

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation Observational Data Unit

Commissioning through Evaluation Project Overview

Percutaneous mitral valve leaflet repair for mitral regurgitation (MitraClip)

1 Executive summary

- 1.1 This overview replaces an interim project report prepared for NHS England by NICE in March 2018. It is written for the Policy Working Group and Clinical Priorities Advisory Group to inform the further development of commissioning policy for percutaneous mitral valve leaflet repair for mitral regurgitation. It is designed to be read together with the updated External Assessment Centre (EAC) evaluation report¹ which describes in detail the Commissioning through Evaluation (CtE) scheme including the study design, data collection and analysis, and findings. The EAC report also includes a review of the published literature.
- 1.2 The final EAC evaluation report and NICE project overview contain additional information from the linked dataset combining CtE registry, hospital episode statistics (HES) admitted patient care (APC) and Office for National Statistics (ONS) records, and the *de novo* economic analysis which were not available at the time of the interim reports.

¹ Willits I et al. Commissioning through Evaluation (CtE) Percutaneous mitral valve leaflet repair for mitral regurgitation (MitraClip). FINAL LINKED DATA REPORT. Newcastle and York External Assessment Centre (NY EAC). 24 December 2018.

The procedure

- 1.3 The mitral valve allows blood to flow from the atrium (upper chamber) to the ventricle (lower chamber) of the left side of the heart. Mitral regurgitation (MR) happens when the valve does not close properly. This allows some of the blood to leak back (regurgitate) through the valve into the atrium when the ventricle contracts. If the volume of blood leaking back into the atrium is large, the pumping efficiency of the heart is reduced. This can lead to shortness of breath. Untreated MR can lead to heart failure, where the heart cannot pump enough blood to meet the needs of the body. The most common form of MR is degenerative MR (also called primary or structural MR) in which 'wear and tear' results in changes to the structure of the valve. In functional MR (also known as secondary MR), the valve itself is structurally normal but changes elsewhere in the heart (for example enlargement of the left ventricle) stop the valve closing properly.
- 1.4 Degenerative MR may require open heart surgery to repair or replace the mitral valve. Functional MR can be managed using drugs for treating heart failure, but open heart surgery to repair the valve may be an option. Percutaneous mitral valve leaflet repair for mitral regurgitation using the MitraClip device (Abbott) is a minimally invasive surgical procedure carried out under local or general anaesthetic. It has been developed to reduce MR in people who are considered to be at too high risk for open heart surgery. During the procedure, the leaflets (flaps) of the mitral valve are partially clipped together using the MitraClip device, which is introduced into a vein in the groin and passed into the heart. The valve continues to open and close on either side of the clip. This allows blood to flow down through the valve while reducing the flow of blood in the wrong direction. Echocardiography is used to determine whether the reduction in MR is sufficient. If the reduction in MR is inadequate with 1 MitraClip device, the device may be removed or a second device may be placed alongside it. Most patients stay in hospital for around 5 nights after the

procedure, and people usually have anti-platelet therapy for 6 months after the procedure.

- 1.5 There remains some uncertainty regarding the safety and efficacy of MitraClip in reducing MR, and there is limited evidence showing how well it works in normal clinical practice, that is, outside a clinical trial. The NICE Interventional Procedures guidance on percutaneous mitral valve leaflet repair for mitral regurgitation ([IPG309](#)) is currently being updated and is due to be published in April 2019. The draft recommendations state that the current evidence on the safety and efficacy of percutaneous mitral valve leaflet repair for MR is adequate to support its use in patients for whom open surgery is contraindicated following risk assessment, provided that standard arrangements are in place for clinical governance, consent and audit. This compares to the current recommendations which state that the procedure should only be used with special arrangements for clinical governance, consent and research. The draft guidance further recommends that patient selection should be done by a multidisciplinary structural heart team, that the procedure should only be done in specialised centres by clinicians with specialist training or under expert mentoring, and that the details of patients having the procedure should be entered onto a national database.

The CtE study

- 1.6 In order to determine the effectiveness and safety of percutaneous mitral valve leaflet repair using MitraClip in general clinical practice in England, NHS England commissioned a time-limited study in which a limited number of eligible people had the MitraClip procedure at one of 3 designated hospitals. People with moderate-severe or severe (grade 3+ or 4+) mitral regurgitation who were considered at high risk for conventional mitral valve surgery, and were symptomatic despite optimal medical therapy, were eligible for the procedure. The study was part of NHS England's CtE programme which enables new clinical and patient experience data to be collected for treatments that are not currently

routinely funded by the NHS, but which nonetheless show significant promise for the future. Details of the CtE process are included in the [appendix](#).

