NHS England

Evidence review: Clinical and Cost-effectiveness and Adverse Events associated with percutaneous mitral valve leaflet repair for severe degenerative mitral regurgitation (MitraClip)

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Contents

1. Introduction 3
2. Summary of results 7
3. Methodology 8
4. Results 10
5. Discussion 21
6. Conclusion 22
7.a. Evidence Summary Table for Clinical studies (single-armed). 24
7.b. Evidence Summary Table for Clinical studies (comparative). 40
7.c. Evidence Summary Table for Economic studies. 44
8. Grade of evidence tables 47
9. Literature Search Terms 54
10. Search Strategy 55
11. Evidence selection 60
12. References 62
Appendix A: Full Search Strategies 69
Appendix B: Quality assessment of included economic studies 83

1. Introduction

Mitral regurgitation

The mitral valve is a unidirectional bicuspid valve situated between the left atrium and ventricle, which allows for the one way flow of blood between these chambers. When the left ventricle contracts during systole, blood passes through the aortic valve and into the aorta and systemic circulation. However, if the mitral valve becomes dysfunctional, mitral valve regurgitation (MR) may occur with blood flowing in a retrograde manner from the ventricle back into the atrium. If the volume of blood pumped into the left atrium is large, this will reduce the efficiency of the heart as a pump and will ultimately lead to heart failure over time. In turn, heart failure may worsen mitral valve functionality.

The prevalence of MR in western populations has been estimated at 2%, primarily affecting older people (Freed et al., 1999). A survey has found that mitral valve dysfunction is the most common reason for surgical valve replacement (Iung et al., 2003). If left surgically untreated, the prognosis of chronic MR is poor, with a 10-year mortality rate of 43% (± 7% standard deviation [SD]) of which 33% (± 7%) is associated with cardiac death (Enriquez-Sarano and Tajik, 1997). Furthermore, MR is associated with the development of a range of morbidities, such as congestive heart failure, atrial fibrillation, thromboembolism and endocarditis (Enriquez-Sarano and Tajik, 1997). Alternatively, other cardiac diseases such as myocardial infarction and heart failure can cause MR. Thus, people with established MR are frequently clinically unwell, suffering from several comorbidities.

Functional and degenerative mitral regurgitation

There are two underlying aetiologies of MR; these are degenerative MR (DMR, sometimes referred to as primary, or structural, MR), and functional MR (FMR, sometimes referred to as secondary MR).

In FMR, the valve leaflets and chordae are structurally normal. Instead, MR results from geometrical distortion of the subvalvular apparatus, secondary to left ventricular enlargement and remodelling due to idiopathic cardiomyopathy, or weakening of the cardiac walls following coronary artery disease (sometimes referred to as ischaemic MR). Thus, functional MR is not primarily considered to be a valvular disease *per se*, but a complication of cardiomyopathic or ischaemic heart disease due to left ventricular dysfunction (Lancellotti et al., 2010). FMR is usually treated with medication (Goel et al., 2014), with the underlying cause of FMR being ameliorated with conservative medical management. Less commonly, the condition may be treated directly using surgical techniques such as undersized annuloplasty (Nickenig et al., 2016b).

In contrast to FMR, DMR is primarily a mechanical problem, characterised by abnormality of the mitral apparatus. Medical therapy can only attempt to control the consequences of a structural abnormality. Compared with FMR, the role of medical therapy is limited, and the only curative management option for DMR is surgical (Adams et al., 2010). However many patients are not offered surgery based on their estimated high surgical risk of mortality. Occasionally, DMR and FMR are found to co-exist, and these patients have a poor prognosis. In these circumstances, it is recommended the disorder is managed according to the predominant aetiology (Joint Task Force on the Management of Valvular Heart Disease

of the European Society of et al., 2012). Because of the lack of viable medical management alternative, the focus of this review is on the use of percutaneous edge to edge repair (MitraClip) in patients with DMR who are considered to be at high risk of surgery. This includes patients with mixed aetiologies.

Degenerative mitral valve regurgitation is a progressive disease, which may be initially asymptomatic (and identified because of the finding of a murmur) before disease progression manifests itself in symptoms (Enriquez-Sarano, 2002). Symptoms include palpitations, dyspnoea, fatigue (particularly relating to exercise) and oedema (swollen feet and ankles). Mitral valve regurgitation is also associated with a diminished quality of life.

Assessment of DMR (MR grade and NYHA class)

Mitral valve regurgitation is typically first identified through clinical history and examination (auscultation). Once suspected, the presence of MR is usually diagnosed through the use of echocardiography. The consequences of mitral regurgitation on ventricular function are assessed by measuring left ventricular size and ejection fraction. Left atrial volume, systolic pulmonary artery pressure, tricuspid regurgitation and annular size and right ventricular function are important additional parameters (Baumgartner et al., 2017).

In order to determine the appropriate management strategy, it is necessary to classify the severity of DMR. Conventionally, DMR is classified according to four severity grades, ranging from 1+ (minor regurgitation) to 4+ (severe regurgitation). There are several classifications of MR (for example, mild, moderate, severe) using a number of different clinical and echocardiographic criteria. One classification system uses various echo-derived criteria including for example, regurgitant volume (or regurgitant fraction) to grade people (into grades of none 1+, 2+, 3+, or 4+). Imaging modalities used are typically echocardiography, although angiography and Magnetic Resonance Imaging (MRI) may be used less commonly (Apostolakis and Baikoussis, 2009). Classification of MR severity is also an important outcome used in clinical research studies and reported in this review.

As well as severity of physical regurgitation, severity of symptoms may be classified. Most commonly, the degree of dyspnoea present is classified using the New York Heart Association (NYHA) classification system, where class I represents no limitation of physical activity, and class IV represents inability to conduct any activity without physical discomfort. Despite limitations in class definition, the NYHA system is a useful tool to assess patient health and prognosis (Raphael et al., 2007), and is also commonly used in research studies.

Management

For patients with DMR, surgical repair or valve replacement is the preferred option in patients who are well enough to tolerate it (Consensus of opinion of the experts and/or small studies, retrospective studies, registries), which has been estimated to be up to 95% of the indicated population (Tesler et al., 2009). In the US, surgical repair is preferred to valve replacement in 70% of cases (Tesler et al., 2009) and is the treatment of choice provided a durable valve is achievable (Baumgartner et al., 2017). For the remaining 5% of patients, there is no viable treatment for DMR other than leaflet to leaflet repair using a

percutaneous approach.

Risk assessment for surgery

Degenerative MR often presents in older, frail patients with multiple comorbidities. These patients have an increased risk of mortality and serious complications with surgery, which may make this management option risky or inappropriate. In order to assess the risk of cardiac surgery (principally coronary artery bypass graft [CABG], but applicable to all invasive cardiac surgery), the EuroSCORE risk stratification clinical decision tool was developed and validated in 1999 (Nashef et al., 1999). This algorithm stratifies patients into low, medium, and high risk groups through an additive calculation of risk factor.

The EuroSCORE tool has since been modified to include a logistic EuroSCORE version, which takes into account that not all the risk factors are independent. The latest version of EuroSCORE is known as EuroSCORE II and is an iterative improvement on the previous algorithms, which tended to overestimate surgical risk (Noyez et al., 2012). The latest EuroSCORE calculators can be found at www.euroscore.org. In the US, the STS (Society of Thoracic Surgeons) Adult Cardiac Surgery Risk Calculator performs a similar role with the advantage that it also discriminates by cardiac condition and mortality or morbidity risk (available at http://riskcalc.sts.org/stswebriskcalc/#/).

Percutaneous mitral valve leaflet repair (MitraClip)

Open surgery for MR (repair or replacement) involves general anaesthesia combined with heart and lung bypass, which, as discussed, some patients cannot tolerate. In the 2000s, research on percutaneous edge-to-edge mitral valve repair techniques led to the development of MitraClip. MitraClip is a catheter-based system which reproduces the Alfieri method of mitral valve repair, by bringing the two mitral valve leaflets together with a clip to create a “double orifice” valve. This reduces, but does not completely abolish, the leak through the valve. However, because the procedure is lower risk than conventional surgery, it provides a treatment option that is otherwise not available to high-risk patients.

MitraClip received a CE mark in 2008 and, to date, over 50,000 patients globally have undergone percutaneous mitral valve repair with the MitraClip system (Abbott, 2017). MitraClip is an option in patients with DMR who meet the anatomical eligibility criteria of coaptation length, coaptation depth, flail gap, and flail width (Abbott, 2017). The MitraClip device is a 4 mm-wide cobalt-chromium implant with two arms that are opened and closed with the use of the bespoke delivery-system. The procedure is performed under general anaesthesia with the use of TOE guidance and the optional use of fluoroscopy (operator dependent, contrast agent may not be required). Access is provided through the femoral vein and an atrial trans-septal puncture is performed to reach the delivery site.

