reliable RCT data beyond 12 months are limited. Preliminary data from the CABANA trial are available to 48 months from a 2018 conference presentation[4]. However, the application of these data is suboptimal for several reasons. Firstly, there were 16% in the ablation and 15% in the medical therapy arm with co-morbid heart failure. These patients were out of scope for this analysis. There was also considerable crossover between arms in the CABANA trial (27.5% to the ablation arm from medical therapy; 9.2% in the other direction) and the recurrence rates were available only as part of an ITT, rather than 'as treated' analysis. While the use of ITT data is more conservative and is usually preferable for assessment of efficacy, an 'as treated' analysis would be helpful in this case to reduce confounding caused by crossover in the trial, particularly given that the economic model assumes no crossover between arms. Finally, data from CABANA are not yet available in peer-reviewed form.

Several observational studies (identified in an informal literature search) have investigated the long-term probability of recurrence among patients receiving a cardiac ablation procedure. Shah et al (2007) estimated the risk of recurrence for those 'AF free' at 1-year post-ablation was 25.5% by five years post-ablation (i.e. an average annual recurrence of 6.4%). Tzou et al (2010) reported a late recurrence of approximately 7% annually. Wokhu et al (2010) reported a 0.9% recurrence each month beyond twelve months (approximately 10.2% per year). Pappone et al (2003) found a lower recurrence of 3.6% per year, based on the difference in 'AF free' patients at Year 1 and Year 3 post-procedure. Given the variation reported here (range 3.6% to 10.2% per year), the value reported by Tzou and colleagues was chosen for the base model (i.e. 7% per annum recurrence beyond twelve months). This was assumed to continue from 12 months for the entirety of the model.

Two RCTs (Singh et al, 2005; Roy et al, 2000) that focused on amiodarone for the treatment of AF were chosen to estimate the probability of recurrence for the medical therapy group beyond 12 months. Pappone et al (2003) also assessed AF recurrence in patients receiving medical therapy, but the study was observational in nature and included drugs other than amiodarone. Using data from onwards of 12 months only, the average annual decline was 22% (to 1,000 days) in Singh et al (2005) and 24% (to 600 days) in Roy et al (2000). Thus, the mean of these estimates was used to inform the base model, allowing for 23% per annum recurrence beyond 12 months.

[4] Preliminary findings from the CABANA trial are available at Cabana trial. Accessed 11 October 2018.

Changes in cardiac hospitalisation probabilities over time

Similar to the recurrence probabilities, the probability of cardiac hospitalisation over a twelve-month period has been taken from a recent systematic review and meta-analysis of 3 RCTs by Khan et al (2018). Consistent with the previous model (described in Report Part 2), these probabilities were used for the first twelve months of the model. However, the application of these probabilities beyond twelve months was considered potentially problematic. The CABANA trial authors reported data for all-cause mortality alongside data for a combined outcome of death or cardiovascular hospitalisation[5]. From these preliminary data, the probability of cardiovascular hospitalisation over the 48 months of follow-up could be calculated using an 'as treated' or an ITT approach. Because of the high crossover discussed above, the 'as treated' analysis was considered more appropriate. The proportion of cardiac hospitalisations over 48 months was assumed to be distributed evenly over the 4 years (48 months of follow-up). This annual probability was applied between 12 and 48 months. In lieu of available data, the probability of cardiac hospitalisation beyond 48 months was assumed to be similar between study arms (the mean between the two arms was applied). While there are issues with applying the CABANA data, detailed above, this solution was considered superior to simply applying the same meta-analysed data used in the original analysis beyond 12 months.

