MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
2 June 2021

Agenda Item No	2.2
National Programme	Internal Medicine
Clinical Reference Group	Cardiac
URN	1903

Title
Catheter ablation for paroxysmal and persistent atrial fibrillation (adults)

Actions Requested	• Support the adoption the policy proposition
	• Recommend its approval as an IYSD

Proposition
For routine commissioning: This is a new policy proposition for an existing service which uses catheter ablation as the means to treat symptomatic atrial fibrillation. The aim of the policy is to ensure the current evidence base is used to inform clinical decision making and reduce repeat ablations where this will not benefit patients. The approach also mandates patients are involved in shared decision making so that patients are fully aware of the treatment options including risks and benefits and that patient related outcome measures are collected to inform future review of the policy. The policy standardises the number of repeat procedures being undertaken which in turn will free up capacity for the anticipated 5% annual growth in new patients. Overall, the total number of procedures undertaken is not expected to change, and hence the policy is approximately cost neutral.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.

2.	The Head of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary x 2
4.	Clinical Panel Report x 2
5.	Equality and Health Inequalities Impact Assessment

No	*Metric*	*Summary from evidence review*
1.	Survival	**Benefit of CA vs medical therapy (MT) for persistent AF** All-cause mortality included all causes of mortality whether or not it was felt to be due to AF or complications of AF treatment. Chen et al (2018) reported all-cause mortality between patient receiving CA treatment and those receiving antiarrhythmic drugs (AADs) for rate control. Three randomised controlled trials (RCTs) (n=559) contributed to the analysis of all-cause mortality. Reduction in all-cause mortality was not significantly different between the two groups (risk ratio (RR) 0.47, [95% CI 0.22 to 1.02]; p=0.05).The meta-analysis suggests that there is no difference in all-cause mortality between CA and medical therapy. This result should be interpreted with caution because of the short-term follow-up in the studies included in the systematic review (median six to 24 months). The method excluded zero total event trials assuming that they make no contribution to the magnitude of the treatment effect. Some experts insist that inclusion of zero total event trials would enable the inclusion of all available RCT data in a meta-analysis, thereby providing the most generalisable estimate of treatment effect. However, the authors also calculated the results using risk difference (RD) as the effect measure and found the result was robust (RD −0.02, [95%CI −0.09 to 0.05]; p=0.55).
		Benefit of CA vs surgical ablation (SA) for persistent AF Not reported.

		Benefit of CA vs MT for paroxysmal AF Not reported.
		Benefit of CA vs SA for paroxysmal AF Not reported.
2.	Progression free survival	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF Not reported.
		Benefit of CA vs SA for paroxysmal AF Not reported.
3.	Mobility	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF Not reported.
		Benefit of CA vs SA for paroxysmal AF Not reported.
4.	Self-care	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF Not reported.
		Benefit of CA vs SA for paroxysmal AF Not reported.
5.	Usual activities	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF Not reported.
		Benefit of CA vs SA for paroxysmal AF Not reported.
6.	Pain	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.

		Benefit of CA vs MT for paroxysmal AF Not reported.
		Benefit of CA vs SA for paroxysmal AF Not reported.
7.	Anxiety / Depression	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF Not reported.
		Benefit of CA vs SA for paroxysmal AF Not reported.
8.	Replacement of more toxic treatment	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF Not reported.
		Benefit of CA vs SA for paroxysmal AF Not reported.
9.	Dependency on care giver / supporting independence	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF Not reported.
		Benefit of CA vs SA for paroxysmal AF Not reported.
10.	Safety	**Benefit of CA vs MT for persistent AF** The most important severe complications related to CA procedure are stroke/transient cerebral ischaemia (TIA), bradycardia, cardiac tamponade, pulmonary vein stenosis, and atrio-oesophageal fistula. AADs adverse effects include thyroid toxicity, pulmonary toxicity, liver dysfunction, bradycardia, and a potential pro-arrhythmic[1] effect. Chen et al (2018) reported ablation or drug-related complication rates between patients receiving CA and medical rhythm control. Pooled results from four studies, reported by Chen et al (2018), showed no significant difference between the CA and medical rhythm control with AADs (RR 1.95, [95%CI 0.52 to 7.25];

[1] Proarrhythmia is a new or more frequent occurrence of pre-existing arrhythmias, this can be a side effect of antiarrhythmic therapy

		p=0.32). However, the studies were highly heterogeneous. Pooled results from another four studies reported no significant difference was between CA and medical rate control (RR 1.64, [95%CI 0.39 to 6.84]; p=0.50). The systematic review suggests that there is no difference in complication rates between CA and medical therapy. Stroke is one of the most severe, and potentially fatal, complications of CA and other procedures used in the treatment of AF. On the other hand, stroke and other thromboembolic events could also result from unsuccessful management of AF. It is important to patients that treatment of AF represents a favourable balance of successful treatment over complications. These results should be interpreted with caution because of the moderate to high heterogeneity found among studies comparing CA with rhythm control and which the authors suspected may be due to somewhat dissimilar patient populations, different ablation strategies, and extent of ablation.
		Benefit of CA vs SA for persistent AF Adverse events (AE) were not specifically defined by Berger et al (2019). However, the WHO defines an AE as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an intervention. Berger et al (2019) reported no difference between CA and surgical ablation procedures in terms of overall death and procedure-related death. Bleeding including cardiac tamponade and haemothorax were the most common adverse effects. Combined minor and major bleeding was remarkably more frequently reported with surgical ablation. CA (1.7%) versus SA (7.7%), but no p values were reported. Thromboembolic events were also higher with surgical ablation (1.4% vs 0.7%). Infection rates were 0.7% and 1.0% for CA and surgical ablation respectively. Taken together, irreversible adverse events occurred more frequently after minimally invasive surgery than after catheter ablation. The systematic review suggests that SA is associated with more adverse effects compared with CA, although there appears to be no difference in overall or procedure related deaths. These results should be interpreted with caution because in all the meta-analyses, the studies were considerably heterogeneous, which reduces the reliability of the result and any conclusive inferences about the clinical implications. The majority of the RCTs with treatment arms on minimally invasive surgical ablation were small and/or single-centre studies, whereas larger, more frequently multicentre RCTs were available on catheter ablation.