The device is steered until it is aligned over the origin of the regurgitant jet and advanced into the left ventricle. The clip is guided directly above the leaflets by 3D-echocardiography, and the orientation of the clip arms is performed perpendicular to the line of coaptation. The device is lowered through the valve into the left ventricle to load the leaflets on the clip arms. The grippers fix the leaflets to the clip arms, and then the arms are closed and the clip can be released from the delivery system (Abbott, 2017). Adequate reduction of MR to a grade of 2+ or less is assessed with the use of echocardiography. If the reduction in mitral

regurgitation is inadequate with one device, the device may be removed or a second device placed. Post-operatively, patients are treated with anti-platelet therapy post-discharge (combined aspirin and clopidogrel for 6 months in the EVEREST studies) (Feldman et al., 2009).

Objectives of review

In recent years, there has been a large increase in the volume of published literature on MitraClip, mostly restricted to observational studies. Only one randomised controlled trial (RCT) has been published to date. This was the EVEREST II RCT which was performed in a mixed aetiology of MR patients who were well enough to receive surgery (Feldman et al., 2011).

Despite the fact that, in contrast to FMR, there is a recognised surgical alternative to Mitraclip therapy for DMR, there has been relatively little literature published specifically on the use of MitraClip in this specific condition. The aim of this review was to identify and analyse disaggregated data and outcomes specifically in patients with degenerative aetiology. The following three questions have been addressed:

This evidence review will address the following primary research questions:

1. What is the clinical effectiveness of the percutaneous mitral valve leaflet repair to treat mitral regurgitation in patients with severe, symptomatic, degenerative mitral regurgitation (grade 3+and 4+ patients) assessed as at high risk for surgery?

- Are there any specific factors, associated with superior outcomes, which would assist selection of patients for maximal clinical effectiveness?

2. What is the safety profile of the percutaneous mitral valve leaflet repair to treat mitral regurgitation) in patients with severe, symptomatic, degenerative mitral regurgitation (grade 3+ and 4+ patients) assessed at high risk for surgery?

- Are there any specific factors, associated with adverse events and complications, which would assist selection of patients?

3. What is the cost effectiveness of the percutaneous mitral valve leaflet repair to treat mitral regurgitation in patients with severe, symptomatic, degenerative mitral regurgitation (grade 3+ and 4+ patients) assessed at high risk for surgery?

- Are there any specific factors, associated with superior outcomes, that would assist selection of patients for maximal cost effectiveness?

2. Summary of results

Fifteen studies (reported in 37 publications) met the predefined inclusion criteria for clinical effectiveness and the safety profile of MitraClip, as well as healthcare resource use. Twelve of these were single-armed observational studies by (primary study cited only) (Tay et al., 2016, Sorajja et al., 2017b, Rudolph et al., 2013, Reichenspurner et al., 2013, Rahhab et al., 2017, Nickenig et al., 2016a, Lim et al., 2014, Geis et al., 2015, Estevez-Loureiro et al., 2013a, Braun et al., 2014, Baldus et al., 2012, Whitlow et al., 2012). Three comparative studies were identified (Whitlow et al., 2012, Velazquez et al., 2015, Swaans et al., 2014). No randomised controlled studies were identified that met the inclusion criteria.

Two further studies informed the economic analysis (Vemulapalli et al., 2017, Mealing et al., 2013).

Clinical effectiveness of MitraClip in DMR patients

The principal outcomes in scope that pertained to clinical effectiveness were reduction in MR grade, improvements in NYHA class, and mortality rate.

There was unequivocal evidence (classed as Grade A) that the MitraClip procedure improved echocardiographic outcomes compared with baseline, as measured by reduction in MR grade. Eight studies reported a large statistically and clinically significant reduction in MR grade, and this improvement appeared to persist for at least 12 months. This was mirrored by parallel improvements in symptoms (as measured by NYHA class, N = 10 studies) with one study additionally reporting a significant improvement in physical and mental health-related quality of life (HR-QoL).

Longer-term mortality was an important outcome that was reported in seven studies (mortality or survival rates at 1 year or more). At 1 year, mortality ranged from 16.3% to 24.7%. Comparative mortality that was measured in three studies, each using retrospective controls, reported a significantly higher death rate in patients receiving conventional medical management (CMM) compared with MitraClip (in a mixed aetiology case mix of patients). However, there were methodological limitations with these studies. The relatively high mortality rate in these DMR patients highlights the high levels of comorbidity in this patient group.

Procedural safety of MitraClip in DMR patients

The procedural and/or technical success rate of MitraClip was reported in all the single-armed observational studies. Direct comparisons between studies are made difficult due to use of different definitions and terminology for “success”; however overall the success rate appears to be around 93% in patients with DMR at high risk of surgery. Although the peri-procedural mortality rate was low, 30-day mortality rate was reported as higher (6.3% in the study rated as being of the highest methodologically quality). These rates were considerably lower than would be predicted using surgical prediction rules such as EuroSCORE or STS (Society of Thoracic surgeons).

Total procedural adverse event rates were reported as being around 15% in three studies, although meaningful synthesis of data was not possible due to different definitions and low

event rates in this restricted DMR population.

Healthcare resource use associated with MitraClip in DMR patients

Data on healthcare resource use were poorly reported by the studies. One study, reported that treatment with MitraClip was associated with a significant decrease in hospital admissions for heart failure. Most patients were discharged directly back to a home setting after a length of hospital stay of 2 to 3 days.

Economic evidence

One cost utility analysis was identified which employed clinical inputs from a mixed aetiology population considered to be at high risk of surgery and a retrospective control group receiving medical management (EVEREST II HRS study). The study was from the perspective of the NHS, and UK relevant costs and utilities were used. It reported that MitraClip was likely to be cost effective at a time horizon of 5 or 10 years with an incremental cost-effectiveness ratio (ICER) of £22,200 and £14,800 per quality-adjusted life-year (QALY) at 5 and 10 years respectively. Results of this study should be treated with caution because of the extrapolated time horizon used, and the relatively low quality (and low numbers of patients enrolled) of the study informing clinical effectiveness.

Evidence from a "before and after" US study found MitraClip was cost-saving due to reductions in admission for heart failure. However, this study had poor generalisability and did not include device or procedure cost, which are substantial.

Factors that may aid patient selection

There was limited evidence that lower age, higher left ventricular ejection fraction, absence of severe tricuspid regurgitation, and the absence of significant renal or lung disease were associated with better prognosis following treatment with MitraClip in patients with DMR.

Limitations of review

This review focussed on patients with DMR who were at high risk from surgery, which was poorly reported in the literature base, with most reported populations being comprised of patients with FMR or of mixed aetiologies. Partly because of this, the quality of evidence was poor, and mainly limited to single-armed studies. Although it was possible to extract disaggregated data on DMR patients, comparative analysis (with CMM or surgery) was generally not possible. In the future, good, high-quality experimental studies, preferably in the form of RCTs, are necessary to determine the clinical and economic effectiveness of MitraClip in this population compared with other treatment modalities.

3. Methodology

NHS England's Policy Working Group prepared Population, Intervention, Comparison and Outcomes (PICO) definitions for this review (see section 9 for PICO and inclusion and exclusion criteria).

Search strategy
The following bibliographic databases were searched from inception to March 2018: MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), Cochrane Database of Systematic Reviews (CDSR), NHS EED, CEA Registry, CEA Registry, National Guidelines Clearinghouse, Guidelines International Network: International Guideline Library, National Institute for Health and Care Excellence. The reference lists of relevant systematic reviews and guidelines published in the last three years were also checked for any eligible studies that might have been missed by the database searches.

Study selection and extraction
Two independent reviewers screened the titles and abstracts and any discrepancies were arbitrated by a third.

The following pragmatic refinements (*in italics*) were made to the inclusion and exclusion criteria in section 9, after first screening of titles and abstracts:

Patients/Population

Studies that included patients with mixed aetiology of mitral MR were only included *if they had ≥ 500 subjects*, or if data were reported separately for the degenerative (DMR) population of interest to NHS England and the DMR cohort size was n ≥ 50 subjects.

Comparison

Single arm observational studies *were included if they reported specifically in DMR patients (n ≥ 50) or mixed aetiology (n ≥ 500)*.

Study design inclusion criteria

Single armed observational studies where n ≥ 500, *or where disaggregated DMR data reported (n ≥ 50)*

One reviewer screened the full texts of potentially relevant full publications meeting the review's eligibility criteria and a second reviewer checked the reasons for exclusion of all rejected full texts. The list of selected studies was submitted to NHS England for review and these were subsequently accepted.

One reviewer extracted data from all selected studies and recorded in evidence summary tables. Studies were quality assessed using the NHS England guidance for conducting evidence reviews (see sections 7 and 8 below). A second reviewer checked 45% of the documents, all of which were full publications.

Synthesis and analysis
The data were synthesised separately for each of the outcomes using a narrative summary

and tables (see sections 4 and 8 below).

4. Results

Identification of studies

At the first stage of this evidence review, 1639 titles and abstracts were screened. From these, 121 records were identified as potentially relevant and full publications were obtained and screened for relevance. Fifteen studies (presented in 37 publications) met the inclusion criteria for clinical effectiveness and adverse events and two economic studies met the inclusion criteria for the cost-effectiveness review. Eighty two publications were excluded.

Four systematic reviews published in the last three years were identified and references checked, but no additional studies of relevance were identified.

Results for Question One

Part one: "What is the clinical effectiveness of the percutaneous mitral valve leaflet repair [MitraClip] to treat mitral regurgitation in patients with severe, symptomatic, degenerative mitral regurgitation (grade 3+and 4+ patients) assessed as at high risk for surgery?"