Table 3 Probabilities used in economic model

Probability	Estimate	Source/rationale
Cardiac ablation probabilities		
Probability that CA procedure will be unsuccessful (no freedom from AF)	0	Australian observational study (Voskoboinik et al, 2018) reported acute procedural success rate was 98.7%. While this refers to successful isolation of all four pulmonary veins (entry & exit block) rather than success in terms of impact on AF, this has been taken in the model as indicative of 'immediate' treatment success.
Proportion of ablation procedures with major or serious complications	0.01	Major or serious complication rate of ~1% or 2% is widely acknowledged and includes events such as cardiac tamponade, cardiac perforation, major vascular complication/ bleeding, oesophageal haematoma, etc. Australian observational study (Voskoboinik et al, 2018) reported that major or serious complications occurred in 0.84% of patients. Assume patients experiencing serious complications have an extended hospital LOS (additional 6.02 days) based on AR-DRG F16A&B. Applies to initial ablation and repeat ablation.
Recurrence		
Annual probability of arrhythmia recurrence within 12 months	0.249	Based on 12-month FU from 8 RCTs in Khan et al (2018) SR
Annual probability of arrhythmia recurrence 12 months and beyond (or 24 months and beyond for those undergoing a repeat ablation)	0.070	Observational study by Tzou et al (2010)
Cardiac hospitalisation		
Annual probability of cardiac hospitalisation within 12 months	0.181	Based on 12-month FU from 3 RCTs in Khan et al (2018) SR
Annual probability of cardiac hospitalisation 12-48 months	0.092	CABANA data to 48 months, unpublished, assuming even distribution of hospitalisation each year
Annual probability of cardiac hospitalisation 48 months and beyond	0.130	Based on CABANA data, mean of ablation and medical therapy arm
Proportion of downstream cardiac hospitalisations that are of major complexity	0.05	Assumption. 5% of hospitalisations may be serious. The Khan et al (2018) SR and the individual RCTs did not provide details of the reasons for cardiac hospitalisations

[5] Preliminary findings available at Cabana trial. Accessed 11 October 2018.

Probability	Estimate	Source/rationale
Repeat ablation		
Annual probability of repeat ablation within 12 months	0.2	Based on data from Medicare Australia. Re-ablation rate of 20-30% within 12 months is stated in the NHFA/CSANZ 2018 guidelines for the diagnosis and management of AF. Re-ablation rates ranged from 0-53.8% in 8 RCTs with FU 6-12 months (AHRQ 2015).
Probability of second repeat re-ablation	0	Based on data from Medicare Australia
Medical therapy probabilities		
Recurrence		
Annual probability of arrhythmia recurrence within 12 months	0.7216	Based on 12-month FU from 8 RCTs in Khan et al (2018) SR
Probability of arrhythmia recurrence 12 months and beyond	0.230	RCTs by Singh et al (2005) and Roy et al (2000). Maximum reported FU 2.73 years (Singh et al, 2005)
Cardiac hospitalisation		
Annual probability of cardiac hospitalisation within 12 months	0.580	12-month FU from 3 RCTs in Khan et al (2018) SR
Annual probability of cardiac hospitalisation 12-48 months	0.169	CABANA data to 48 months, unpublished, assuming even distribution of hospitalisation each year
Annual probability of cardiac hospitalisation 48 months and beyond	0.130	Based on CABANA data, mean of ablation and medical therapy arm
Proportion of cardiac hospitalisations that are of major complexity	0.05	Assumption

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; AR-DRG, Australian Refined – Diagnosis Related Group; CA, cardiac ablation; CSANZ, Cardiac Society of Australia and New Zealand; FU, follow up; LOS, length of stay; NHFA, National Heart Foundation of Australia; RCT, randomised controlled trial; SR, systematic review.

2.2.2 Utility weights

MSAC did not dispute the utility weights applied to the previous model. As such, the same utility weights have been applied to the extended model, with one exception. For consistency with the approach used by CADTH (Assasi et al, 2010), a total decrement of 1.0 is applied for 7 days to patients who experience major or serious complications from the ablation (or re-ablation) procedure. This same 7-day decrement is applied to patients experiencing a major cardiac hospitalisation. For the remainder of the cycle, a 'with AF' utility decrement is applied.

Patients 'without AF' are assumed to have a mean utility weight of 0.737, which reflects the Australian population norm for people aged 61 to 70 years old. A utility decrement of 0.046 is applied to patients 'with AF', and to patients experiencing minor cardiac hospitalisation.

Table 4 Utility weights used in the economic model

Utility weights	Estimate	Source/rationale
Person with no AF	0.737	Norm mean utility for Australians aged 61-70 years (Norman et al, 2013)
Decrease in utility associated with AF	0.046	Taken from CADTH (Assasi et al, 2010), based on transformed SF-36 responses from the FRACTAL trial (Reynolds et al, 2009). Average change in utility among patients with no documented recurrences of AF over 12 months was 0.046. CADTH claimed this value to best represent the change in utility moving from an AF to a normal sinus rhythm health state (other studies evaluated intervention-specific changes in utility values). Implicitly takes into account AF symptom severity
Person with AF, minor hospitalisation or during first month post-ablation or starting medical therapy	0.691	Calculated

Utility weights	Estimate	Source/rationale
Decrease in utility associated with ablation complications (extended to include major hospitalisation)	1.0	Taken from CADTH (Assasi et al, 2010).
Utility weight for person with a major or serious complication related to the ablation procedure	-0.263	Calculated. It is noted that this utility decrement represents a 'state worse than death' and is applied for 7 days only. For the remainder of the month people in these categories were assumed to have a utility of someone with AF.