		Benefit of CA vs MT for paroxysmal AF Adverse events (AE) or complications were not specifically defined by Skelly et al (2015). However, the WHO defines this as any unfavourable and unintended outcomes temporarily associated with the use of an intervention. Skelly et al (2015) reported on other complications attributable to CA such as cardiac tamponade within 24 months (n=512) [pooled risk from four RCTs of 1.7% (95% CI 0.8 to 3.6)], pericardial effusion within 48 months (n=519) [pooled risk from three RCTs 0.6% (95% CI 0.2 to 1.8)], pulmonary vein stenosis at 12 months [pooled risk based on two studies (n=122) was 1.6% (95% CI 0.4 to 6.3) and pooled risk based on two studies (n=283) with 24-month follow-up was 0.7% (95% CI 0.2 to 2.8). Other ablation-related harms reported in the HTA included perforation at the trans-septal puncture (one RCT n=194, 0.5%), perimyocarditis (two RCTs n=333, 0% to 1.7%) and haematoma at catheter insertion site (2 RCTs n=276, 1.6% to 2.2%). There were no reports of atrio-oesophageal fistula, diaphragmatic paralysis, heart block and pneumothorax. The authors also reported drug intolerance requiring discontinuation based on one RCT (n=99) in 23.2% of patients in the MT arm and 0% in the CA arm.
		Benefit of CA vs SA for paroxysmal AF Major peri-procedural complications were defined as events within 30 days from the ablation procedure resulting in prolonged or repeat hospitalization, bleeding requiring transfusion or intervention, and long-term disability. Jan et al (2018) reported a trend of major peri-procedural complication rates higher in SA treated 3/24 patients (12.5%) versus 0/26 (0%) who underwent CA. No test of statistical significance was reported. The RCT suggests a higher incidence of major peri-operational complications associated with SA compared to CA however, it is uncertain whether this is significant. In general, minimally invasive surgical approaches to AF ablation carry a higher risk of peri-procedural complications compared to CA. The result of this study has shown a similar pattern. This result is limited in its generalisability because it is a small single-centre study and the statistical significance of the difference is not reported.
11.	Delivery of intervention	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF Not reported.

		Benefit of CA vs SA for paroxysmal AF Not reported.

No	Metric	Summary from evidence review
1.	Freedom from AF	**Benefit of CA vs MT for persistent AF** Freedom from AF was defined as freedom from atrial arrhythmia lasting at least 30 seconds at follow-up. Chen et al (2018) reported AF freedom rates based on results from 3 RCTs that enrolled 262 persistent AF patients. The pooled results found a significant improvement in freedom from AF with CA compared with medical therapy (rhythm control) (RR 2.08, [95%CI 1.67, 2.58]; p<0.00001). Pooled results from three RCTs with 338 patients who were completely off AADs at follow up (mean follow-up six to 24 months) also showed a significant benefit in favour of CA (RR 1.82, [95%CI 1.33, 2.49]; p=0.0002). The systematic review suggests that CA is better at improving freedom from AF than medical therapy. People with AF have higher risks of developing comorbidities such as heart failure (HF) and stroke as well as higher all-cause mortality rate. The goal of AF treatment is to establish sinus rhythm or achieve rhythm control. Many clinicians believe that achieving either of these goals may lead to a reduction in major cardiovascular events. Following CA, continuation of AADs treatment is sometimes required for some patients to maintain AF freedom. However, avoiding AADs where possible is considered a better outcome especially as it could obviate the ubiquitous undesirable side effects of these drugs. These results should be interpreted with caution because the number of RCTs included in the meta-analysis and the sample sizes of most studies were relatively small. There was moderate heterogeneity among the included studies for this outcome and different studies had a somewhat dissimilar patient population and different ablation strategies; therefore, the results may not be generalisable. The follow-up duration ranged from six to 24 months, which is not long enough to detect late AF recurrence.
		Benefit of CA vs SA for persistent AF AF freedom was defined as absence of any atrial arrhythmia (AF, atrial flutter and atrial tachycardia). Berger et al (2019) reported on the rate of AF freedom; at 12 months, after surgical ablation vs catheter ablation, based on two