Key findings

Patient characteristics

1.7 One hundred and ninety nine people with a mean age of 76.2 years (range 37 to 94 years) were eligible for the MitraClip procedure and included in the analysis. Most people (60.0%) had functional MR, and 40.0% had degenerative MR. People with degenerative MR were significantly older than those with functional MR. Most of the people were recruited electively (84.4%), with 13.6% admitted urgently and 2.0% undergoing the procedure as an emergency. Nearly all the people (99.5%) had moderate-severe or severe MR (grade 3+ or 4+) with most people (92.4%) also having moderate to severe symptoms of heart failure such as dyspnoea (New York Heart Association [NYHA] class 3 or 4). The mean EuroSCORE II (the percentage risk of dying from cardiac surgery) was 6.4 (range 0.7 to 42.5).

Outcomes of interest

1.8 A MitraClip device was implanted in 187 (94.0%) of the patients. For the remaining 12 people, either the implantation was unsuccessful or the records did not note whether a device was implanted successfully or not. The procedural success rate (defined as successful device implantation with no major complications) was 85.9% (95% CI 80.3% to 90.4%).

1.9 The in-hospital major complication rate was 8.2% (95% CI 4.7% to 12.9%), with 16 of the total cohort of 199 people having a major complication including death, complications requiring additional surgery, major bleed and heart attack. Ten patients died in hospital from causes considered to be directly attributable to the MitraClip procedure, giving a procedural mortality rate of 5.1% (95% CI 2.5% to 9.2%). Four people (2.0%) required additional surgical interventions before discharge (1

percutaneous retrieval of embolised device, 1 bailout/urgent percutaneous coronary intervention, 1 mitral valve surgery and 1 conversion to open heart surgery). Some people had multiple major complications. Fifteen people had a minor complication including minor bleeds, mitral stenosis (narrowing of the mitral valve opening), and partial detachment of the MitraClip device, giving an in-hospital minor complication event rate of 7.6% (4.3% to 12.2%). There was no association between procedural success rate and procedural urgency.

- 1.10 Length of stay was significantly different between the elective (median 5 nights, range 0 to 37 nights) and urgent/emergency procedures (median 24 nights, range 0 to 46 nights), $p < 0.0001$.
- 1.11 In patients successfully treated, there was an immediate and significant improvement in MR, with the proportion of people having moderate-severe or severe MR (grade $\geq 3+$) reducing from 99.5% before the MitraClip procedure to 6.7% after the procedure. Improvements in MR were accompanied by improvements in the symptoms of heart failure, including dyspnoea.
- 1.12 Patients were followed up for a maximum of 2 years after the procedure. Data from 1 or more follow-up appointments was available for 170 (90.9%) of the 187 people who had the MitraClip device implanted, with an overall follow-up period of 111.2 person years (the total accumulated number of years that all the people in the scheme were followed). The reduction in MR was sustained in most patients, with 76.4% having mild or absent MR (grade $\leq 2+$) at 1 year. There were corresponding sustained and statistically significant ($p < 0.0001$) improvements in the symptoms of heart failure, with 17.9% of patients having a NYHA status of class 3 or 4 at 1 year, compared with 92.4% of patients before the MitraClip procedure. This was accompanied by significant improvements in quality of life, as measured by EQ-5D. Improved scores for mobility, usual activities, pain and discomfort, and anxiety and depression were matched by self-assessed scores for overall health.