Abbreviations: AF, atrial fibrillation; CADTH, Canadian Agency for Drugs and Technologies in Health; SF-36, 36-item Short Form Survey.

2.2.3 Other key assumptions

Other assumptions used in the economic model are shown in Table 5. Several of these assumptions were applied pragmatically in keeping with this 'focused' economic analysis.

Of note, the model assumes no transition in the first month; people in the ablation arm are assumed to be alive and recovering from the procedure. As such, the first cycle (cycle 0) in the model contributes both QALYs and costs to the model. Similarly, for medical therapy, it is assumed that onset of response is not immediate; people remain in the 'AF' state for the first month while the dosing of amiodarone is adjusted. QALYs and costs are thus also assigned in this first month for the medical therapy arm.

Table 5 Other key assumptions used in the economic model

Assumption	Source/rationale
Cardiac ablation arm	
Patients undergoing the CA procedure do not experience improved HRQoL until 1 month after the procedure	Model assumes HRQoL decrement in the first month (while patients are recovering from the procedure) is similar to that of patients with AF. Based on RMH Patient Information stating that ".. it is not uncommon to experience abnormal or irregular heartbeat or rhythm for up to 4 weeks after the procedure. Rarely, AF may be worse for a few weeks after the procedure due to inflammation where the ablation was performed."[6]
Patients with arrhythmia recurrence cannot transition directly to an 'AF free' state	Simplifying assumption. Patients with arrhythmia recurrence are assumed to require an intervention to restore normal sinus rhythm. The probability of a hospitalised individual becoming 'AF free' is the complement of that sum of monthly probabilities for having AF recurrence, dying from any cause, receiving a re-ablation procedure (in the first twelve months) or remaining in hospital for the next cycle.
Repeat ablation is distributed evenly over the first 12 months of the model	Simplifying assumption in lieu of reliable data on time to repeat ablation in this population. Patients are assumed to have a second ablation procedure within the first year only.
Patients who undergo repeat ablation can only transition to an 'AF-free' health state	Re-ablated patients must pass into the 'AF free after re-ablation' state before moving to any other health state in the model. The assumption is that the CA procedure is never unsuccessful (i.e. normal sinus rhythm is restored in all patients, at least for 1 model cycle). This same assumption applies to initial ablation. Note that the risk of complications applies to both initial and repeat ablation.
Patients take an OAC for 3 months immediately before and after the procedure (initial and re-ablation)	According to the literature, if not already taking an oral anticoagulant, patients may start treatment 6 weeks before ablation. Some patients may continue taking an oral anticoagulant indefinitely depending on risk of stroke (using $CHADS_2$ score). The model assumes all patients receive warfarin for a 3-month period after ablation or re-ablation (i.e. those receiving two ablation procedures would take warfarin for >3 months in total). This is consistent with CADTH (Assasi et al, 2010). Drug costs and INR monitoring costs are incorporated.
Patients in the CA arm do not continue AADs or commence AADs	In practice, a proportion of patients may receive AADs but no reliable Australian data are available to support this.

[6] Available at Melbourneheartrhythm. Accessed 07 November 2018.

Assumption	Source/rationale
Medical therapy arm	
All patients (who could otherwise be considered for CA) receive maintenance treatment with amiodarone after failing a Class I or another III AAD (flecainide or sotalol)	Simplifying assumption, based on NHFA/CSANZ 2018 guidelines for the diagnosis and management of AF (Appendix B). Compared with amiodarone, flecainide results in earlier and more effective conversion to sinus rhythm. Amiodarone can be considered for maintenance of sinus rhythm as a second-line agent, or as a first-line agent in patients with LV systolic dysfunction, moderate LV hypertrophy or CAD [*Strong recommendation*]. The dose regimen of amiodarone used in the model is based on the Australian PI.
Patients take an OAC continuously with an AAD	Assumption. Monthly drug costs, INR monitoring costs, and occasional GP visits are incorporated.
Improvement in HRQoL is not immediate on commencement of treatment	Assumes that MT is not immediately effective in controlling AF. This assumption may underestimate the HRQoL benefit of MT.
There is no HRQoL decrement associated with MT	This assumption may overestimate the HRQoL benefit of MT. In reality, patients may experience treatment-related side effects from amiodarone and warfarin that impact on HRQoL.
Patients with arrhythmia recurrence cannot transition directly to an 'AF free' state	Simplifying assumption. Patients with arrhythmia recurrence are assumed to require an intervention (hospitalisation) to restore normal sinus rhythm. The probability of an individual hospitalised becoming 'AF free' is the complement of that sum of monthly probabilities for having AF recurrence, dying from any cause, or remaining in hospital for the next cycle.
Patients with arrhythmia recurrence continue amiodarone at the same dose	Assumption. Amiodarone has rate and rhythm control properties. Limited pharmaceutical options are available for patients who convert to persistent (chronic) AF. It is possible that patients remain on treatment because it reduces the frequency of AF attacks (although this was not an outcome captured in the clinical data).