		direct comparison RCTs involving 67 patients with persistent AF. These studies showed numerically but not statistically significantly higher AF freedom after surgical ablation compared to catheter ablation (OR 2.58, [95%CI 0.83 to 8.03], p value not reported). Patients were off AADs after the procedure. Berger et al (2019) also reported the results of indirect comparison between CA and SA with and without AADs. AF freedom was higher after minimally invasive SA than after CA. This effect was further enhanced when AADs use was permitted during follow-up. In 7,502 CA patients from 41 studies vs 339 SA patients from five studies, without AADs, 51% [95% CI 46 to 56%] of CA patients vs 69% [95% CI 64 to 74%] SA patients were free from AF at 12 months; p value was not reported. AF freedom rates on AADs were higher with both treatments. In 3133 CA patients (29 studies) versus 196 SA patients (3 studies) 58% [95% CI 54 to 63%] of CA patients vs 71% [95% CI 64 to 74%] SA patients were free from AF at 12 months; p value not reported. The systematic review suggests that there are no statistically significant differences in rates of AF freedom between surgical ablation patients and CA patients when compared directly. However, SA appears better at increasing the rate of AF freedom when indirect comparisons are made. Achieving freedom from AF is of importance to patients because it may reduce the need for cardioversion and cardiac-related hospitalisations. This will therefore be valuable to patients. These results should be interpreted with caution. The results from the direct comparisons are based on two small studies (67 patients), and the confidence interval is very wide. In all the meta-analyses, there were considerable heterogeneity, which reduces the reliability of the results and any conclusive inferences about the clinical implications. The majority of the RCTs with treatment arms on minimally invasive surgical ablation were small and/or single-centre studies, whereas larger, more frequently multicentre RCTs were available on catheter ablation. Potentially, the minimally invasive surgery studies reflect dedicated programs in specialised centres.
		Benefit of CA vs MT for paroxysmal AF AF burden was defined as the percentage of time in AF (AF episodes longer than 1 minute) according to 7 day Holter recording during follow up. At 5 years, significantly more patients in the radiofrequency ablation (RFA) group (CA) were free from any AF (n=126/146 (86%) versus 105/148 (71%), RR 0.82; 95% CI 0.73 to 0.93)

		p=0.001 and symptomatic AF (137/146 (94%) versus 126/148 (85%), RR 0.91; 95% CI 0.84 to 0.98) p=0.015. Burden of any AF at 5 years was significantly lower in the CA than in the AADs group. 85% and 95% percentiles for the CA group were 0%, 56% respectively versus 7%, 97% respectively for the AADs group; p=0.003. Corresponding percentiles for symptomatic AF were: 0%, 7% (CA) versus 0%, 11% (AADs), p=0.02. This study suggests that CA is more effective than AADs at reducing AF burden at 5-year follow-up. Freedom from symptomatic paroxysmal AF is of clinical value to patients in terms of reduced risk long-term complications of AF, e.g. stroke and heart failure (HF). AADs, which may be required due to AF recurrence, are often associated with side effects. Long-term AF freedom is also of economic benefit to the health system in terms of reduced requirement for repeat ablation or hospitalisation. These results should be interpreted with caution because of certain limitations to the conduct of the study. Although Holder analysis was blinded, treatments could not be blinded. There was significant loss to follow up although the majority of patients lost to follow-up were included in the analyses. Only AF episodes >1 minute were taken into account, not >30 seconds as currently recommended. AF freedom was based on a single 7-day Holter recording obtained 5 years after the start of the study. No data regarding the occurrence of burden of AF from 2- to 5-years' follow-up were recorded. It cannot be excluded that comparisons between groups would have been different using more intensive monitoring or another cut-off for AF episode length.
		Benefit of CA vs SA for paroxysmal AF Not reported.
2.	Freedom from recurrence of any arrhythmia	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF Freedom from recurrence was variably defined across trials, with some trials defining it based on the presence of symptoms and others defining it based on duration and frequency of recurrent

		episodes of arrhythmia (any including AF). The blanking period[2] ranged from 1 to 3 months. Pooled results from 4 RCTs in the health technology appraisal (HTA) by Skelly et al (2015) reported a significant difference in freedom of recurrence of AF between PAF patients treated with CA versus MT. At 12 months 226/286 (79%) of CA patients versus 64/245 (26.1%) of MT patients; risk ratio (RR) 3.06 (95% CI; 2.35 to 3.90) favours CA, $p<0.05$. There was equally a significant difference at 24 to 48 months (3 RCTs) 226/311 (72.6%) of CA patients versus 178/308 (57.8%) in the MT group. RR 1.24 (95% CI 1.11 to 1.47) favours CA, $p<0.05$. The systematic review suggests that CA is better at preventing any arrhythmia than MT. People with AF have higher risks of developing comorbidities such as heart failure and stroke as well as higher all-cause mortality rate. The goal of AF treatment is to establish sinus rhythm and/or achieve rhythm control. Many clinicians believe that achieving either of these goals may lead to a reduction in major cardiovascular events. Following CA, continuation of AADs treatment is sometimes required for some patients to maintain AF freedom. However, avoiding AADs where possible is considered a better outcome especially as it could obviate the ubiquitous undesirable side effects of these drugs. The results should be interpreted with caution because of the limitations of the data included and in the meta-analyses. There was substantial heterogeneity across included studies and a formal assessment of publication bias was not conducted. There was wide variability across studies (in the quality of reporting of study methods, in how outcomes were defined, and in which patients were included). Only one trial was considered to be good quality by the HTA authors; the remaining trials were all considered fair quality. Other important limitations of the evidence base include the small sample size of the available trials, discrepancies in baseline characteristics, unclear randomisation concealment and lack of assessor blinding. These factors make it difficult to draw strong conclusions regarding the effects and benefits of CA.
		Benefit of CA vs SA for paroxysmal AF Freedom from AF is normally defined as freedom from atrial arrhythmia lasting at least 30 seconds at follow-up. However recurrence was defined as any episode lasting 6 minutes or more.