- 1.13 Of the 170 people with follow-up data, 25 people had a major complication during the 2 year follow-up period, resulting in an overall major complication rate after discharge of 14.7% (95% CI 9.7% to 20.9%). Of these, 20 patients died giving a post-discharge mortality rate of 11.8% (95% CI 7.3% to 17.6%). Six patients (3.5%) had other major complications (2 neurological events and 4 complications requiring additional surgery). Some patients had more than one complication. Twenty two patients reported minor complications, including 21 cases of mitral stenosis and 1 partial detachment of the MitraClip device, giving a post-discharge minor complication rate of 12.9% (95% CI 8.3% to 18.9%).
- 1.14 Overall, of the 199 eligible patients, 30 people (15.1%) died during the CtE study either in hospital or following discharge and 3 people (1.8%) needed an additional mitral valve intervention. Using time to event analysis over a total aggregated follow-up period of over 100 person years, the event rates per 100 person years were 27.0% (95% CI 18.2% to 38.5%) for death and 3.1% (95% CI 0.6% to 9.1%) for additional mitral valve intervention. The survival rate at 1 year was 81.8% (95% CI 75.0% to 89.4%).
- 1.15 There were no significant differences in mortality rate, MR grade, NYHA class or adverse events in patients with degenerative or functional MR. Patients receiving MitraClip as an urgent or emergency case had a greater risk of death, with a mortality rate of 68.2% (95% CI 29.5% to 134.3%) per 100 person years compared with 22.1% (95% CI 13.9% to 33.5%) per 100 person years in the elective cohort (p=0.0105). This was driven by in-hospital mortality. There was no association between procedural urgency and major complications. There were 22 (13.1%) deaths in elective patients and 8 (26.7%) deaths in urgent/emergency patients.
- 1.16 To validate the CtE registry and provide longer-term follow-up data, individual patient records from the registry were matched to routinely collected hospital admission and mortality records. Records from 166

people (88.8% of the 187 people who had a device implanted) were successfully linked across the 3 data sets with an overall follow-up period of 271.9 person years. The baseline characteristics of the subset of people included in the linked dataset were similar to those of full CtE registry cohort.

- 1.17 Thirteen additional in-hospital complications (major and minor combined, including deaths and additional surgical interventions) were identified in the linked data set when compared with the corresponding registry records, giving a total of 42 complications. This resulted in an overall in-hospital complication rate of 25.3%.
- 1.18 The linked data identified an additional 4 people needing additional mitral valve intervention during the CtE scheme. In total 9 patients required additional intervention with 3 requiring additional mitral valve repair and 7 patients required mitral valve replacement. Of these, 1 patient required repair followed by replacement. A total of 10 patients required a cardiac pacemaker system and 2 required a cardioverter defibrillator after the MitraClip implantation.
- 1.19 Fifteen additional deaths that were not recorded in the CtE registry were identified in the linked data, giving an overall total of 37 deaths either in-hospital or post-discharge. The total event rate for all-cause mortality was 13.6% (95% CI 9.6% to 18.8%) per 100 person years. Despite the additional deaths mortality rate was lower for the linked data than for the registry data alone (27.0 deaths per 100 person years). Freedom from death was 0.87 (95% CI 0.82 to 0.93) at 1 year and 0.77 (95% CI 0.71 to 0.85) at 2 years. The all-cause mortality rate was higher in the urgent/emergency cohort (31.3%; 95% CI 14.3% to 59.5%) compared with the elective cohort (11.5%; 95% CI 7.7% to 16.6%). The 1-year survival rates were 0.90 (95% CI 0.85 to 0.95) and 0.71 (95% CI 0.54 to 0.94) for the elective and urgent/emergency cohorts, respectively. The corresponding 2-year rates were 0.81 (95% CI 0.74 to 0.88) and 0.52 (95% CI 0.33 to 0.82) for the two cohorts.

- 1.20 Three cases of infective endocarditis were identified in the linked dataset.
- 1.21 In the year following discharge from hospital, there were 151 admissions in 90 identified patients, giving a readmission rate of 176.1 (95% CI 151.9 to 198.8) per 100 person years, with 62 patients (69%) having at least one admission. The biggest single reason for readmission identified by HES was for cardiac-related morbidity, with an adjusted rate of 70.3 admissions per 100 person years (including 36.2 admission per 100 person years for reasons associated with heart failure).

Costs and resources

- 1.22 The MitraClip procedure including the device is estimated to cost £32,912 per person (range £29,007 to £34,528). *De novo* economic analysis using a 'before and after' approach showed that, in the linked dataset, people had fewer hospital admissions, fewer days in hospital and less *per patient* hospitalisation costs in the year after MitraClip than in the year before the procedure. While MitraClip reduces future hospital admissions and associated resources, it is unlikely to offset the initial device and procedure costs.

2 Commissioning through Evaluation questions

- 2.1 Table 1 lists the questions agreed by NHS England for the CtE scheme, the EAC conclusions and a commentary by NICE.