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; CA, cardiac ablation; CAD, coronary artery disease; CSANZ, Cardiac Society of Australia and New Zealand; GP, general practitioner; HRQoL, health-related quality of life; INR, international normalised ratio; LV, left ventricular; MT, medical therapy; NHFA, National Heart Foundation of Australia; OAC, oral anticoagulant; PI, Product Information; RMH, Royal Melbourne Hospital; SF-36, 36-item Short Form Survey.

2.2.4 Costs

With the exception of device costs, the costs applied to the extended model are identical to those applied to the previous model considered by MSAC. The cost of ablation is comprised of costs related to preparation for ablation (lead-up consultation and tests), peri-procedural costs (fees for services rendered for imaging, mapping, ablation, anaesthetics, as well as device costs), plus costs relating to theatre use and overnight hospital stay. The cost of re-ablation is assumed to be the same as for initial ablation. It is assumed that low cost consumables associated with the ablation procedure (e.g. cables, sheaths, needles, etc.) are covered by theatre banding fees.

As requested by the Department, the extended analysis applies bundled prices (in $1,000 increments) for all cardiac catheters (ablation and mapping) required for an ablation procedure.

Consistent with the previous analysis, costs associated with major or severe procedural complications have been captured in the model as additional theatre, accommodation and coronary care costs, using the relevant Australian-Refined Diagnostic Related Group (AR-DRG) with complications (AR-DRG F16A).

The cost of medical therapy is based on the Pharmaceutical Benefits Scheme (PBS) price for amiodarone and the Australian Product Information (PI), which provides details of the dose regimen for initiation and maintenance therapy. Alive patients in the medical therapy arm were assumed to continue taking amiodarone (which has rate and rhythm control properties), together with warfarin, for the duration of the model.

Standard follow up visits and tests were assumed for the cardiac ablation and medical therapy arms as per current clinical practice. Follow up costs also included cardiac hospitalisations.

Table 6 Costs used in the economic model for the cardiac ablation arm

Cost component	Source of unit cost	Rationale/justification	Units	Unit cost ($)[a]	Total ($)[a]
Lead up costs (initial and repeat)					
Cardiology consultation	MBS item 104	Patients visit the cardiologist on the day before the procedure.	1	73.85	73.85
Blood test (INR)	MBS item 65120	A blood test is required before the procedure to establish that patients have therapeutic INR levels.	1	11.65	11.65
12-lead ECG	MBS item 11700	Day before procedure	1	26.60	26.60
Cardiac CT	MBS item 56301	Patients are assumed to have a diagnostic contrast chest CT	1	250.75	250.75
Peri-procedural costs (initial and repeat)					
Pre-anaesthesia consultation	MBS item 17610	Assumes brief consultation with anaesthetist	1	32.75	32.75
Anaesthesia initiation	MBS item 20410	Initiation of management of anaesthesia for electrical conversion of arrhythmias	1	74.25	74.25
Anaesthetist attendance	MBS item 23121	3:51 to 4:00 hours, based on patient information stating that the procedure takes up to 4 hours	1	297.00	297.00
Trans-oesophageal echocardiogram	MBS item 22051	Intra-operative transoesophageal echocardiography to monitor structure and function of the heart chambers, valves and surrounding structures in real time	1	133.65	133.65
Electrophysiology study (mapping) service	MBS item 38212	Intraoperative mapping for RF ablation or cryoablation	1	514.65[b]	514.65[b]
Cardiac ablation service	MBS item 38290[c]	Ablation of arrhythmia circuits or foci, or isolation procedure involving both atrial chambers and including curative procedures for atrial fibrillation	1	2,004.00	2,004.00
Mapping and ablation catheters (bundled price)	Request from Department of Health	To explore the impact of the device cost on the ICER, the model tests a range of 'bundled prices' per ablation procedure.	1	1,000 – 8,000	1,000 – 8,000
Physician assistant	MBS item 51303	Assistance during operation	1	534.40[d]	534.40[d]
Hospitalisation for ablation procedure – no complications	AR-DRG F16B	Accommodation and theatre costs for 'Interventional coronary procs, not adm for AMI, W/O stent implant, minor complications'. Length of stay (according to AR-DRG) is 1.69 days.	0.99 (per Table 3)	3,457.00	3,422.43
Hospitalisation for ablation procedure – with complications	AR-DRG F16A	Accommodation, theatre and coronary care costs for 'Interventional coronary procs, not adm for AMI, W/O stent implant, major complications'. Length of stay (according to AR-DRG) is 7.71 days.	0.01 (per Table 3)	7,315.00	73.15