[2] In the period immediately after AF ablation, early recurrences of atrial arrhythmias (ERAA) are common and may not necessarily imply long-term ablation failure. Therefore, guidelines recommended implementation of a “blanking period” post-ablation during which AF or OAT recurrences need not be counted against long-term ablation success.

		Jan et al (2018) reported a significant reduction in recurrence of AF/AT/AFL with surgical ablation (SA) compared with CA. At a mean follow-up of 30.5 months, recurrence was observed in 8/24 (33.4%) of SA versus 17/26 (65.4%) CA patients; odds ratio (OR) 3.78 (95% CI 1.17 to 12.19), p=0.048. The study suggests that SA is better at reducing recurrence of AF/AT/AFL compared with CA. People with AF have higher risks of developing comorbidities such as heart failure and stroke as well as higher all-cause mortality rate. The goal of AF treatment is to establish and maintain sinus rhythm and/or achieve rhythm control. Many clinicians believe that achieving either of these goals may lead to a reduction in major cardiovascular events. This result should be interpreted with caution because of limitations to the study. Firstly, the small number of patients included limits the strength of its findings. Secondly, all patients received an Implantable Loop Recorder (ILR); recurrence of AF/AT/AFL was defined as any episode lasting 6 minutes or more. This remarkably longer than the usual definition for AF recurrence. It is still not clear whether this threshold for recurrence represent significant reduction in the risk of AF complications, or what the impact of this level of reduced recurrence is on the patients' quality of life. Finally, only point-by-point method of CA was used, therefore the results may not be easily extrapolated to continuous cryoballoon technique of CA.
3.	Maintenance of sinus rhythm	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF Sinus rhythm maintenance, which refers to continuation of normal sinus rhythm without appearance of an arrhythmia such as AF, was mainly based on the last ECG recording. Bertaglia et al (2017) reported no significant difference in the long-term maintenance of sinus rhythm between PAF patients treated with CA versus AADs. At 12 years: CA n=22/42 (51.2%) versus AADs n= 22/50 (44%); p=0.402. The goal of AF treatment is to establish sinus rhythm and/or achieve rhythm control. Many clinicians believe that achieving either of these goals may lead to a reduction in major cardiovascular events.

		Following CA, continuation of AADs treatment is sometimes required for some patients to remain in sinus rhythm. However, avoiding AADs where possible is considered a better outcome especially as it could obviate the ubiquitous undesirable side effects of these drugs. This result should be interpreted with caution because of certain limitations to the study. Sinus rhythm maintenance was mainly based on the last ECG. Without routine ambulatory monitors and ECGs, long-term arrhythmia recurrence rates and sinus rhythm rates could be overestimated because of the inability to detect subclinical arrhythmias. Although amiodarone was the preferred AADs, the final decision was left to the physician who was not reported to be blinded to the treatment. The physician's belief about the residual risk in each patient could have biased their choice of AADs. Although over 60% of patients had a structural heart disease, most of them had well-preserved systolic function. The data cannot, therefore, be extrapolated to patients with more severe heart disease and impaired systolic function.
		Benefit of CA vs SA for paroxysmal AF Not reported.
4.	Need for cardioversion	**Benefit of CA vs MT for persistent AF** Need for cardioversion is defined as requirement for cardioversion after the blanking period (usually three months after CA), during the follow up period. Chen et al (2018) reported rates of patients needing cardioversion after the blanking period. Pooled results from three RCTs (n=394) showed that, compared to AADs, CA significantly reduced the number of participants needing cardioversion (RR 0.59, 95%CI [0.46, 0.76]; $p < 0.0001$). Number needed to treat (NNT) with CA to prevent one case of cardioversion was 4.2. The systematic review suggests that CA is better at preventing the need for cardioversion than medical therapy. Requiring cardioversion after the blanking period is an objective indication of treatment failure. These results are important because they reflect whether or not the primary or secondary treatment of AF with CA or medical therapy has been successful or not. These results should be interpreted with caution because the criteria for deciding which patients required cardioversion was not specified and could have varied between the different trials and clinical centres.
		Benefit of CA vs SA for persistent AF Not reported.

		Benefit of CA vs MT for paroxysmal AF Not reported.
		Benefit of CA vs SA for paroxysmal AF Not reported.
5.	Hospitalisation	**Benefit of CA vs MT for persistent AF** Hospitalisation was not specifically defined by the authors of the review. However, in other related reviews hospitalisation refers to admission related to the condition or complications of the treatment. In the meta-analysis by Chen et al (2018), two RCTs (n=349) contributed to analysis of hospitalisation. A significant reduction in hospitalisation was detected in patients who were treated with CA compared with AADs (RR 0.54, [95%CI 0.39 to 0.74]; p=0.0002). NNT with CA to prevent one hospitalisation was 6.7. The meta-analysis suggests that CA is better at reducing hospitalisation than medical therapy. Hospitalisation, especially when it involves overnight stay is an important contribution to burden of illness. Depending on the nature of hospitalisation it could consume significant healthcare resources, and increase the risk of further complications like infection, therefore avoiding this would be valuable to the patient. These results should be treated with caution as it is not certain what the nature of the hospitalisations were and whether or not they were always related to AF, HF or other cardiovascular conditions.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF Not reported.
		Benefit of CA vs SA for paroxysmal AF Not reported.
6.	Cardiac hospitalisation/ re-admission	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.