Table 1: CtE questions with responses

Q	CtE project question	Conclusions/results from project	NICE comments
1	Can UK clinical teams undertaking MitraClip reproduce the reduction in mitral regurgitation seen in the early clinical trials?	Evidence reported from the CtE registry shows that the MitraClip procedure results in immediate and significant improvement in MR grade with the proportion of patients with moderate-severe or severe MR ($\geq 3+$) reduced from 99.5% before the procedure to 6.7% after the procedure. This large effect is consistent with all the studies identified in the literature. However, after 6 weeks there is evidence that there is some deterioration in mitral valve function, with 23.6% of patients reporting moderate-severe or severe MR. This is fully consistent with the majority of the published literature, however, in 1 recent RCT (COAPT) and 1 observational study, 95% of people had absent, mild or mild moderate MR 1 year after the MitraClip procedure.	MR grade is not reported in HES therefore the linked data could not be used to address this question or improve certainty in the analysis.
2	Is reduction in mitral regurgitation mediated by MitraClip associated with improvements in quality of life?	The CtE registry reported significant improvements in quality of life at all follow-up time points compared with baseline. There were statistically significant improvements in all domains of EQ-5D at 6 months. The use of MitraClip was also associated with an immediate and sustained improvement in the symptoms of heart failure. These results were consistent with those published in the literature.	There are limited data on quality of life associated with MitraClip reported in the literature. The CtE registry data make a useful contribution to the evidence base for this outcome measure.

Q	CtE project question	Conclusions/results from project	NICE comments
3	Does MitraClip improve survival rates?	<p>The CtE registry reported an in-hospital mortality rate of 5.0% (95% CI 2.4% to 9.0%) and a 1 year mortality rate of 11.6% (95% CI 7.5% to 16.8%). The linked data reported a 1 year mortality rate of 12.7% (95% CI 7.5% to 15.9%) and 2 year mortality rate of 22.7% (95% CI 15.3% to 29.4%), however the improved coverage (271.9 person years compared with 111.2 person years reported for the registry) meant that the annualised mortality rate was lower, at 13.6% (95% CI 9.8% to 18.8%) per 100 person years. As linked data were considered to be more comprehensive than the registry data, these data are preferred for analysis and comparisons with other studies. These data appear consistent with results from observational studies performed in patients with similar characteristics. One recent RCT in patients with functional MR (COAPT) reported that MitraClip was associated with a significant clinical reduction in mortality after 2 years follow-up when compared with standard care alone. This was not observed in another RCT of functional MR patients (MITRA-FR) with 1 year follow-up.</p>	<p>The mean baseline EuroSCORE and EuroSCORE II of the CtE cohort of patients were 20.1% and 6.4%. This indicates a high risk of death from cardiac surgery. Data from the registry was limited by short follow-up. The linked data reduced uncertainty in the registry data by improving the duration of follow-up (271.9 person years compared with 111.2 person years reported for the registry).</p>

Q	CtE project question	Conclusions/results from project	NICE comments
4	Does MitraClip reduce the frequency of subsequent hospital admissions?	<p>The linked data reported that 69% of patients had at least one admission to hospital in the year following the MitraClip procedure, with an overall annualised rate of 176.1 (95% CI 151.9 to 198.8) admissions per 100 person years. The commonest cause of readmission identified by HES was cardiac disease, with an adjusted rate of 70.3 admissions per 100 person years, including 36.2 admission per 100 person years for reasons associated with heart failure. Evidence from observational studies indicated that the rate of readmission for MitraClip patients is high in the first year, ranging from approximately 20 to 60%. One RCT (MITRA-FR) reported that the rate of unplanned readmission for heart failure was close to 50 per 100 person years in both MitraClip and medical management arms, with no significant difference between them. This contrasts with another RCT (COAPT), which reported that MitraClip significantly reduced the rate of readmission for heart failure compared with medical management alone.</p>	
5	Are the early benefits in reduction in mitral regurgitation maintained in the medium-term? Is there a need for repeat treatment over time (either by a repeat percutaneous procedure or surgery)?	<p>The benefits of MitraClip (reduction in MR and improvements in the symptoms of heart failure and quality of life) were sustained for the duration of the CtE registry. From the linked dataset, 9 patients (5.4%) required additional mitral valve intervention following the MitraClip procedure, with 1 patient requiring repair</p>	<p>The robustness of this analysis was improved by data linkage.</p>