Cost component	Source of unit cost	Rationale/justification	Units	Unit cost ($)[a]	Total ($)[a]
Follow up costs (all applied within first three-months post ablation/re-ablation)					
Warfarin	PBS code 2211J	Assume all patients receive an OAC for a 3-month period. According to the Australian PI, most patients are satisfactorily maintained at a dose of 2 to 10 mg daily (assume 5 mg/day). General patient charge $22.39, Max. Qty 50 units, 2 repeats.	2	22.39	44.78
INR test	MBS item 65120	Monthly warfarin monitoring.	3	11.65	34.95
GP visits	MBS item 23	GP consultation lasting less than 20 minutes for warfarin monitoring	1	37.60	37.60
Cardiology consultation	MBS item 105	Scheduled visit to cardiologist during follow up (subsequent)	3	37.15	111.45
ECG	MBS item 11700	Twelve-lead ECG, tracing and report during consultation	3	26.60	79.80
Hospitalisation costs					
Cardiac hospitalisation (minor complexity)	AR-DRG F76B	Use total cost of hospitalisation for 'arrhythmia, cardiac arrest and conduction disorders', with average length of stay 1.67 days	As per Table 3	1,834.00	-
Cardiac hospitalisation (major complexity)	AR-DRG F76A	Use total cost of hospitalisation for 'arrhythmia, cardiac arrest and conduction disorders, with average length of stay 6.4 days	As per Table 3	5,481.00	-
Post-hospitalisation cardiology consultation	MBS item 104	Visit to cardiologists after cardiac-related hospitalisation. Assumed to be a new episode of care.	As per Table 3	73.85	-
Post-hospitalisation ECG	MBS item 11700	Twelve-lead ECG, tracing and report during cardiology consultation	As per Table 3	26.60	-

Abbreviations: AMI, acute myocardial infarction; AR-DRG, Australian-Refined Diagnosis Related Groups; CT, computed tomography; ECG, electrocardiography; GP, general practitioner; INR, international normalised ratio; MBS, Medical Benefits Schedule; OAC, oral anticoagulant; PBS, Pharmaceutical Benefits Scheme; PI, Product Information; PLAC, Prostheses List Advisory Committee; RF, radiofrequency ablation; W/O, without.
a The unit cost for MBS items refers to the appropriate benefit rather than the Schedule Fee.
b This item has been discounted because the Multiple Operation Rule applies.
c For simplicity, it is assumed that all catheter ablation procedures use the MBS item that is specific for AF ablation in two atrial chambers.
d Calculated as one-fifth of the highest cost procedure.

Table 7 Costs used in the economic model for the medical therapy arm

Cost component	Source of unit cost	Description	Units	Unit cost ($)[a]	Total ($)
Lead up costs (once-off)					
Cardiology consultation	MBS item 104	Patients visit the cardiologist to initiate treatment with amiodarone. According to the Australian PI, treatment should be initiated in hospital.	1	73.85	73.85
ECG	MBS item 11700	Recommended before starting treatment according to Australian PI.	1	26.60	26.60
Serum potassium and liver function tests	MBS item 66509	Recommended before starting treatment according to Australian PI.	1	13.35	13.35
Thyroid function test	MBS item 66716	TSH quantification, recommended before starting treatment according to Australian PI.	1	21.30	21.30