Outcomes that informed the clinical effectiveness of the MitraClip procedure were reduction in MR grades, reductions in deaths, proportion of deaths at follow up, improvements in NYHA class, changes to health-related quality of life (HR-QoL), and impact on admissions for heart failure. All of these outcomes were regarded as critical to decision making and were measured after a discrete interval of follow up.

All outcomes of studies were specific to a population with DMR at high risk from surgery with the exception of the TRAMI study (Puls et al., 2014) and the "Netherlands registry" (Rahhab et al., 2017) which reported a mixed population but predominantly with FMR, and the three identified comparative studies (Whitlow et al., 2012, Velazquez et al., 2015, Swaans et al., 2014).

Reduction in MR grade

Reduction in MR grade was a key echocardiographic outcome and intermediate measurement of clinical efficacy. This outcome was reported as longitudinal data (comparing baseline MR grade with later follow up times) in eight studies. Studies reported this outcome used recognised grades ranging from MR grade 1+ (absent or negligible) to MR grade 4+ (severe regurgitation), or a mild, moderate/severe, and severe classification. Studies either reported the proportion of patients in each grade, the mean population grade, or dichotomised the results (e.g.. MR grade ≤ 2+ and MR ≥ 3+). Although these outcomes were not always directly comparable, they did allow for qualitative pooling of results. Follow up in these studies ranged from hospital discharge to 12 months post-procedure.

All the studies reported large and clinically significant reductions in MR grade associated with treatment with MitraClip. In all cases where it was reported, improvements in MR were statistically significant. In general, MR grade at follow up improved by 2 grades or more at follow up in around three quarters of the patients treated with MitraClip. One large study registry reported that 75% of DMR patients had a MR grade of 2 or less following treatment with MitraClip (Reichenspurner et al., 2013). All the studies showed that few, if any, patients had severe MR (grade 4+) following treatment with MitraClip.

Summary: There is unequivocal evidence that treatment with MitraClip is associated with a statistically and clinically significant reduction in MR grade.
Grade of Evidence: A

Reduction in deaths
Reduction in deaths requires analysis with a suitable comparator. Three studies were identified that reported survival outcomes in patients receiving MitraClip with patients receiving predominantly CMM (Whitlow et al., 2012, Velazquez et al., 2015) or both CMM and surgery (Swaans et al., 2014). These studies enrolled patients considered to be at high risk of surgery but they did not have specifically DMR aetiology, hence the applicability is indirect.

One study (Whitlow et al., 2012) reported that the 12 month survival rate with MitraClip (75.4%) was significantly better than with CMM (55.3%). One study reported that MitraClip was associated with significantly reduced mortality at 12 months (optimally matched cohorts, hazard ratio [HR] 0.66, 95% CI 0.45 to 0.99) (Velazquez et al., 2015). One study did not find a difference in 1, 2, or 3 year survival rates with MitraClip compared with surgery, but reported that MitraClip was superior to CMM (HR 0.41, 95% CI 0.22 to 0.78, p = 0.006) (Swaans et al., 2014).

Summary: Evidence from three comparative observational studies suggests that, in a case mix of patients with FMR and DMR, treatment with MitraClip reduces mortality compared with CMM, but not compared with surgery (repair or replacement).
Grade of Evidence: C

Proportion of deaths at follow up
Seven single-armed studies reported mortality or survival rates, with six of these being exclusively in patients with DMR. As there were no comparator data, these are expressed as simple proportions at discrete follow up times, or were derived using Kaplan-Meier analysis (12 months).

The mortality at 12 months ranged from 16.3% to 24.7%. One study which recorded mortality at 2 years reported a rate of 33.6% at this time point, more than double that observed after 12 months (Rudolph et al., 2013).

Summary: The mortality rate of patients 12 months after treatment with MitraClip appears to be around 20%.

Grade of Evidence: A

Improvements in symptoms: NYHA class

The NYHA classification system is a measure of the level of dyspnoea (breathing difficulty), which is the principal symptom associated with MR. It is classed from I (no symptoms) to IV (severe symptoms). Ten studies, eight exclusive to patients with DMR, reported longitudinal NYHA class data at baseline or at least one follow up time point. This outcome was typically reported in terms of proportions of patients in each class, but also as reductions in class, and dichotomous outcomes with merged classes (e.g. NYHA class ≤ 2 or ≥ 3). Thus a qualitative description of results is given. Follow up ranged from post-implant to 12 months.

There was unequivocal evidence from the combined studies that NYHA class was associated with important clinical reductions in NYHA class. Seven studies reported that the proportion of patients in NYHA class I or II at follow up ranged from 58% to 91% (Tay et al., 2016, Seeger et al., 2017, Reichenspurner et al., 2013, Nickenig et al., 2014, Lim et al., 2014, Estevez-Loureiro et al., 2013b, Baldus et al., 2012), with the median value being 83%. Two studies reported a reduction of NYHA class or 2 or more in 91.1% (Braun et al., 2014) and 84% (Rahhab et al., 2017) of patients. The mean reduction in NYHA class was reported as 2.0 ± 0.3 (SD, $p < 0.001$) at 12 months in one study (Geis et al., 2018). There was no evidence of deterioration over time following treatment with MitraClip, although follow up was relatively short in all the studies.

Summary: There is unequivocal evidence from observational studies that treatment with MitraClip in patients with DMR results in statistically and clinically significant improvements in NYHA class. This would be of important benefit to the treated patient.

Grade of Evidence: A

Health related quality of life (HR-QoL)

One study reported longitudinal HR-QoL data in patients with DMR receiving MitraClip treatment (Lim et al., 2014). The study used the SF-36 patient reported survey to measure HR-QoL. There was a statistically significant improvement in physical health (physical summary 32.0 [8.7 SD] at baseline, 39.2 [10.5] at 12 months, $p < 0.0001$) and mental health (mental summary 46.1 [12.5] at baseline, 51.8 [10.5] at 12 months, $p < 0.0001$). There were significant improvement in QoL in all 8 individual domains and nearly all time-points compared with baseline.

Summary: There is directly applicable evidence from one observational study that treatment with MitraClip improves both mental and physical HR-QoL for up to 12 months compared with baseline in patients with DMR.

Grade of Evidence: A

Impact on admissions for heart failure

Deteriorating MR in patients with degenerative disease leads to progressive heart failure, thus readmission to hospital for heart failure can be considered a surrogate

outcome for clinical effectiveness (as well as having an important economic impact on healthcare resources). Three studies reported this outcome exclusively in patients with DMR.

Two studies reported hospital readmission rates for heart failure at approximately 12 months. The large TVT registry reported a rate of 20.5% (Sorajja et al., 2017a) whereas a smaller observational study reported a higher rate of 45% in successfully treated patients (Rudolph et al., 2013). The study by Lim et al. (2014), which enrolled high-risk DMR patients from the EVEREST II studies, reported that the rate of admission for heart failure before MitraClip treatment was 0.67 (95% CI 0.54 to 0.83) per patient year. Following treatment for MitraClip, this reduced to 0.18 (95% CI 0.11 to 0.28) per person year. This was a relative reduction of 73% and was statistically significant ($p < 0.0001$).

Summary: Evidence from a large registry in the US reported, in this setting, that the rate of rehospitalisation for heart failure is 20.5% in the first year. Evidence from an observational study suggests that the rate of readmission for heart failure decreases significantly following treatment with MitraClip.
Grade of Evidence: A

Part two: "Are there any specific factors, associated with superior outcomes, which would assist selection of patients for maximal clinical effectiveness?"

The population relevant to this review has been defined *a priori* as being patients with DMR who are at high risk of surgery. Thus, this question asks whether any subgroups of this population, in terms of baseline characteristics that could be reasonably diagnosed or measured prior to MitraClip treatment, are associated with improved outcomes pertinent to the clinical effectiveness of the intervention. As this is effectively subgroup analysis of what itself is a subgroup, only limited data were identified.

Studies excluded from analysis
Several studies in patients with MR of mixed aetiology have reported extensive subgroup analysis. For instance, the TRAMI registry, included in this review, has published subgroup analyses on cardiac comorbidities (Schwencke et al., 2017), tricuspid valve regurgitation (Kalbacher et al., 2017), atrial fibrillation (Jabs et al., 2017), previous aortic valve replacement (D'Ancona et al., 2017), baseline characteristics (Schueler et al., 2016), non-cardiac comorbidities (Zuern et al., 2015), surgical risk (Wiebe et al., 2014), criticality of illness (Rudolph et al., 2014), and age (Schillinger et al., 2013). However, as this study was conducted in a population which were predominantly of FMR aetiology, these analyses were not within the scope of this question.

One study was identified that did provide subgroup analysis in an exclusively DMR population. The analysis of high risk DMR patients from the EVEREST II studies (Lim et al., 2014) reported subgroup analysis on clinical outcomes in patients stratified by their MR grade subsequent to MitraClip intervention. However, as this is

by definition determined post-procedurally, it cannot be used to guide suitability for MitraClip selection.

Studies included for analysis

Four of the selected studies were identified as reporting relevant data to answer this question.