Q	CtE project question	Conclusions/results from project	NICE comments
		followed by replacement. A recent RCT (COAPT) in which MitraClip was compared with standard care alone in patients with functional MR reported that the benefits of MitraClip in terms of reduction in mortality and rehospitalisation accrue over a period of 2 years.	
6	What proportion of patients referred to a specialist MitraClip service as defined in the CtE documents were assessed by the MDT as suitable for the intervention? What proportion of the patients considered suitable for the procedures received it and what proportion of them benefitted?	The CtE registry cannot be used to answer these questions. This is because patients who were not recommended for MitraClip at the MDT stage were not recorded or followed up. The EAC did not identify any robust UK-based data which would inform this question, however results from the EVEREST II HRS study, suggest that about half of patients with severe functional MR unable to tolerate surgery may be suitable for the MitraClip procedure. Of the 199 eligible for the CtE scheme, 187 patients (94.0%) had a MitraClip device implanted. Approximately three quarters (75.8%) of these patients benefitted from the procedures (that is, MR was mild or absent at 1 year following the procedure).	Ongoing data collection should be encouraged to answer these questions. It is likely that referral practice and the application of selection criteria will improve with experience and the proportion of patients accepted for the procedure is likely to increase.
7	What are the short and medium term risk of complications from MitraClip use?	A MitraClip device was successfully deployed in 94.0% of the patients it was attempted in, with a procedural success rate (device implanted and no major complications) of 85.9%. Sixteen people (8.2%) experienced a major complication in hospital and 5.1% of people died before	The robustness of this analysis was improved by data linkage.

Q	CtE project question	Conclusions/results from project	NICE comments
		<p>discharge. Following discharge, there was a major complication rate of 14.75%, with death being the most common contributor (11.8%). These values appear to be broadly consistent with those reported in the literature, although comparisons of complications are limited due to issues with generalisability.</p>	
8	<p>Are clinical outcomes with MitraClip associated with particular patient characteristics (clinical or demographic)?</p>	<p>Limited data meant that subgroup analysis was limited to procedural urgency and disease aetiology. Patients in the CtE registry who were admitted urgently or as an emergency had an increased risk of in-hospital mortality, but there was no association between major complications and procedural urgency. There were no significant differences in outcomes in patients with functional or degenerative MR. Data from published studies indicate that patients with functional MR have an increased mortality rate and are more likely to be readmitted to hospital than patients with degenerative MR.</p>	
9	<p>What are the full procedural costs of using MitraClip to the NHS?</p>	<p>The base case estimate of the cost of a MitraClip procedure is £32,912 (range £29,007 to £34,528).</p>	<p>Procedural costs were estimated by combining procedural information from the registry and resource use from the centres. Where information was not available the 3 lead clinicians reached a consensus view on the appropriate resources required.</p>

Q	CtE project question	Conclusions/results from project	NICE comments
10	What are the potential cost savings for the NHS arising from patients receiving MitraClip?	<i>De novo</i> economic analysis from the EAC, derived from the linked data reported that, overall, MitraClip is associated with decreases in hospital admission rates, total hospitalisation days, gross hospitalisation costs, and mean <i>per patient</i> hospitalisation costs when compared with standard care. These savings were driven by a reduction in admission for cardiac reasons and heart failure. However, the EAC consider that these savings are unlikely to offset the cost of the procedure and device.	The EAC performed a <i>de novo</i> 'before and after' economic analysis. Extra costs incurred through the assessment of patients for the MitraClip procedure (including people for whom the procedure was considered unsuitable) are not included in the analysis. In addition, the cost of the procedure and the MitraClip device itself was not included in this analysis.
11	Is MitraClip cost-effective from the perspective of the NHS?	This question would require detailed modelling including comparative data which were not available to the CtE project.	Further robust economic analysis is required to determine the cost-effectiveness of the procedure.

3 Interpretation of the results

- 3.1 The following issues should be considered when reviewing the evidence on MitraClip and the answers to the specific questions in section 2.

Comparison of the CtE findings with the published evidence

Clinical evidence

- 3.2 As the registry was single-armed, a parallel literature search was undertaken in order to present the registry findings from real world NHS practice in the context of published studies in other populations, and to assess whether the procedural outcomes were consistent with previously reported studies. Summaries of the key studies (3 randomised controlled trials [RCTs], 3 prospective observations studies and 5 observational registries or databases) are included in the EAC evaluation report.
- 3.3 The procedural success rate in the CtE registry (85.9%) was at the lower end of the range of rates reported in the published literature (79.5% to 100%), however the definitions of success vary across the studies making a direct comparison difficult.
- 3.4 The in-hospital major complication rate (includes including death, complications requiring additional surgery, major bleed and myocardial infarction) of 8.2% was at the lower end of the published values which ranged from 3.1% to 27.8%. This wide range was probably due to differences in the definitions of major complications, and in the populations studied. The in-hospital mortality rate of 5.1% was at the higher end of the published 30 day mortality rates which ranged from 0% to 7.7%.
- 3.5 The immediate reduction in MR after the MitraClip procedure was consistent with the published literature. The deterioration in MR seen in some patients at 1 year in the CtE registry (with 24.2% of people having moderate-severe or severe MR compared with 6.7% immediately after the procedure) was also consistent with the majority of the published