Cost component	Source of unit cost	Description	Units	Unit cost ($)[a]	Total ($)
Medical therapy (each year)					
Amiodarone, 200 mg tablet	PBS code 2343H	Assume all patients continue amiodarone for the duration of MT, according to the Australian PI, treatment should be started with 200 mg three times daily and may be continued for one week. The dosage should then be reduced to 200 mg twice daily for a further week. After the initial period the dosage should be reduced to 200mg daily, or less if appropriate. Rarely, the patient may require a higher maintenance dose. General patient charge $24.75, Max Qty 30 units, 5 repeats	13[7]	24.75	321.75
Warfarin, 5 mg tablet	PBS code 2211J	Assume all patients initiated an oral anticoagulant before starting amiodarone and will continue for the duration of medical therapy. According to the Australian PI, most patients are satisfactorily maintained at a warfarin dose of 2 to 10 mg daily (assume 5 mg/day). General patient charge $22.39, Max. Qty 50 units, 2 repeats.	8	22.39	179.12
Follow up/monitoring (each year)					
GP visit	MBS item 23	GP visit lasting less than 20 minutes for monitoring.	4	37.60	150.40
INR test	MBS item 65120	Monthly warfarin monitoring.	12	11.65	139.80
Thyroid function test	MBS item 66716	Regular TSH quantification during treatment with amiodarone, as per Australian PI.	4	21.30	85.20
Hepatic liver function	MBS item 66509	Regular monitoring of liver function during treatment with amiodarone, as per Australian PI.	4	13.35	53.40
ECG	MBS item 11700	According to the Australian PI, regular ECG monitoring is recommended in patients on long-term therapy with amiodarone.	4	26.60	106.40
Ophthalmology test	MBS item 10911	Australian PI for amiodarone recommends regular ophthalmological monitoring (e.g. slit lamp biomicroscopy, visual acuity, ophthalmoscopy) because corneal deposits develop in almost all patients. Assume comprehensive consultation for more than 15 minutes in patients at least 65 years of age.	1	56.80	56.80
Chest X-ray	MBS item 58500	Australian PI for amiodarone recommends that regular chest X-ray should be performed routinely in patients undergoing long-term therapy.	1	30.05	30.05
Hospitalisation costs					
Cardiac hospitalisation (minor complexity)	AR-DRG F76B	Use total cost of hospitalisation for 'arrhythmia, cardiac arrest and conduction disorders', with average length of stay 1.67 days	As per Table 3	1,834.00	-

[7] 13 for Year 1 only to allow for amiodarone loading, reduced to 12 (1 box per month) for subsequent years.

Cost component	Source of unit cost	Description	Units	Unit cost ($)[a]	Total ($)
Cardiac hospitalisation (major complexity)	AR-DRG F76A	Use total cost of hospitalisation for 'arrhythmia, cardiac arrest and conduction disorders, with average length of stay 6.4 days	As per Table 3	5,481.00	-
Post-hospitalisation cardiology consultation	MBS item 104	Visit to cardiologists after cardiac-related hospitalisation. Assumed to be a new episode of care.	As per Table 3	73.85	-
Post-hospitalisation ECG	MBS item 11700	Twelve-lead ECG, tracing and report during cardiology consultation	As per Table 3	26.60	-

Abbreviations: AR-DRG, Australian-Refined Diagnosis Related Groups; CT, computed tomography; ECG, electrocardiography; GP, general practitioner; INR, international normalised ratio; MBS, Medical Benefits Schedule; MT, medical therapy; PBS, Pharmaceutical Benefits Scheme; PI, Product Information; PLAC, Prostheses List Advisory Committee; RF, radiofrequency ablation; TSH, thyroid stimulating hormone.

3 Results of the extended economic analysis

3.1 INDICATIVE COST-EFFECTIVENESS

Indicative total and incremental costs and QALYs per patient are shown in Table 8, together with an estimation of the incremental cost-effectiveness for cardiac catheter ablation compared with medical therapy. Cardiac ablation has a much higher up-front cost compared with medical therapy (which is relatively inexpensive). A higher rate of arrhythmia recurrence and cardiac hospitalisation results in lower total QALYs in the medical therapy arm.

As expected, the extended time horizons capture longer-term benefits of freedom from AF (in terms of health-related quality of life) and this improves the incremental cost-effectiveness of cardiac catheter ablation relative to medical therapy. Over a 10-year time horizon, the cost-effectiveness of cardiac ablation is likely to be below a threshold of $50,000 per QALY at a bundle price of approximately **$6,500**.