The ACCESS-EU study (n = 567) reported disaggregated data on patients with DMR (n = 117) (Reichenspurner et al., 2013). However, a primary aim of this study was to compare patients at high risk of surgery with low risk patients. Overall, the cohort was considered to be at high risk of surgery (mean logistic EuroSCORE 15.5 ± 13.7 [SD]). These patients were then stratified to a high risk group (*logistic EuroSCORE ≥ 20*, n = 33, mean logistic EuroSCORE 22.1 ± 11.5) and a low risk group (*logistic EuroSCORE < 20*, n = 84, mean logistic EuroSCORE 8.6 ± 5.1), and clinical outcomes from these groups were compared.

As expected there were significant differences in the baseline characteristics (in addition to logistic EuroSCORE) including age (greater in high risk group), presence of congestive heart failure (greater in high risk group), NYHA class (more severe in higher risk group), and left ventricular dimensions (enlarged heart). However, there was no significant differences reported between the subgroups in MR grade (p = 0.76) or NYHA class at 12 months follow up. The mortality rate at 12 months was 24.2% in the high risk cohort compared with 14.3% in low risk cohort. This difference was not significant (p = 0.51); however, this study was likely to be underpowered with respect to this outcome.

The TVT registry (Sorajja et al., 2017a) analysed data on 2952 patients, 94.8% of whom had DMR or mixed MR aetiology. This study reported that the presence and severity of tricuspid regurgitation was associated with excess mortality, with patients with severe tricuspid regurgitation having a significantly greater risk of death after 12 months compared with those with moderate or mild/no tricuspid regurgitation. Further subgroup analysis reported that increased age (HR 1.13, 95% CI 1.04 to 1.24, p = 0.005); left ventricular ejection fraction (HR 0.93, 95% CI 0.89 to 0.96, p = 0.0001); renal dialysis (HR 2.19; 95% CI 1.28 to 3.74, p = 0.004); moderate or severe lung disease (HR 1.36, 95% CI 1.06 to 1.74, p < 0.02), and residual MR were significantly associated with 12 month mortality. Similarly, age (HR per 5 years 1.08; 95% CI 1.01 to 1.15; p = 0.02); renal dialysis (HR 2.09; 95% CI 1.37 to 3.28, p = 0.001), left ventricular ejection fraction (HR per 5% 0.92, 95% CI 0.88 to 0.95, p = 0.001), moderate or severe lung disease (HR 1.28, 95% CI 1.05 to 1.58, p < 0.02), and post-procedural residual MR were significantly associated with the combined endpoint of 12 month mortality and hospitalisation for heart failure. All these parameters, with the exception of post-procedural MR, could be used to guide patient selection for MitraClip.

The aim of one observational study (Estevez-Loureiro et al., 2013b) was to compare central DMR (n = 49) with non-central DMR (n = 30). No significant differences were reported any in patient characteristics with the exception of the distance of vena

contracta (6.9 mm for central DMR compared with 8.5 mm for non-central DMR, p = 0.039). No significant differences were found in any of the clinical outcomes, including MR grade, NYHA class, and mortality at 12 months.

A small prospective observational study (Rudolph et al., 2013) performed subgroup analysis in patients with DMR, but no significant differences in clinical outcomes were reported.

Summary: There is limited evidence the following factors may be associated with *improved* outcomes (reduced 12 month mortality and reduced combined mortality and readmission for heart failure) for patients with DMR receiving MitraClip (**Grade of evidence**):

- Lower age: **B**
- Not receiving renal dialysis (reduced 12 month mortality and readmission for heart failure): **B**
- Not having moderate or severe lung disease: **B**
- Higher left ventricular ejection fraction: **B**
- Absence of severe tricuspid valve regurgitation: **B**

There is limited evidence the following factors do not affect clinical outcomes in patients with DMR receiving MitraClip:

- Surgical risk as measured by logistic EuroSCORE: **B**
- Central or non-central DMR: **B**

Results for Question Two

Part one: "What is the safety profile of the percutaneous mitral valve leaflet repair to treat mitral regurgitation) in patients with severe, symptomatic, degenerative mitral regurgitation (grade 3+ and 4+ patients) assessed at high risk for surgery?"

The outcomes relevant to this question refer to peri-procedural and 30-day endpoints, namely procedural complications and clinical outcomes occurring within 30 days post-procedure (regarded as critical to decision making). Complication and adverse event rates have been limited to reporting of mortality and aggregate measures, because small patient samples and low event rates on more granular data (i.e. outcomes in DMR patients) limited meaningful analysis. However, these are reported in individual studies in Table 7a. Additionally, procedural success has been included as this outcome was widely reported in the included literature, and essentially reflects the inverse of serious complications.

Procedural and technical success rate

All 12 of the single-armed studies reported a procedural or technical success rate, with 10 of these being exclusively in patients with DMR. All the results reflected single measurements calculated immediately or soon after the procedure. However, the definitions of these differed between studies and were often poorly defined in the

publications. Some outcomes of success included measurement of MR with success requiring significant reduction in this. Other measurements only reflected successful clip placement without serious adverse events.

Values ranged from “an overall success rate” of 88% (Rudolph et al., 2011), to a “procedural success rate” of 97% (Baldus et al., 2012) (the latter value being in a mixed aetiology population). One study, the TVT registry, that was performed in a case mix with around 95% of patients having DMR or mixed aetiology, had a particularly large sample size (more than all other studies combined, n = 2952) and clearly defined the success rate (Sorajja et al., 2017a). This study reported success rates of 91.8% (post-implant MR grade ≤ 2, no mortality, and no cardiac surgery) and 60.9% (post-implant MR grade 1, no mortality, and no cardiac surgery). The mean and median unweighted average success rate of all the studies were both 93%. This was unchanged when the two studies with mixed aetiologies were excluded.

Summary: The “success rate” of the MitraClip procedure (loosely speaking meaning successful clip attachment without serious adverse events) in patients with DMR at high risk of surgery was about 93%.
Grade of Evidence: A

Procedural and 30 day mortality rate
Ten studies, eight of which were exclusively in DMR, reported this outcome. Two studies reported the procedural or peri-procedural mortality rate, three studies reported the in-hospital mortality rate, and five studies reported the 30-day mortality rate.

The peri-procedural death rate was reported as 0.3% in a large retrospective study of mixed aetiology (Rahhab et al., 2017) and as 1.2% in a smaller prospective study of DMR patients (Estevez-Loureiro et al., 2013b). The in-hospital death rate was reported as 2.7% in the large TVT registry of predominantly DMR aetiology (Sorajja et al., 2017a), 2.4% in the TRAMI registry of predominantly FMR aetiology (Baldus et al., 2012), and 4.9% in DMR patients of the Pilot European Sentinel Registry (Nickenig et al., 2014). The 30-day mortality rate was reported as 2.0%, 3.8% and 6.7% in three prospective observational studies of DMR patients (Seeburger et al., 2014, Geis et al., 2018, Tay et al., 2016). The two observational studies reporting this outcome, that were considered to be of higher quality, reported 30-day rates of 6.0% (Reichenspurner et al., 2013) and 6.3% (Lim et al., 2014) and are considered more representative of the indicated population.

Summary: The peri-procedural mortality rate associated with MitraClip deployment are low, but increase throughout the term of hospital stay. Evidence from the most robust observational studies suggest that the 30-day mortality rate is around 6%.
Grade of Evidence: A

Procedural and 30 day adverse event rates
Five studies, four of which were exclusively in DMR patients, reported aggregate

adverse event rates. These outcomes were not comparable because of different definitions, inclusions, and timeframes.

The ACCESS-EU study (Reichenspurner et al., 2013) reported a "total" adverse event rate at 30 days of 14.3%, which was similar to the "all complication" rate of 12.6% reported by another observational study of DMR patients (Estevez-Loureiro et al., 2013b), and "major adverse event" of 14.7% (Tay et al., 2016). The study by Braun et al, (2014) reported 16.7% of procedures were "unsuccessful" (Braun et al., 2014). The TRAMI registry, which was predominantly in FMR patients reported a 30-day MACCE (major adverse cardiac and cerebrovascular events) rate of 3.1% (Puls et al., 2016). All six reported events in this study were strokes.

Summary: Aggregate data for complications of adverse events are not comparable between studies, but vary between 3.1% and 16.7% in those that reported it.
Grade of Evidence: A

Part two: "Are there any specific factors, associated with adverse events and complications, which would assist selection of patients?"

As discussed on question 1, subgroup analysis of the DMR cohort was limited in the selected studies with respect to these outcomes.

The ACCESS-EU registry selectively reported on DMR patients in one published study, which focussed on a comparison between patients with DMR who were considered to be at (relatively) high or low risk from surgery (Reichenspurner et al., 2013). The study analysed differences in 30-day outcome data in these sub-cohorts, but found no significant differences. However, the study was probably underpowered to detect differences in these outcomes.

One prospective study compared procedural adverse events in patients with central and non-central DMR. No significant differences were reported (Estevez-Loureiro et al., 2013b). This study was probably underpowered to detect differences in these outcomes.

Summary: Only limited subgroup analyses on procedural and 30-day adverse events have been reported. There was no evidence that:

- Surgical risk impacted on 30-day adverse events.
- Central and non-central DMR differed with respect to procedural adverse events.