literature, however, in 1 recent RCT (COAPT) and 1 observational study, 95% of people had absent, mild or mild-moderate MR 1 year after the MitraClip procedure. The results from the other medium-term outcomes (patient symptoms and quality of life, and major complications) was also consistent with the literature. It is worth noting however that comparisons of complications are limited due to issues with generalisability because studies have used different terminology and methodology, and were conducted in different populations.

- 3.6 The mortality rate at 1 year (12.7% for the linked dataset) was comparable to the published rates for similar patients, of between 6% and 25.8%.
- 3.7 The proportion of patients admitted urgently or as an emergency is poorly reported in the literature, making comparisons between the registry data and the literature difficult.
- 3.8 The CtE registry alone was unable to provide robust information on the impact of the MitraClip procedure on hospital readmission, or long-term outcomes. However, analysis of the linked data gave an all-cause hospital readmission rate of 176.1 per 100 person years and rate of 36.2 readmissions per 100 person years for reasons associated with heart failure. Limited data from published studies suggest cardiac readmissions are high in the first year (between 20% and 60%). with hospitalisation rates for heart failure of 35.8 and 48.7 per 100 person years in the COAPT and MITRA-FR RCTs, respectively. The published evidence also suggests that MitraClip may lose efficacy (in terms of MR reduction) at longer follow-up times (4 years and above).
- 3.9 The CtE registry does not allow comparison of outcomes between MitraClip and standard care because it did not include people who had standard care without MitraClip. The MITRA-FR and COAPT RCTs compared MitraClip to medical therapy alone in people with functional MR using similar primary outcomes. In the MITRA-FR trial MitraClip did not improve mortality or hospital admission rates at 1 year following the procedure when compared with medical management. The COAPT trial

showed that the MitraClip procedure was associated with fewer deaths and less hospital admissions 2 years after the procedure. This was consistent with data from comparative observational studies.

- 3.10 The reasons for the conflicting results between MITRA-FR and COAPT is not fully understood, however variations in the baseline characteristics of the patients and their responsiveness to other heart failure treatments, as well as procedural differences have been proposed. It should also be noted that the Kaplan–Meier survival curves in the COAPT trial only appear to diverge after 1 year. It will be interesting to see if a similar divergence between the MitraClip and medical therapy groups happens in the MITRA-FR trial over the 2 year follow-up period. NICE notes that the more pragmatic nature of the MITRA-FR study underlines the need for careful patient selection if the results of the COAPT study are to be achieved in clinical practice. Results from another observational study suggest that about half of patients with severe functional MR unable to tolerate surgery may be suitable for the MitraClip procedure.
- 3.11 NICE notes that neither the COAPT nor the MITRA-FR trial reported data on the efficacy and safety of MitraClip in people with degenerative MR. This group formed 40% of the CtE registry cohort.
- 3.12 Two further trials (Reshape-HF2 and MATTERHORN), also both recruiting patients with functional MR, are ongoing and may provide additional data on the efficacy and safety of MitraClip in the functional MR population. NICE is also aware of another trial (CLASP) in which patients with degenerative MR and determined to be at prohibitive risk for mitral valve surgery are being recruited. The trial will use a recently CE-marked device that works using a similar mode of action to MitraClip (PASCAL System; Edwards Lifesciences).

Cost-effectiveness evidence

- 3.13 The EAC conducted a review of the published evidence on the cost-effectiveness of MitraClip. Summaries of the 4 key publications are

included in the EAC evaluation report. Although the findings from these studies cannot be generalised directly to NHS England, they do provide evidence on the impact of the MitraClip procedure on hospitalisation rates and costs. They reported that MitraClip could save costs associated with hospital readmission due to congestive heart failure, but that these savings did not offset the procedural costs (most of which are associated with the device itself). The results from the *de novo* economic analysis of the CtE data is consistent with this finding.