The limitations of the current analysis (refer to Section 3.3) should be taken into consideration when interpreting these findings.

Table 8 Indicative cost-effectiveness

Bundled price per ablation[a]	Cost per patient			QALYs per patient			Cost per additional QALY
	Cardiac ablation arm	Medical therapy arm	Incremental value	Cardiac ablation arm	Medical therapy arm	Incremental value	
5-year time horizon							
$1,000	$11,503.05	$7,934.81	$3,568.24	3.24	3.17	0.08	**$46,684**
$2,000	$12,687.37	$7,934.81	$4,752.56	3.24	3.17	0.08	**$62,179**
$3,000	$13,871.69	$7,934.81	$5,936.88	3.24	3.17	0.08	**$77,674**
$4,000	$15,056.01	$7,934.81	$7,121.20	3.24	3.17	0.08	**$93,169**
$5,000	$16,240.33	$7,934.81	$8,305.52	3.24	3.17	0.08	**$108,664**
$6,000	$17,424.65	$7,934.81	$9,489.84	3.24	3.17	0.08	**$124,159**
$7,000	$18,608.97	$7,934.81	$10,674.16	3.24	3.17	0.08	**$139,653**
$8,000	$19,793.29	$7,934.81	$11,858.48	3.24	3.17	0.08	**$155,148**
10-year time horizon							
$1,000	$12,450.57	$12,581.77	-$131.20	5.66	5.53	0.13	**-$1,018**
$2,000	$13,634.89	$12,581.77	$1,053.12	5.66	5.53	0.13	**$8,174**
$3,000	$14,819.21	$12,581.77	$2,237.44	5.66	5.53	0.13	**$17,366**
$4,000	$16,003.53	$12,581.77	$3,421.76	5.66	5.53	0.13	**$26,557**
$5,000	$17,187.85	$12,581.77	$4,606.08	5.66	5.53	0.13	**$35,749**
$6,000	$18,372.17	$12,581.77	$5,790.40	5.66	5.53	0.13	**$44,941**
$7,000	$19,556.49	$12,581.77	$6,974.72	5.66	5.53	0.13	**$54,133**
$8,000	$20,740.81	$12,581.77	$8,159.04	5.66	5.53	0.13	**$63,325**

Abbreviations: QALY, quality-adjusted life year.

a The 'bundled price' includes all ablation and mapping catheters required for an ablation procedure. The price applies to any type of catheter (radiofrequency or cryoablation).

3.2 SENSITIVITY ANALYSES

Selected one-way sensitivity analyses were undertaken to test the main area of uncertainty, namely extrapolation of treatment effect to 10 years. The results of these analyses are shown in Table 9.

Table 9 Sensitivity analysis at a bundled price of $6,000

Parameter	Base case assumption	Sensitivity assumption	Cost per additional QALY (10-year time horizon)
Base case			***$44,941***
Ablation arm			
Annual recurrence probabilities beyond 12 months as estimated from the Pappone et al (2003) study (lower limit)	7% annual recurrence for 12 months and beyond	3.6% annual recurrence for 12 months and beyond	$38,076
Annual recurrence probabilities beyond 12 months as estimated from the Wokhlu et al (2010) study (upper limit)	7% annual recurrence for 12 months and beyond	0.9% monthly recurrence (~10.2% annually) for 12 months and beyond	$52,935
Annual recurrence probabilities beyond 12 months as estimated from the preliminary CABANA results	7% annual recurrence for 12 months and beyond	Recurrence probabilities for 12 months and beyond as in the ITT analysis between 12 months and 48 months for first AF recurrence (7.5% annual recurrence for ablation)	$46,081
Medical therapy arm			
Annual recurrence probabilities beyond 12 months as estimated from the preliminary CABANA results	23% annual recurrence for 12 months and beyond	Recurrence probabilities for 12 months and beyond as in the ITT analysis between 12 months and 48 months for first AF recurrence (8.3% annual recurrence for medical therapy)	$76,878
Both arms			
Annual recurrence probabilities beyond 12 months as estimated from the preliminary CABANA results	Difference assumed as in Table 3	Recurrence probabilities for 12 months and beyond as in the ITT analysis between 12 months and 48 months for first AF recurrence (8.3% annual recurrence for medical therapy versus ~7.5% for ablation)	$80,289
Annual recurrence probabilities beyond 12 months	Difference assumed as indicated in Table 3	No difference beyond 12 months (mean of values beyond 12 months i.e. 0.15 annual probability)	$100,227
Annual hospitalisation probabilities beyond 48 months	Assumed no difference between arms	Probabilities between 12 and 48 months for both arms, as indicated in Table 3, continue	$42,596
Adding a half-cycle correction	No half-cycle correction	Half-cycle correction as applied in the previous model (to QALYs only, not to costs due to upfront nature of ablation costs)	$45,306
Removing assumption of re-ablation population as a subset of the recurrent population	Re-ablation population considered a subset of the recurrent population	Considered to be mutually exclusive with application of non-conditional probabilities	$55,860