		Benefit of CA vs MT for paroxysmal AF Hospitalisation or re-hospitalisation for cardiac causes was reported in two of the RCTs included in the HTA by Skelly et al (2015). The studies did not provide further details regarding reasons for hospitalisation. Skelly et al (2015) reported that at 12 to 24 months following CA, patients had fewer cardiac hospitalisations or re-admissions than those on MT based on results from two RCTs. One RCT (n=67) reported, at 12 months, CA 9.4% versus MT 54.3% and the other (n=294), at 24 months, CA 0% versus MT 1.4%. However, results were not pooled and no tests of statistical significance were reported. The systematic review suggests that CA is better at hospitalisation or re-hospitalisation than MT. This can have a positive impact on complications and morbidity, for example due to infection. In general, acute hospital beds are a limited resource and increased hospital admissions are an important burden to health resources as well as for the patients. This result should be interpreted with caution because of the small size of the studies included. In addition, the studies did not provide further details regarding reasons for hospitalisation and the extent to which hospitalisation for re-ablation procedures or crossover from medical therapy to ablation was included.
		Benefit of CA vs SA for paroxysmal AF Not reported.
7.	Improvement in left ventricular ejection fraction (LVEF)	**Benefit of CA vs MT for persistent AF** Improvement in LVEF was defined as the median absolute increase in LVEF from baseline to the 60-month follow-up. Four RCTs (n=205) included in Chen et al (2018) compared CA with medical rate control therapy in patients with persistent AF and concomitant HF. A significant increase in EF was detected in patients who were treated with CA compared with the medical therapy (rate control) [mean difference (MD) = 7.72, 95%CI 4.78 to 10.67; $p < 0.00001$]. The systematic review suggests that CA is better than MT at improving LVEF in patients with persistent AF. A clinical improvement in this outcome is likely to be valuable to patients and can have a positive effect on long-term outcomes. This result should be interpreted with caution because of the relatively small number and size of the studies included in the meta-analysis. Although the studies showed no heterogeneity, the different studies use different methods to determine the left ventricular ejection fraction; sensitivity analysis was not carried

		out. The follow up period (12 to 24 months) was also too short to give sufficient insight into the long-term outcomes in this population.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF Improvement in LVEF was defined as the median absolute increase in LVEF from baseline to the 60-month follow-up. At 60 months, Marrouche et al (2018) reported a median LVEF increase in patients with heart failure and AF: CA (n=14) 7% (5 to 16) versus MT (n=11) 8% (-1 to 23); However, the difference was not statistically significant, p=0.81. The study suggests no difference between CA and MT in improving LVEF. A significant increase in LVEF could have a positive impact on clinical outcomes like hospitalisation and quality of life outcomes like walking distance. Therefore this would be beneficial to the patients. This result should be interpreted with caution because of the relatively small number of paroxysmal AF patients assessed for this outcome (14 CA versus 11 medical therapy). Although patients' characteristics were well balanced between the two treatment arms in this study, the relative characteristics were not compared for the subgroup of paroxysmal AF patients reported on in the study. Furthermore, the study was not blinded and a greater number of patients in the ablation group than in the medical therapy group crossed over to the other treatment group. Patients with a worse LVEF at baseline could therefore have been more likely to cross over to the medical therapy group.
		Benefit of CA vs SA for paroxysmal AF Not reported.
8.	Re-ablation	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF Repeat ablations (i.e. re-ablation for arrhythmia recurrence) were reported only if they occurred after the blanking period, which was typically three months. Skelly et al (2015) reported that, based on data from three RCTs (n=184), the frequency of re-ablation following CA ranged from

		0% to 43% within 12 months of CA. The results were not pooled. Over follow-up periods ranging from longer than 12 months to 48 months, frequency of re-ablation varied across four trials including 619 patients, this ranged from 12.5% to 49.2% with a pooled risk of 24.2% (95% CI 12.6 to 41.5). The HTA suggests that re-ablation is very common in patients who have undergone CA. These results are important because they reflect whether or not the primary or secondary treatment of AF with CA has been successful. These results should be interpreted with caution because the criteria for deciding which patients required re-ablation was not specified and could have varied between the different trials and clinical centres.
		Benefit of CA vs SA for paroxysmal AF Not reported.
9.	Re-intervention	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF Not reported.
		Benefit of CA vs SA for paroxysmal AF Re-intervention refers to cardioversion or re-ablation after a 3-month blanking period. In the RCT by Jan et al (2018), through the entire follow-up period (30.5±SD 6.9 months), 9/26 (34.6%) patients after CA and 4/24 (16.7%) after SA required re-intervention. No test of statistical significance was reported. It is unclear from the RCT whether there is a significant difference in the re-intervention rates between SA and CA. The requirement for re-intervention, which signifies failure of the initial intervention, exposes the patients to further risks of complications and is a significant burden on healthcare resources. This result is inconclusive because it is based on very small numbers and no statistical analysis of significance was recorded.
10.	Stroke occurrence	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.