This analysis is ungraded because of the low sample size and subsequent low event rates.

Results for Question Three

Part one: "What is the cost effectiveness of the percutaneous mitral valve leaflet repair [MitraClip] to treat mitral regurgitation in patients with severe, symptomatic, degenerative mitral regurgitation (grade 3+ and 4+ patients) assessed at high risk

for surgery?"

This question has been addressed in two ways. Firstly, by reporting the results that impact on the economics or healthcare resource use associated with MitraClip in the selected clinical studies. And secondly, by reporting results of the secondary economic studies that were identified and selected regarding MitraClip. These studies have limited applicability because they did not utilise clinical data specifically on DMR patients (rather, they used populations with mixed aetiologies).

Evidence from selected studies

Four outcomes were identified as being largely related to healthcare resource use, although these outcomes also had important implications for clinical efficacy and effectiveness, as well as patient well-being. The outcomes were re-intervention rate ("critical"), length of stay in hospital, discharge destination, and repeat of MitraClip procedure (all "important" outcomes). Of note, there is some overlap between the former and latter of these outcomes. In addition, the outcome "impact of on admissions for heart failure" has been discussed under the clinical evidence section, but will have important implications for healthcare resource use.

Re-intervention rate
This outcome was poorly defined, but was addressed by three studies. Definitions from individual studies were not comparable so a brief narrative is reported.

The prospective observational study by Rudolph et al. (2013) reported an overall rate of re-intervention of 8% in MR patients of mixed aetiology over a median of 13.3 months (Rudolph et al., 2013). Most (n = 10) of the re-interventions were repeat MitraClip procedures, with the remainder (n = 7) being mitral valve surgery. The freedom from re-intervention rate at 12 months specifically in DMR patients was 94.7%, compared with 88.4% in patients with FMR. This difference was not significant.

The Pilot European Sentinel Registry (Nickenig et al., 2014) reported an overall re-intervention rate of 3.8% 12 months after the initial procedure in a mixed aetiology population. MitraClip implantation occurred in 2.9% of these patients, surgical mitral valve repair in 0.7%, and mitral valve replacement in 0.2%. Disaggregated data for DMR were not reported, but there was no significant difference between the groups when subgroup analysis was undertaken.

Three high risk patients with DMR from the EVEREST II studies had a surgical re-intervention within 12 months (2.4%) (Lim et al., 2014).

Summary: Evidence from three studies reported the re-intervention rate following the MitraClip procedure was between 2.4% and 8% after 12 months. This included both repeat MitraClip interventions and surgery.
Grade of Evidence: B

Length of stay in hospital
This outcome was reported in three studies, all exclusively in patients with DMR.

The ACCESS-EU study reported a mean hospital stay in acute care (e.g. intensive care unit [ICU]) of 2.4 ± 3.1 (SD) days. The mean post-procedural length of stay in ICU in high risk patients from the EVEREST II study population was 1.4 ± 1.8 (SD) days. The overall length of hospital stay was 2.9 ± 3.1 (SD) days. Data from the TVT registry reported a median length of stay of 2.0 day (inter-quartile range [IQR] 1.0 to 5.0 days) (Maisano et al., 2013).

Summary: Data from three studies indicated that the length of stay in acute care following MitraClip treatment was between 1.4 and 2.4 days. For overall hospital stay, the range was 2.0 days to 2.9 days. Thus treatment with MitraClip does not usually necessitate protracted recovery in hospital.
Grade of Evidence: A

Discharge destination
Two studies reported this as an outcome; both were deemed of high-quality and were exclusively in patients with DMR. However, the generalisability of these data (from Germany and the US) is unclear.

The ACCESS-EU study reported that 83.1% of low risk DMR patients were discharged directly to home, slightly more than those considered to be at high risk (71.9%) (Reichenspurner et al., 2013). The TVT registry reported that 85.9% of patients with predominantly DMR aetiology were referred directly home, compared with 8.1% to extended care, and 6.0% "other".

Summary: The large majority of patients with DMR receiving MitraClip treatment (probably about 85% who do not have especially high clinical needs) are discharged directly home.
Grade of Evidence: A

Rate of repeat MitraClip procedure
This outcome relates to the re-intervention outcome, discussed above. Two studies, both conducted in DMR specific populations, directly reported this outcome.

One study reported that repeat MitraClip procedures were required in 5.6% of cases (4/72 patients) (Braun et al., 2014). One study reported 10 patients (4.3%) required a repeat MitraClip procedure in the follow up period (Rudolph et al., 2013).

Summary: Limited evidence from two observational studies suggests that the MitraClip procedure may need to be repeated in about 5% of DMR patients.
Grade of Evidence: B

Part 2: "Are there any specific factors, associated with superior outcomes, that would assist selection of patients for maximal cost effectiveness?"

The ACCESS-EU study reported that the overall length of hospital stay was significantly increased in high risk patients compared with low risk patients (mean 7.2 ± 4.3 [SD] days for high risk compared with 6.5 ± 5.4 days for low risk) (Reichenspurner et al., 2013). Additionally, high risk patients were less likely to be discharged directly home.

Summary: There is limited evidence that patients with DMR considered to be at high risk of surgery are likely to remain in hospital longer and discharged to a place other than home compared with patients with DMR considered at low surgical risk (**B**).

Economic studies

Seven economic studies were identified as being potentially relevant to the scope. Upon retrieval and consideration of these studies, two were selected as being within scope and appropriate to include. Details of these studies are described in Table 7.c. The reasons for exclusion of the other studies was because the population was not in scope (N = 1 in a subgroup of advanced kidney disease and N = 2 in patients with predominantly FMR). In two studies, the clinical data used to inform economic analysis were derived from the EVEREST high risk study (HRS) (Whitlow et al., 2012). These data were also used in the included study by Mealing et al. (Mealing et al., 2013). However, as this latter study was based on the perspective of UK third party payer (i.e. the NHS), with costs reported in British pounds, it was preferred to the other studies which were excluded on the basis of double counting of participants.

Study by Mealing et al. (2013)

The study undertaken by Mealing et al. (2013) was the only one with an NHS perspective and using costs from English national datasets (Mealing et al., 2013). However, resource use was mainly taken from the EVEREST HRS study, so these may not generalise to the NHS.

The authors developed a decision analytic model with a lifetime horizon to compare MitraClip with CMM in patients with severe mitral regurgitation who were ineligible for surgery. Estimates for mortality, adverse events, and NYHA class were obtained from the EVEREST II HRS (Whitlow et al., 2012). Utility decrements were obtained from a heath technology assessment on Cardiac Resynchronization Therapy, while unit costs were obtained from national databases. The ICER for MitraClip was £22,200 and £14,800 per QALY gained at 5 and 10 years respectively. The results were sensitive to the time horizon, the utility decrement associated with NYHA II and cost of the MitraClip procedure. Limitations included the dependence on the small non-randomized study (n = 78 in the MitraClip arm and n = 36 in the CMM arm) with a short-term follow-up period (1 year). An additional limitation included the absence of health states for hospitalisations for reasons other than heart failure. The authors concluded MitraClip was cost-effective at the conventional UK willingness to pay (WTP) threshold.

Summary: Evidence from one cost utility analysis study, set in the UK NHS but

using US clinical data, reported that MitraClip is cost effective compared with CMM at the conventional WTP threshold from 5 years onwards.
Grade of Evidence: B

Study by Vemulapalli et al. (2017)

Vemulapalli et al. (2017) linked 403 patients with FMR and DMR at high surgical risk enrolled from the EVEREST II High-Risk Registry and REALISM Continued-Access Study to Medicare data (Vemulapalli et al., 2017). Pre- and post-MitraClip all-cause death, stroke, myocardial infarction, heart failure, and bleeding hospitalizations were identified. Inpatient costs, adjusted to 2010 US dollars, were calculated, and event rate ratios and cost ratios were estimated. Results showed a statistically significant reduction in all-cause hospitalization. The savings related to heart failure admissions, whereas admissions for bleeding increased ($p < 0.001$). Mean Medicare costs per patient were similar pre- and post-MitraClip, although there was a significant decrease in mean costs among patients that survived a full year after MitraClip ($18,131 vs. $11,679, $p = 0.02$). The authors concluded MitraClip may save payer costs among appropriate patients likely to survive for 1 year. However, an important limitation was that this study did not include the cost of the MitraClip device or the related procedure. This cost would exceed by some margin the savings of $6,452 per patient.