Abbreviations: AF, atrial fibrillation; ITT, intention-to-treat; QALY, quality-adjusted life year.

3.3 LIMITATIONS

The extended economic analysis overcomes the major criticism of the previous analysis considered by MSAC, namely the short time horizon of 12 months. However, a number of other important shortcomings remain that limit the interpretation and reliability of results. Although the modelled time horizon has been extended to 10 years, it is important to note that there is no clinical evidence to support the assumptions relating to maintenance of treatment effect over this time period. Furthermore, the model does not take into account inevitable crossover to alternative treatment, which is common in clinical practice. In the CABANA trial, where crossover was permitted, at a median follow up of approximately four years, 9.2% of patients crossed over from ablation to medical therapy and 27.5% crossed over from medical therapy to ablation.

The probabilities applied to the model were derived from a published systematic review or from observational studies where necessary, rather than an individual study and refer to the entire population in each arm (i.e. the probabilities are not conditional, excepting recurrence which is considered a subset of those undergoing repeat ablation). The impact of this limitation is that some of the transitions permitted between health states in the model are not entirely logical, despite being possible. For example, patients can transition within one model cycle between 'AF free' and 're-ablation'. The cardiac hospitalisation and AF recurrence health states are assumed mutually exclusive in the model, while in reality there would be some overlap (e.g. the probabilities of recurrence and hospitalisation in the medical therapy arm if applied in yearly cycling would exceed 1).

Consistent with the previous analysis, another limitation of the model is the very simple application of utility weights. Although the utility weights used in the model have been applied in other economic models of treatment for AF, a full literature search and critical appraisal was not conducted to determine the validity of these values.

The full HRQoL benefit of cardiac ablation may be underestimated in the model because ablation may reduce the frequency of AF attacks, which is likely to have a positive effect on patient HRQoL. This is not captured in clinical trials, where freedom from AF is the ultimate measure of treatment success. It can therefore be argued that the utility decrement associated with AF should be smaller in patients who undergo ablation compared with patients on medical therapy. However, the same argument may also apply to medical therapy, given that some patients continue taking AADs despite incomplete resolution of AF symptoms.

The model does not capture out-of-pocket costs for patients who may also incur additional charges from the cardiologist and anaesthetist. In some circumstances, patients may be fitted with an implanted loop recorder during the ablation procedure, which is not covered under the MBS for this indication.

Continuous OAC is assumed in the medical therapy arm of the model but only for a 3-month period in the ablation arm. In practice, however, some patients in the ablation arms may recommence OAC on recurrence or may take OAC continuously (depending on $CHADS_2$ score). In both arms, the cost and HRQoL consequences of risks associated with anticoagulation are not explicitly modelled, although these risks may be captured to some extent through downstream cardiac hospitalisations (which are not assumed to be solely dependent on AF recurrence).

Likewise, the model does not capture the cost and HRQoL consequences of adverse events associated with long-term AAD therapy. However, the impact of this omission may not be consequential given that there are real-world data available to indicate that a large proportion of patients who undergo cardiac ablation still take AADs after the intervention (Van Brabandt et al 2012).

Only AF recurrences resulting in cardiac hospitalisation incurred additional cost in the model, likely leading to an underestimate of the cost of medical therapy, since many of those patients would likely seek outpatient care and hence would incur additional costs.

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APPENDIX A LITERATURE SEARCH STRATEGY

Table App 1 Databases and search strings

Database	Search date	Search string	Records screened
EMBASE.com (concurrently searches Medline and EMBASE)	17 Jan 2019	'cabana':ti,ab,kw,de OR 'catheter ablation versus anti*arrhythmic drug therapy for atrial fibrillation':ti,ab,kw,de Filters: ([conference abstract]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [book]/lim OR ([animals]/lim NOT [humans]/lim)) AND [english]/lim AND [2018-2019]/py	4