		Benefit of CA vs MT for paroxysmal AF None of the trials included in this study provided criteria or definitions for stroke diagnosis although they distinguished stroke from transient ischaemic attack (TIA). Skelly et al (2015) reported no difference in stroke occurrence within 30 days based on pooled results from three RCTs (n=481) [CA 0% to 0.7% versus medical therapy 0%; no test of statistical significance reported] and beyond 30 days based on two RCTs [CA n=0/98 (0%) versus MT n=0/96 (0%), p=NS]. No transient ischaemic attacks (TIAs) were reported at 12 or 48 months; however, one RCT (n=294) reported 0.7% in both the CA (1/146) and MT (1/148) groups. No p values were reported. The systematic review suggests no difference between CA and MT in the occurrence of stroke. AF is associated with an increased risk of stroke, which affects nearly 7% of AF patients with heart failure each year. Furthermore, ischaemic stroke that occurs in the setting of AF tends to be either fatal or of moderate to high severity in most patients. Therefore avoiding this would be beneficial to patients. This result should be interpreted with caution because none of the studies included in this systematic review provided criteria or definitions for stroke diagnosis. Anticoagulation was used in all patients receiving CA but anticoagulant used was variable reported for the medical group. The follow up period was too short to give any conclusive insight into the risk of strokes in the longer term.
		Benefit of CA vs SA for paroxysmal AF Not reported.
11.	Major bleeding	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF Major bleeding complications were defined as the occurrence of cardiac tamponade or haemopericardium that required intervention or caused symptoms, the need for transfusion, haematoma requiring intervention, massive haemoptysis, haemothorax and retroperitoneal bleeding. There was no difference in the risk of 30-day major bleeding, haemorrhage, or transfusion between treatment groups. Major bleeding occurred in 2/32 (6.3%) CA patients versus 1/35 (1.9%)

		in the MT group. No tests of statistical significance were reported. The systematic review suggests no difference in bleeding between CA and MT. Bleeding, including requirement for hospitalisation and transfusion, is a known risk in the management of AF. The requirement for effectiveness anticoagulation in the pre, peri and post procedure stages further contribute to this risk. Major bleeding could lead to complications like subarachnoid haemorrhage, intestinal bleeding and subdural bleeding. These results are limited as they are based on only one study. The risk could also be heterogenous depending on the method of ablation and experience of the centre. Further larger multicentre trials are required to establish the risk of bleeding in this population.
		Benefit of CA vs SA for paroxysmal AF Not reported.
12.	Composite of death or hospitalisation for worsening heart failure (HF)	**Benefit of CA vs MT for persistent AF** This refers to a composite of death from any cause or worsening of heart failure (HF) that led to an unplanned overnight hospitalisation. Patients requiring intravenous medication for HF or substantial increase and/or addition of thiazide to a loop diuretic were deemed to have worsening HF. Reasons for worsening of HF may include AF, acute coronary syndrome and hypertension. At a median follow up of 37.6 months, Marrouche et al (2018) reported composite of death or hospitalisation for worsening HF in 34/125 persistent AF patients treated with CA (27.2%) vs. 48/120 persistent AF patients treated with medical therapy (40.0%) (hazard ratio (HR) 0.64 [95% CI, 0.41 to 0.99], p value not reported). AF and HF are common co-existing conditions, with AF increasing the risk of stroke, hospitalisation for HF and death. Successful treatment of AF can therefore substantially alter long-term outcomes in patients with HF, therefore valuable to patients. This study suggests that CA is better at reducing this this composite outcome compared with medical therapy although the HR for the difference between groups was only just statistically significant. These results should be interpreted with caution because there was a lack of blinding with regards to randomisation and treatment. It would have been quite difficult to perform a truly blinded trial with a sham ablation procedure, but the lack of

		blinding could have led to bias in decisions such as whether to admit a patient for worsening HF. A greater number of patients in the CA group than in the MT group crossed over to the other treatment group, but the results of per-protocol and as-treated analyses were similar to those of the primary analysis. Finally, although MT (for both atrial fibrillation and heart failure) was managed systematically, we cannot exclude the possibility that a different or more aggressive approach to medical management might have influenced the trial results. Furthermore, side effects and unwillingness to take AADs were listed as recruitment criteria; it is therefore not clear whether this affected the outcome in the MT arm.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF This refers to a composite of death from any cause or worsening of heart failure that led to an unplanned overnight hospitalisation. Patients requiring intravenous medication for HF or substantial increase and/or addition of thiazide to a loop were deemed to have worsening HF. Reasons for worsening of HR may include AF, acute coronary syndrome and hypertension. At a median follow-up of 37.6 month, Marrouche et al (2018) reported composite of death or hospitalisation for worsening HF in: CA n=17/54 (31.5%) versus MT n=34/64 (53.1%); HR 0.60 (95% CI 0.34 to 1.08), in favour of CA, p value was not reported. This study suggests no difference between CA and MT at reducing composite of death or hospitalisation for worsening HF than MT. AF and HR are common co-existing conditions, with AF increasing the risk of stroke, hospitalisation for HF and death. Successful treatment of AF can therefore substantially alter long-term outcomes in patients with HF. These results should be interpreted with caution because there was a lack of blinding with regard to randomisation and treatment. It would have been quite difficult to perform a truly blinded trial with a sham ablation procedure, but the lack of blinding could have led to bias in such decisions as whether to admit a patient for worsening HF. A greater number of patients in the CA group than in the MT group crossed over to the other treatment group, but the results of per-protocol and as-treated analyses were similar to those of the primary analysis. Finally, although MT (for both AF and HF) was managed systematically, we cannot exclude the possibility that a different or more aggressive approach to medical management might have influenced the trial results. Furthermore, side effects and unwillingness to take AADs were listed as recruitment criteria,