Summary: Evidence from one costing study suggested that MitraClip may save money through reduced hospitalisation. However, the generalisability of this study was limited because it was set in the US, costed in US dollars, and did not factor in the costs of the MitraClip device or related procedural costs.
Grade of Evidence: C

5. Discussion

In total, 12 single-armed observational clinical studies were identified as being in scope, with 10 of these studies reporting disaggregated data on patients with DMR. In the short term, there was good evidence (Grade A) that MitraClip was associated with relatively low complication rates and 30-day mortality in patients with DMR, compared with predicted outcomes from surgical risk scores (EuroSCORE and STS). Following the MitraClip procedure, there was unequivocal evidence from the studies that there was an immediate statistically and clinically significant reduction in MR, lasting for at least 12 months (Grade A). Furthermore, this reduction was associated with a parallel reduction in dyspnoea, as measured by the NYHA classification system (Grade A). There was evidence from one study that this improvement in symptoms improved physical and mental HR-QoL (Grade B). Regarding longer-term mortality, there was limited evidence from three observational studies with retrospective controls that MitraClip reduced the death rate at up to 3 years follow up (Grade C). There was only limited evidence on

healthcare resource use, and, as this was not comparative, meaningful conclusions cannot be drawn. However, it is plausible that reductions in future hospital admissions for heart failure could result in cost savings for the NHS. One cost utility study, set in the NHS, reported that MitraClip was cost-effective compared with medical management extrapolated at 10 years in patients with mixed aetiology (Grade C).

The clinical data reported in the selected studies were broadly consistent with each other with no conflicting or unexpected evidence identified. Although mortality rates were high, this is probably a reflection of the baseline characteristics of patients presenting with DMR, who tend to be old and, typically, present with multiple comorbidities.

The main limitation of the identified studies was that they were single-armed and thus reported outcomes were restricted to observational measurements or longitudinal “before and after” data. The three nominally comparative studies that reported mortality data used historical cohorts and were thus subject to confounding and bias. Furthermore, the clinical input of the economic studies were necessarily restricted to these studies; hence results of these studies should be treated with caution. Finally, whilst some of the studies reported subgroup analysis, this was not sufficiently robust to guide patient selection due to low sample size and event rates in this cohort.

Thus there is good evidence that treatment with MitraClip reduces MR grade and symptoms of dyspnoea, with a substantially lower complication and short-term mortality rate, compared with surgical risk prediction tools. However, in order to address the lack of comparative data available in patients with DMR, an experimental study, ideally an RCT, is necessary.

The authors of this review are aware of three on-going RCTs that will compare MitraClip with medical management (Obadia et al., 2015, Mack et al., 2017, Anker and Schillinger, 2017), and one that will compare the procedure with surgery (Volker and Baldus, 2017), in patients with FMR. However, no similar studies have been identified in patients with DMR. It is therefore recommended that further research, in the form of an RCT, should be undertaken in the relevant population (i.e. patients with DMR at high risk of surgery). Additionally, longer-term observational studies would be useful in determining the longevity of clinical effectiveness.

6. Conclusion

This review aimed to ascertain the safety profile and clinical and economic effectiveness of MitraClip in a population with severe DMR who are at high risk of surgery. To answer this, a literature search was undertaken to specifically identify studies reporting on this population, or studies which could be reasonably

extrapolated to this population. Despite there being a large volume of studies published recently on MitraClip, only limited evidence was identified in this specific DMR patient group.

The identified clinical studies were single-armed or had historical controls. These showed unequivocally that MitraClip was associated with clinically important reductions in MR and improvements in NYHA class compared with baseline. Statistically significant reductions in mortality were reported compared with medical management, but these results were subject to confounding and bias. Evidence from economic studies is subject to the same constraints as the clinical evidence, with one study reported that MitraClip may be cost effective over a 5 or 10-year period. However, this was extrapolated from a clinical study restricted to 12 months follow up.

More research, ideally in the form of an RCT, as well as longer-term observational studies, are needed to answer areas of uncertainty regarding the use of MitraClip in this population with DMR. Particular research questions that need to be addressed include the effectiveness of MitraClip in reducing longer-term mortality, the persistence of MR and symptom reduction, and the cost effectiveness of the intervention.

7.a. Evidence Summary Table for Clinical studies (single-armed).

<table>
<tr><th colspan="8">Use of MitraClip* in patients with DMR who are at high risk from surgery</th></tr>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Outcome measures</th><th>Results**</th><th>Quality of Evidence Score***</th><th>Applicability†</th><th>Critical Appraisal Summary</th></tr>
<tr><td colspan="8">Large single-armed observational studies (n ≥ 500, not specific to DMR aetiology)</td></tr>
<tr>
<td>ACCESS-EU study. Study characteristics reported in (Maisano et al., 2013). DMR analysis in (Reichenspurner et al., 2013).

Other reports:

(Schafer et al., 2016)

(Gafoor et al., 2016)</td>
<td>Prospective, European, multicentre (14 sites), observational study (phase 1).

Subgroup analysis of DMR patients.

1 year FU.

<u>Statistics</u>:
Descriptive statistics (mean [SD], median [IQR]).
Serial paired data analysis.</td>
<td>Study enrolled 567 patients (21% DMR):

Overall DMR cohort (reported in results, n = 117) LE 15.5

Male: 49.6%
Mean age (years): 75.6 ± 12.1 (SD)

HR DMR (n = 33), LE 33.1
LR DMR (n = 84), LE 8.6

MR grade ≥3: 97%
NYHA class ≥III: 74%

Patients enrolled October 2008 to April 2011.</td>
<td>Procedural and 30-day outcomes</td>
<td>Overall success rate: 94.9%

Table reporting adverse events (at 30 days)

<table>
<tr><th>30-day safet outcome</th><th>DMR Total (n = 117) (%)</th><th>DMR HR (n = 33) (%)</th><th>DMR LR (n = 84) (%)</th></tr>
<tr><td>Death</td><td>6.0</td><td>9.1</td><td>4.8</td></tr>
<tr><td>Stroke</td><td>0.9</td><td>0</td><td>1.2</td></tr>
<tr><td>MI</td><td>0.9</td><td>3.0</td><td>0</td></tr>
<tr><td>Renal failure</td><td>2.6</td><td>3.0</td><td>2.4</td></tr>
<tr><td>Need for resuscitation</td><td>0.9</td><td>3.0</td><td>0</td></tr>
<tr><td>Cardiac tamponade</td><td>0.9</td><td>3.0</td><td>0</td></tr>
<tr><td>Bleeding complication</td><td>3.4</td><td>6.1</td><td>2.4</td></tr>
<tr><td>Repeat MitraClip</td><td>0.9</td><td>0</td><td>1.2</td></tr>
<tr><td>Mitral Valve surgery</td><td>1.7</td><td>0</td><td>2.4</td></tr>
<tr><td>Total AE</td><td>17.9</td><td>27.3</td><td>14.3</td></tr>
</table>
</td>
<td>The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data are adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 2).

Total score: 8</td>
<td rowspan="2">Directly applicable for DMR subgroups analysed.</td>
<td rowspan="2">The ACCESS-EU registry was a large, prospective, multi-centre, single-armed, observational study of patients receiving MitraClip.

The study employed no specific inclusion criteria, but reflected real-world practice of the selected centres.

The study reported patient enrolment and follow-up status, with a substantial number of patients (31%) being lost to follow up after 1 year.

A range of procedural and clinical outcomes were reported. This study is on-going with longer-term follow-up expected.

The study recruited patients with MR of mixed aetiology, but provided extensive analysis of subgroups, including DMR</td>
</tr>
<tr>
<td>Clinical outcomes (1 year FU)</td>
<td><u>Freedom from MR ≥2</u>
Overall DMR: 74.6% (53/71)
HR DMR: 80.0% (16/20)
LR DMR: 72.5% (37/51)
<u>NYHA improvement (≥ 1 class)</u>
Overall DMR: 68% 53/78)
LR DMR: 72% (41/57)
HR DMR: 57% (12/21)
<u>NYHA class I or II at 12 months</u>
Overall DMR: 80.8% (63/78)</td>
</tr>
</table>

Use of MitraClip* in patients with DMR who are at high risk from surgery

<table>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Outcome measures</th><th>Results**</th><th>Quality of Evidence Score***</th><th>Applicability†</th><th>Critical Appraisal Summary</th></tr>
<tr><td></td><td></td><td></td><td></td><td>LR DMR: 89.5% (51/57)
HR DMR: 57.1% (12/21)
MLHFQ (HRQoL) 40 at baseline, 27 at 12 months (p = 0.03) (n = 44)

Table reporting adverse events (at 1 year)
<table>
<tr><th>1 year safety outcome</th><th>DMR Total (n = 117) (%)</th><th>DMR HR) (n = 33) (%)</th><th>DMR LR (n = 84) (%)</th></tr>
<tr><td>Death</td><td>17.1</td><td>24.2</td><td>14.3</td></tr>
<tr><td>Stroke</td><td>0.9</td><td>0</td><td>1.2</td></tr>
<tr><td>MI</td><td>0.9</td><td>3.0</td><td>0</td></tr>
<tr><td>Renal failure</td><td>6.0</td><td>12.1</td><td>3.6</td></tr>
<tr><td>Need for resuscitation</td><td>0.9</td><td>3.0</td><td>0</td></tr>
<tr><td>Cardiac tamponade</td><td>0.9</td><td>3.0</td><td>0</td></tr>
<tr><td>Bleeding complication</td><td>3.4</td><td>6.1</td><td>2.4</td></tr>
<tr><td>Repeat MitraClip</td><td>3.4</td><td>3.0</td><td>3.6</td></tr>
<tr><td>Mitral Valve surgery</td><td>7.7</td><td>3.0</td><td>9.5</td></tr>
<tr><td>Total AE</td><td>41.0</td><td>57.6</td><td>34.5</td></tr>
</table></td><td></td><td></td><td>stratified by surgical risk (LR and HR subgroups).