Strengths and limitations

- 3.14 The registry had several strengths. It enrolled patients consecutively, reported important clinical as well as patient-related outcomes, and represented a pragmatic real-world cohort of patients receiving MitraClip as it might be performed in the NHS. Thus the external applicability of the registry to future practice is high, although improvements in the procedure protocol and a learning curve effect may ultimately lead to improved outcomes.
- 3.15 Following an initial disappointing response from centres in providing follow-up data, this improved considerably such that there was 111.2 person years follow-up available for analysis by the end of the project. Follow-up was particularly robust up to 1 year after the MitraClip procedure, with 79.4% of eligible patients having follow-up data at this time. The completion of individual data fields varied, but overall, data completeness was regarded as good.
- 3.16 Linkage of registry data to HES APC and ONS records, provided a more comprehensive estimate of mortality and additional mitral valve intervention event rates due to increased coverage and longer duration of follow-up (271.9 person years).
- 3.17 The linked dataset identified 15 additional deaths and 5 additional people requiring mitral valve interventions who had not been identified in the CtE registry. It also identified 3 patients who were admitted to hospital with a

diagnosis of infective endocarditis. No cases of infective endocarditis were identified in the CtE registry. By analysing these data in combination with the data directly reported from the registry, there is a high degree of confidence that the outcome data accurately reflects real clinical event rates.

3.18 The CtE registry had several limitations. It was a single-armed study therefore comparisons had to be made implicitly with results published in the literature. This had 2 limitations. Firstly, no statistical or quantitative comparisons could be made with the comparator of interest, which was conservative medical management. Secondly, some of the published literature was not directly comparable to the registry. Specifically, comparison of the CtE data with trial data was limited by differences in outcome terminology and measurement, and possible issues with generalisability of the population. Thus inferences of equivalence (or not) are subject to considerable uncertainty. Other specific and non-specific limitations with the registry include the following:

- Two of the key outcome measures were MR grade and symptoms of heart failure (NYHA class). Both of these can be considered as subjective outcomes, and may result in detection bias and performance bias, respectively.
- The registry was funded for a maximum follow-up of 2 years, meaning that data on long-term efficacy outcomes or complications were not available.
- Although data completeness was nearly 89% for the minimum data set, most patients did not reach the 2 year follow-up date because the procedures were carried out sequentially during the duration of the CtE scheme. Of the 187 patients with an implanted device, only 45 (28.3% of the total cohort) had a MitraClip device implanted and reached the second anniversary of their procedure during the data collection phase of the CtE scheme. Data was collected for 11 of these patients (24.4%) at 2 years. However, the issue with data completeness was substantially mitigated with the inclusion of

outcomes derived from the linked dataset.

- It is possible that the cohort of patients receiving treatment early in the project may not be representative of the overall cohort (for example, because the outcomes improved with the number of procedures carried out, that is, there was a learning effect).
- The analyses rely on complete reporting of all event data. Patients who are lost to follow-up are censored from the analysis of the registry data, but it is unclear if these are representative of the overall cohort. This is another important reason to undertake the data linkage.
- In addition, patients may have multiple events (excluding death), but the Kaplan-Meier protocol only analyses time to first event, meaning that if a minor event is followed by a major event, the latter will not be counted.
- Finally, the CtE registry study reported on a case mix of patients admitted electively or as urgent/emergency cases. Although these represented different cohorts with different patient characteristics, sample sizes (particularly in the latter cohort) were insufficient for the analyses to be reported separately for each group. Aggregate data has therefore generally been reported. There were similar issues with other defining patient characteristics (such as patient aetiology).

3.19 In conducting data linkage the following assumptions were made:

- The EAC assumed that the identifiers and matching process were correct for the 166 patient records that had a 'green flag' (that is, patients who had no conflicting data fields across their registry, HES APC and ONS mortality records).
- The proportion of patients with a 'red flag' (that is, patients who had conflicting data fields across their registry, HES APC and ONS records; 21/187 patients, 11.2%) was higher than would be expected in a well-characterised cohort. In excluding these patients, the EAC have assumed that the remaining 166 patients are i) representative of all those successfully implanted and ii) have had their data successfully linked.

- ONS is regarded as the gold standard for death reports, however there is a delay in some deaths appearing in the ONS mortality dataset due to a lack of death certification (that is, those under investigation). Therefore, the additional deaths recorded in the registry and confirmed in HES but not appearing in ONS were also included in the total number of deaths.
- Long-term follow-up in the registry was poor, therefore long-term analysis (following discharge from hospital) relied on HES/ONS data.
- Due to geographical limitations with the routine datasets (ONS only includes deaths registered in England and Wales and HES APC only includes NHS episodes of care in hospitals in England), it is possible that the estimated event rates are lower than the actual rates, due to incomplete data coverage.