		and it was not clear whether this could have affected the outcome in the MT arm.
		Benefit of CA vs SA for paroxysmal AF Not reported.
13.	All-cause mortality	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF All-cause mortality was defined as any death past the 30-day peri-procedural time up to 12 (or 13) months or for which timing of mortality was not reported. All-cause mortality included all causes of mortality whether or not it was felt to be due to atrial fibrillation (AF) or complications of AF treatment. Skelly et al (2015) reported no difference in all-cause mortality between the intervention groups within 30 days based on pooled results from three randomised controlled trials (RCTs) (n=570) [catheter ablation (CA) 0% to 0.7% versus medical therapy (MT) 0%]; however, no test of statistical significance was reported. There was also no difference between the two study arms at up to 12 months [three RCTs (n=333) CA 0% to 1% versus MT 0% to 3.6%)] and at 24 months [two RCTs (n=408) CA 1.4% versus MT 2.8%] p value not reported for both. The systematic review suggests no difference in all-cause mortality between CA and MT. This result should be interpreted with caution because the study sizes were likely insufficient to effectively determine the effect of AF ablation on mortality or detect statistical differences between treatment groups.
		Benefit of CA vs SA for paroxysmal AF Not reported.
14.	Change in 6-minute walk distance (6MWD)	**Benefit of CA vs MT for persistent AF** The six-min walk distance (6MWD) is mainly used to therapeutically evaluate exercise tolerance in HF patients. In the meta-analysis by Chen et al (2018) pooled results from three RCTs (n=150) contributed to the analysis of the 6MWD changes. There was no significant difference between the CA arm and the medical rate control arm (MD = 19.17, [95%CI −11.43 to 49.76]; p= 0.22).

		The meta-analysis suggests that there is no difference in 6MWD between CA and MT. Walking distance and general exercise capacity is an important outcome to patients with heart failure and is a measure of deterioration of disease and general morbidity. An improvement in this would be valuable to patients. This result should be interpreted with caution because, although heterogeneity was not significant among the included studies, the number of patients in these studies was particularly small and a follow-up duration of only six to 12 months might not be sufficient for the effect of restoration of sinus rhythm to fully manifest.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF Not reported.
		Benefit of CA vs SA for paroxysmal AF Not reported.
15.	Reduction in Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores	**Benefit of CA vs MT for persistent AF** MLHFQ score is a validated measure of therapeutic efficacy which is associated with favourable prognostic outcomes in HF. Three studies, reported by Chen et al (2018), provided data on MLHFQ (n=140) score changes. A pooled analysis detected a significant reduction in MLHFQ score, indicating improved quality of life scores in the ablation arm compared with that in the medical rate control arm (MD 11.13, [95% CI 2.52 to 19.75]; p=0.01). This meta-analysis suggests a significant reduction in MLHFQ scores after CA compared with MT, although the clinical significance of this is not clear. With comprehensive evaluation of quality of life (QoL), MLHFQ score reflects not only exercise tolerance but also HF symptoms, mental states, and sexual function. It may be attributed to reinstatement of stable sinus rhythm, lesser burden of symptoms, and better cardiac function. This would be valuable to patients. This result should be interpreted with caution because, although heterogeneity was not significant among the included studies, the number of patients in these studies was small and the clinical significance of the improvement in MLHFQ scores is not clear.
		Benefit of CA vs SA for persistent AF

		Not reported.
		Benefit of CA vs MT for paroxysmal AF Not reported.
		Benefit of CA vs SA for paroxysmal AF Not reported.
16.	Quality of life (QoL)	**Benefit of CA vs MT for persistent AF** Not reported.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF QoL was assessed using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) physical (PCS) and mental component scores (MCS) (range 0 to 100, higher scores indicating better well-being). Skelly et al (2015) reported no statistical differences between treatment groups for the SF-36 MCS at 12 months based on two RCTs (n=406); this held true whether the analysis was done using the difference in mean scores at follow-up 2.26 (95% CI -2.12 to 7.40) or using the difference in change from baseline scores 1.88 (95% CI -0.47 to 4.50). For PCS, CA was favoured over MT when the pooled estimate was calculated using differences in mean follow-up scores (overall effect 2.85; 95% CI 0.93 to 4.82), however when the analysis was based on the change from baseline the effect was no longer statistically meaningful (overall effect 2.88; 95% CI 0.18 to 5.25). No p values were reported. The authors also reported no difference in both QoL measures at 24 months, MCS scores [one RCT (n=294) CA: 51.1 ± standard deviation(SD) 9.2 versus MT 50.9 ± SD 8.0] and PCS scores [one RCT (n=294) CA: 50.0 ± SD 8.8 versus MT 47.9 ± SD 8.9] and 48 months for MCS scores [one RCT (n=198) CA: 52.9 ± SD 9 versus MT 51.9 ± SD 9] and PCS scores [one RCT (n=198) CA: 52.3 ± SD 9 versus MT 52.6 ± SD 8]. No other details were reported. The study suggests no difference in QoL between CA and MT at 24-month follow-up. Quality of life is likely to be valuable to patients.