Overall the reviewers considered this a high quality study for this type of design.</td></tr>
<tr><td></td><td></td><td></td><td>Healthcare resource use</td><td><u>Mean (SD) hospital stay</u> (acute)
Overall DMR: 2.4±3.1 days
HR DMR: 2.5±3.8 days
LR DMR: 2.4±2.8 days
<u>Mean (SD) hospital stay</u> (overall)
HR DMR: 7.2±4.3 days
LR DMR: 6.5±5.4 days
<u>Discharge destination</u>
HR DMR: 83.1% admitted home
LR DMR: 71.9% admitted home</td><td></td><td></td><td></td></tr>
<tr><td>“Netherlands registry”.

Reported in (Rahhab et al., 2017)</td><td>Multi-centre retrospective analysis of all MitraClip procedures carried out in Netherlands (13 hospitals).</td><td>Study analysed data from 1151 patients receiving MitraClip from January 2009 and June 2016.

Male: 59%
Median age 76 years (IQR 69 to 82)</td><td>Procedural and 30-day outcomes</td><td>Device success: 91%
Technical success: 95%
Intra-procedural death: 0.3%
Emergency surgery: 0.5%

<u>MR reduction (post implant)</u>
No reduction: 7%
1 class: 9%
2 classes: 51%</td><td>The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the</td><td>Indirectly applicable

Data reported from a population with predominantly FMR (17%</td><td>This was a retrospective observational study that was intrinsically limited and deemed of poor methodological quality.</td></tr>
</table>

Use of MitraClip* in patients with DMR who are at high risk from surgery

<table>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Outcome measures</th><th>Results**</th><th>Quality of Evidence Score***</th><th>Applicability†</th><th>Critical Appraisal Summary</th></tr>
<tr><td></td><td>Limited FU (immediately post-procedure)

<u>Statistics</u>:
Categorical variables analysed with Pearson Chi Square Test or the Fisher's exact test.

Continuous variables analysed with Student's t-test or the Mann-Whitney U test.</td><td><u>Aetiology of MR</u>:
DMR: 17%
FMR: 72%
Mixed aetiology: 10%

<u>Severity of MR</u>:
Moderate: 2%
Moderate-severe: 34%
Severe: 65%</td><td></td><td>3 classes: 33%
≥1 class: 94%</td><td rowspan="2">research (score of 1); the methods are clearly described (score of 1); the data are adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 0).

Total score: 5</td><td rowspan="2">DMR).

Limited subgroup analysis.</td><td rowspan="2">The study only reported limited, short-term outcomes and had poor generalisability to the population in the scope.

One strength of the study was that it consecutively included all available patients receiving MitraClip in the Netherlands and thus give a good insight into clinical practice in this country.</td></tr>
<tr><td></td><td>Comparison of DMR vs. FMR</td><td>Patients with DMR were statistically older with more severe MR. Patients with FMR had more often "significant" [2 classes] MR reduction (95% vs. 91%, p = 0.025)</td></tr>
<tr><td>Pilot European Sentinel Registry.

Reported in (Nickenig et al., 2014).

Also reported in (Pighi et al., 2017).</td><td>Prospective multi-centre European registry.

25 centres in 8 countries (including UK)

1 year FU.

<u>Statistics</u>:
Between group comparison – Chi square test, Fisher's exact test.

Univariate analysis.

Multivariate logistic regression analysis.</td><td>Study enrolled 749 patients, 22% with DMR (n = 143).

Characteristics of DMR cohort:

Age: 78.3 ± 8.5 (SD) years.

Male: 52.5%

EuroSCORE I: 16.3±13.7.

MR severity (n = 85):
None/mild – 0%;
Moderate – 9.8%;
Severe – 90.2%

NYHA class: I - 3.5%; II 19.6%; III – 63.6%; IV – 13.3%.</td><td>Procedural and 30-day outcomes</td><td>Procedural success (total cohort): 95.4% (93.7% for DMR).

Table reporting procedural and in-hospital outcomes.
<table>
<tr><th>Outcome</th><th>Overall (n=628)</th><th>FMR (n=452)</th><th>DMR (n=143)</th></tr>
<tr><td>Death</td><td>2.9</td><td>2.0</td><td>4.9</td></tr>
<tr><td>Tamponade</td><td>1.1</td><td>0.7</td><td>1.8</td></tr>
<tr><td>Stroke</td><td>0.2</td><td>0.0</td><td>0.7</td></tr>
<tr><td>Severe bleeding</td><td>1.1</td><td>0.9</td><td>2.1</td></tr>
<tr><td>Transfusion</td><td>10.1</td><td>9.7</td><td>12.4</td></tr>
<tr><td>Vascular complication requiring intervention</td><td>0.7</td><td>1.0</td><td>0.0</td></tr>
<tr><td>New onset AF</td><td>11.7</td><td>12.6</td><td>10.2</td></tr>
<tr><td>Procedural success</td><td>95.4</td><td>95.8</td><td>93.7</td></tr>
<tr><td>Clip embolised</td><td>0.7</td><td>0.5</td><td>0.9</td></tr>
<tr><td>Inability to reduce MR</td><td>3.5</td><td>3.0</td><td>4.4</td></tr>
<tr><td>Implant ≥2 clips</td><td>37.5</td><td>36.5</td><td>44.3</td></tr>
</table></td><td>The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data are adequate to support the authors' interpretation (score of 2); the results are generalisable (score of 2).

Total score: 9</td><td>Directly applicable for DMR subgroup.</td><td>This was a large prospective observational study that consecutively recruited patients with MR subsequently treated with MitraClip. It had inherent confounding and biases relevant to this study type.

The registry was multi-centre study including a UK centre (Royal Brompton); however, there were substantial differences in the characteristics of patients between participating centres.

The study had a high standard of reporting with clinical outcomes</td></tr>
</table>

Use of MitraClip* in patients with DMR who are at high risk from surgery

<table>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Outcome measures</th><th>Results**</th><th>Quality of Evidence Score***</th><th>Applicability†</th><th>Critical Appraisal Summary</th></tr>
<tr><td></td><td>Kaplan Meier analysis (survival curves)</td><td></td><td></td><td>
<table>
<tr><td>Procedure duration (mi s)</td><td>138.3±67 9</td><td>137.2±68.2</td><td>132.1±65.6</td></tr>
<tr><td>Median hospital stay (IQR, days)</td><td>5 (3 to 7)</td><td>5 (4 to 7)</td><td>5 (3 to 7)</td></tr>
<tr><td colspan="4">Results reported as percentages unless otherwise stated.
Overall cohort includes 17 patients with mixed aetiologies.
No significant differences detected between groups.</td></tr>
</table>
</td><td></td><td></td><td>at 1 year FU. The study reported DMR and FMR cohorts separately and reported some comparative data.</td></tr>
<tr><td></td><td></td><td></td><td>Clinical outcomes (at FU)</td><td>
Degree of MR before and after procedure (DMR cohort, n=85).
<table>
<tr><td>Degree of MR</td><td>Pre-Clip</td><td>Post-Clip</td><td>1 year FU</td></tr>
<tr><td>None/mild</td><td>0</td><td>72.1</td><td>57.4</td></tr>
<tr><td>Moderate</td><td>9.8</td><td>26.2</td><td>36.1</td></tr>
<tr><td>Severe</td><td>90.2</td><td>1.6</td><td>6.6</td></tr>
<tr><td colspan="4">Significant improvement in MR post-procedure and at 1 year FU (p<0.001).</td></tr>
</table>
Table reporting NYHA class before and after procedure (DMR cohort, n=68).
<table>
<tr><td>NYHA class</td><td>Pre-Clip</td><td>1 month</td><td>1 year FU</td></tr>
<tr><td>I</td><td>4.4</td><td>35.3</td><td>36.8</td></tr>
<tr><td>II</td><td>11.8</td><td>48.5</td><td>47.1</td></tr>
<tr><td>III</td><td>66.2</td><td>16.2</td><td>14.7</td></tr>
<tr><td>IV</td><td>17.7</td><td>0</td><td>1.5</td></tr>
<tr><td colspan="4">Significant improvement in MR post-procedure and at 1 year FU (p<0.001).</td></tr>
</table>
Estimated 1 year mortality rate (KM analysis):
Overall: 15.3%
FMR: 15.0%
DMR: 16.3% (ns)
</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td>Healthcare resource use</td><td>Freedom from composite of death or readmission because of heart failure at 1 year FU: 69.0% (SD 2.3%). Difference between FMR vs. DMR ns.