3.20 Specific limitations in the economic analysis include the following:

- The analysis was based on a “before and after” design. While this allowed patients to act as their own controls, this design does not prove causality of the MitraClip procedure on the outcomes measured.
- The analysis used a novel approach to costing, the validity of which has not yet been extensively analysed.
- Admissions in the 1 year before the MitraClip procedure may include procedure work-ups which were conducted in an inpatient setting, however the EAC was unable to differentiate these in the HES extract. The consequence of this is that the true cost difference in admitted patient care between the year before and the year following MitraClip implantation will be smaller than that estimated by the analysis.
- The cost of the MitraClip procedure (ranging from £29,007 to £34,528 with a base case estimate of £32,912) was not included in this cost analysis. Therefore, the cost difference in admitted patient care between the year before and the year following MitraClip implantation is significantly overshadowed by the cost of the procedure itself.

- Costs only represent those accrued in admitted patient care. Other healthcare resources (such as outpatient, accident and emergency costs) were not included in the analysis.

Reflections from NICE

- 3.21 The CtE registry has demonstrated that for patients who survive the procedure and post-operative period, percutaneous mitral valve leaflet repair using MitraClip reduces both MR and the associated symptoms of heart failure in at least the short term.
- 3.22 The lack of long-term outcome data from the registry reflects the slow initial uptake of the CtE scheme which was 1 of the first such projects. The learning from this informed future schemes which now routinely include a 6 month feasibility phase. This ensures that procedures can be undertaken and data collected from the start of the scheme.
- 3.23 Ongoing data submission should be encouraged to assess longer term outcomes (>2 years) and ensure that patient selection methods continue to evolve in order to achieve patient benefits suggested by the COAPT RCT and the CtE scheme.
- 3.24 The registry captured information on the resources required to conduct the MitraClip procedure, enabling the cost of the procedure to be estimated. This information together with the quality of life data may be of use in any future cost-effectiveness studies.
- 3.25 The availability of a linked dataset combining registry, HES APC and ONS mortality data has improved the robustness of the analyses. By conducting data linkage the EAC were able to identify 15 additional deaths, 3 additional patients with a diagnosis of infective endocarditis and 5 additional mitral valve interventions occurring after the MitraClip implantation, which were not captured in the registry. Despite the identification of additional deaths and major complications, the outcomes and conclusions drawn from the registry were unchanged with the

analysis of the linked data because the duration of follow-up was increased, giving confidence in the original registry data.

- 3.26 The methodology of the data linkage was complex with an unpredictable timeline that was difficult to manage. The governance requirements for data linkage continue to develop therefore lessons from this project are unlikely to be directly transferrable to other projects but it is clear that the data linkage application process with NHS Digital should be started as early as possible. These are common challenges in the field of real world data and evidence, and sharing learning from individual projects like this is important when the use of observational data is becoming more widespread. The EAC and NICE have published the scientific learning from CtE schemes and plan to continue to do so. NICE is also a contributor to the EUnetHTA project which aims to improve the quality and relevance of real world data.

4 Equality considerations

- 4.1 No particular equality issues relating to people who have MR were identified in the CtE data or in the literature presented, although MR is more people aged over 75 years.

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Appendix: CtE project process and oversight

NHS England commissions CtE projects from NICE, and NICE manages the projects to a timescale, process and methods devised by NHS England. In June 2017, NHS England published a policy document governing these projects ([Methods: Commissioning through Evaluation](#)) but the majority of the MitraClip scheme was developed, conducted and concluded before this document was published. Generally, however, the process followed was similar to the currently published process.

A Cardiology CtE Steering Group was established by NHS England to oversee the project and involved clinical leads and other stakeholders. NICE and the EAC worked closely with the steering group and with the MitraClip Individual Technology Group, in the design of the MitraClip registry and to ensure all parties were aware of data collection requirements and to reinforce clinical ownership of the project.

NICE is accountable to Ann Jarvis, Programme Director (Clinical Strategy) for Specialised Commissioning at NHS England, for delivery of the CtE schemes. For this scheme, NICE reported on a quarterly basis via standard reports and monitoring meetings with NHS England.

The National Institute for Cardiovascular Outcomes Research (NICOR) was contracted by Newcastle and York EAC to design and host the on-line registry for MitraClip procedures, to provide a project management function to promote data entry quality and completeness by commissioned CtE centres, and to link registry data with HES and ONS mortality datasets.