		These results should be interpreted with caution because of the heterogeneity found among studies comparing CA with MT which may be due to dissimilar patient populations and extent of ablation.
		Benefit of CA vs SA for paroxysmal AF Not reported.
17.	Incremental cost effectiveness ratio (ICER): Cost/ quality-adjusted life year (QALY)	**Benefit of CA vs MT for persistent AF** ICER, usually measured as cost/QALY, is a summary measure representing the economic value of an intervention, compared with an alternative. An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect) to provide a ratio of 'extra cost per extra unit of health effect'. In a systematic review of health economic studies, Neyt et al (2013) reported data from two studies that included persistent AF patients. For first line ablation compared with second line rate control, reported ICERs ranged from: $60,804 (£46,837)/QALY (age 65 years; CHADS2 score 1) to $80,615 (£62,100) (age 75 years; CHADS2 score 3). In the UK the QALY is most frequently used as the measure of health effect, enabling ICERs to be compared across disease areas. In decision-making ICERs are most useful when the new intervention is more costly but generates improved health effect. ICERs reported by economic evaluations are compared with a pre-determined threshold to decide whether choosing the new intervention is an efficient use of resources. There is no published official ratio that defines what is cost effective, but in the UK, a threshold of £20,000 to £30,000 is generally assumed to reflect cost effectiveness. These results should be treated with a lot of caution because the reliability of the underpinning data is questionable. The outcome measure and the two models used were based on an unpublished systematic review of literature and other undisclosed sources. Some of the studies had conflicting results, so there was likely to be significant heterogeneity in the analyses. The study was from a US payer and societal perspective and relevance to the NHS in England is not known.
		Benefit of CA vs SA for persistent AF Not reported.
		Benefit of CA vs MT for paroxysmal AF The incremental cost-effectiveness ratio (ICER), usually measured as cost/quality-adjusted life year (QALY), and is a

		summary measure representing the economic value of an intervention, compared with an alternative. An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect) to provide a ratio of 'extra cost per extra unit of health effect'. In a cost effectiveness analysis from a UK NHS perspective, Reynolds et al (2014) reported an ICER of £21,957 per QALY gained, with the use of cryoballoon ablation versus AADs. The authors concluded that, beyond a threshold of £22 000 per QALY gained, ablation becomes the more cost effective intervention, with probabilities of 86% and 97.2% of being cost effective at thresholds of £30,000 and £40,000 per QALY gained, respectively. In the UK the QALY is most frequently used as the measure of health effect, enabling ICERs to be compared across disease areas. In decision-making ICERs are most useful when the new intervention is more costly but generates improved health effect. ICERs reported by economic evaluations are compared with a pre-determined threshold in order to decide whether choosing the new intervention is an efficient use of resources. There is no published official ratio that defines what is cost effective, but in the UK, a threshold of £20,000 to £30,000 is generally assumed to reflect cost effectiveness. These results should be treated with caution because, although the analysis took a UK NHS perspective, there were limitations to the methodology and other factors that could have biased the results. The efficacy assessment was based on one single RCT CA versus AADs, which showed a beneficial effect of CA over AADs; however this effect size is considerably greater than that observed in other CA versus AADs studies, mostly due to a higher recurrence rate in the AADs group. The results of this study might have exaggerated the contribution of CA to the base case analysis. The study was supported by Medtronics International, and all the authors of the study had either received honoraria from or worked for Medtronics (manufacturers of balloon dilation catheters).
		Benefit of CA vs SA for paroxysmal AF Not reported.

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: **1) mobility:** Patients have moderate to severe problems in walking about.

2) **ability to provide self-care:** Patients have no to moderate problems in washing or dressing.
3) **undertaking usual activities:** Patients have no to severe problems in doing their usual activities.
4) **experience of pain/discomfort:** Patients have no to moderate pain or discomfort.
   experience of anxiety/depression: Patients are slightly to extremely anxious or depressed.

Further details of impact upon patients:
Individuals can experience Atrial Fibrillation (AF) differently. Some individuals may have no symptoms, others have intermittent symptoms, and some experience constant symptoms. Symptoms include shortness of breath, tiredness, chest pain, feeling dizzy or a feeling of the heart beating rapidly.

The policy proposition includes assessment of how the ablation treatment impacts upon activities of daily living, both before and after the procedure in a Patient Related Outcome Measure (PROM). The PROM asks patients to rank their experiences of pain, mobility, fatigue, anxiety and depression, eating and drinking (and other factors of everyday life) and score the level of impact.

Further details of impact upon carers:
Where a patient's mobility and self-care is restricted by pain and/or breathlessness, or if a patient experiences severe anxiety or depression there could be a greater need for carer assistance for personal care and to complete work and family roles.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
Not applicable.

Considerations from review by National Programme of Care
The proposal received the full support of the Internal Medicine NPoC on 16 March 2021. It was noted catheter ablation for AF is an existing service and the purpose of the policy is to ensure clinical practice is informed by the evidence base and that prior approval is required when more than 2 ablations are being considered. It was noted use of this treatment is expected to grow and the policy criteria will guide clinical decision making to reduce repeat ablations where this will not benefit patients and support reduction in this anticipated growth. • The NPoC welcomed the use of a Shared Decision Making Tool to help support patients in understanding risks and benefits, and particularly that ablation can provide symptom control only.

- The NPoC welcomed the use of PROMs tools to support collection of patient related outcomes to inform review of the policy in the future.