Re-intervention at 1 year FU (n = 17): 3.8% (additional MitraClip implantation in 2.9%, surgical MV repair in 0.7%, and MV replacement in 0.2%). Difference between FMR vs. DMR ns.</td><td></td><td></td><td></td></tr>
</table>

Use of MitraClip* in patients with DMR who are at high risk from surgery							
Study reference	**Study Design**	**Population characteristics**	**Outcome measures**	**Results****	**Quality of Evidence Score*****	**Applicability†**	**Critical Appraisal Summary**
TRAMI registry. Methodology reported in (Baldus et al., 2012), 1 year results reported in (Puls et al., 2016). Additional interim or subgroup analyses reported in: (Ledwoch et al., 2018) Schwencke et al., 2017) (Kalbacher et al., 2017) (Jabs et al., 2017) (D'Ancona et al., 2017) (Schueler et al., 2016) (Zuern et al., 2015) (Eggebrecht et al., 2015) (Wiebe et al., 2014) (Rudolph et al., 2014) (Ledwoch et al., 2014) (Schillinger et al., 2013)	Multi-centre registry in Germany (15 centres). Prospective cohort enrolled between August 2010 and July 2013, Retrospective cohort analysed patient data from January 2009 to July 2010. 1 year FU. <u>Statistics</u>: Categorical comparisons made with Chi square and Fisher's exact test.	749 patients reported 1 year FU data. DMR: 27.8% FMR: 71.3% (Data not disaggregated). Median age: 75 years (IQR 70 to 80 years). Male: 59% Severe MR: 93.8% NYHA class III/IV: 89.0% Logistic EuroSCORE: 20.0% (IQR 12.0 to 31.0%) STS score: 11% (IQR 4 to 19%)	Procedural and 30-day outcomes	Procedural success: 97% *<u>MR grade post procedure</u>*: None/mild: 85.2% (631/741) Moderate: 12.6% (93/741) Severe: 2.3% (17/741) <u>MACCE</u> (total): 3.1% (22/712) In-hospital mortality: 2.4% (18/749) 30-day mortality: 4.5% (34/749) MI: 0.0% (0/711) Stroke: 0.8% (6/712) <u>Non-MACCE</u> TIA: 0.8% (6/712) Respiratory failure (re-intubation): 2.3% (16/711) Severe bleeding/transfusion: 7.0% (50/711) Low cardiac output: 1.3% (9/711) Pericardial tamponade: 1.7% (12/710) Clip embolisation: 0.0% (0/710) Partial clip detachment: 0.7% (5/749) *<u>Additional MV procedure</u>*: 1.5% (11/710, see below) Surgical: 0.8% (6/710) Percutaneous: 0.7% (5/710)	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 1); the data are adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 0). **Total score: 5**	**Indirectly applicable** Majority of patients had FMR and data not disaggregated. Subgroup analysis between DMR vs. FMR not reported.	This was a was a large registry including patients with MR and at high risk of surgery (76% at high surgical risk). It was subject to confounding and bias inherent to this study type. The registry was derived from both prospective and retrospective sources, reported combined and separately, from several centres; however inclusion and exclusion criteria were not clearly defined. Procedural data were reported extensively, but follow up data were limited. Data on DMR and FMR were not disaggregated; hence although it reflected real-world practice in Germany, generalisability to the decision problem was limited.
			Clinical outcomes (1 year FU)	*Mortality*: 19.8% (95% CI 17.2 to 22.8%) KM analysis. *<u>NYHA class</u>* I/II: 63.3% (305/482) III/IV: 36.7% (177/482) *<u>EQ VAS</u>* Baseline: 60.0 mm (50.0 to 70.0 mm) 1 year: 50.0 (40.0 to 60.0 mm). $p < 0.0001$. <u>Adverse events (MACCE)</u> *Death*: 20.3% (152/749, crude rate) MI: 0.9% (4/425) Stroke: 2.1% (9/423) <u>Mon-MACCE:</u> TIA: 3.8% (16/426) Bleeding complications: 12.6% (56/443) Need for resuscitation: 2.1% (9/426)			
			Healthcare resource use	*Rehospitalisation* (1 year FU): 64.3% (354/566) Cardiac decompensation: 14.1% (80/566) Other cardiac reason: 17.8% (101/566) Non-cardiac reason: 25.8% (146/566) *Additional MV procedure*: 8.5% (37/436) Surgical: 2.3% (10/436) Percutaneous: 5.2% (23/436)			

Use of MitraClip* in patients with DMR who are at high risk from surgery

<table>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Outcome measures</th><th>Results**</th><th>Quality of Evidence Score***</th><th>Applicability†</th><th>Critical Appraisal Summary</th></tr>
<tr>
<td>TVT registry.

Reported in (Sorajja et al., 2017a).

Related TVT studies reported in:

(Galper et al., 2018)

(Grover et al., 2017)

(Sorajja et al., 2016)</td>
<td>Prospective multicentre registry in US. Analysis of data extracted from the Society of Thoracic Surgeons/American College of Cardiology TVT registry.

All patients who underwent commercial therapy with the MitraClip system at 145 hospitals between November 2013 and September 2015 were enrolled onto TVT registry. Clinical data from registry linked with administrative databases using direct patient identifiers (for longer term clinical outcomes).

<u>Statistics</u>:
Discrete variable reported as frequencies or percentage, continuous variables reported as median (with IQR).
KM analysis.
HR analysis.</td>
<td>Data from 2952 patients (November 2013 to August 2014) included. Patients were eligible for inclusion if they had severe (grade 3 or 4) MR of DMR origin and were considered to be at prohibitive surgical risk, as measured by STS predictive risk of mortality criteria.

Median age: 82 (IQR 74 to 86) years
Male: 55.8%

DMR: 85.9%
FMR: 8.6%
Mixed DMR/FMR: 8.9%
Other/indeterminate: 3.5%.

Median STS-PROM:
MV repair 6.1% (IQR 3.7 to 9.9%)
MV replacement 9.2% (IQR 6.0 to 14.1%)

MR grade
Grade 2 – 4.9%
Grade 3 – 16.6%
Grade 4 – 76.4%

NYHA class:
II – 11.9%
III – 61.3%
IV – 23.7%</td>
<td>Procedural and 30-day outcomes</td>
<td><u>All patients (n = 2952)</u>

Post-implant MR:
None/trace/trivial – 15.0%
Mild (grade 1) – 46.8%
Moderate (grade 2) – 31.2%
Moderate-severe (grade 3) – 2.9%
Severe - 4.1%

Successful procedure:
Post-implant MR grade ≤ 2, no in-hospital mortality, and no cardiac surgery – 91.8%
Post-implant MR grade 1, no in-hospital mortality, and no cardiac surgery – 60.9%

Table reporting procedural and in hospital complications:
<table>
<tr><th>Complication type</th><th>Specific complication</th><th>Complication rate (%)</th></tr>
<tr><td colspan="2">Cardiac perforation</td><td>1.0</td></tr>
<tr><td colspan="2">Trans-septal complication</td><td>0.9</td></tr>
<tr><td colspan="2">Bleeding</td><td></td></tr>
<tr><td rowspan="3"></td><td>Access site</td><td>1.1</td></tr>
<tr><td>Haematoma</td><td>1.6</td></tr>
<tr><td>Major/life-threatening (VARC)</td><td>3.9</td></tr>
<tr><td colspan="2">MI</td><td>0.1</td></tr>
<tr><td colspan="2">Stroke</td><td>0.4</td></tr>
<tr><td rowspan="3"></td><td>TIA</td><td>0.1</td></tr>
<tr><td>Ischaemic</td><td>0.4</td></tr>
<tr><td>Haemorrhagic</td><td>0.03</td></tr>
<tr><td colspan="2">Device related adverse events</td><td></td></tr>
<tr><td rowspan="5"></td><td>Single leaflet device detachment</td><td>1.5</td></tr>
<tr><td>Device embolisation</td><td>0.1</td></tr>
<tr><td>Delivery system component embolisation</td><td>0.0</td></tr>
<tr><td>Device thrombus</td><td>0.0</td></tr>
<tr><td>Other</td><td>0.7</td></tr>
<tr><td colspan="2">Open heart surgery</td><td>0.7</td></tr>
<tr><td colspan="2">In hospital mortality</td><td>2.7</td></tr>
</table>
</td>
<td>The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data are adequate to support the authors' interpretation (score of 2); the results are generalisable (score of 2).

Total score: 9</td>
<td>Directly applicable.

The TVT registry enrolled predominantly patients with DMR at prohibitive risk of surgery.

Limited subgroup analysis of DMR vs. FMR.</td>
<td>This was a large registry (n = 2952) that was considered to have high internal validity and external validity for a study of this type.

The registry consecutively enrolled all patients within a set time frame and so accurately reflects patients in real-life US practice.

Linked data were used to report longer term clinical outcomes in a large subset of patients.

The study was well reported and reported cross-sectional and longitudinal data. However, it was intrinsically limited by the lack of a comparator meaning comparative analysis was not possible.</td>
</tr>
</table>

<table>
<tr><th colspan="8">Use of MitraClip* in patients with DMR who are at high risk from surgery</th></tr>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Outcome measures</th><th>Results**</th><th>Quality of Evidence Score***</th><th>Applicability†</th><th>Critical Appraisal Summary</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td>Clinical outcomes (30 day and 1 year FU)</td><td><u>All patients (n = 1867)</u>

Table reporting 30 day and 1 year outcomes:
<table><tr><td>Event</td><td>30 days (%)</td><td>1 year (%)</td></tr><tr><td>Death</td><td>5.2</td><td>25.8</td></tr><tr><td>MI</td><td>0.2</td><td>2.5</td></tr><tr><td>Stroke (any)</td><td>1.0</td><td>2.7</td></tr><tr><td>Stroke (haemorrhagic)</td><td>0.4</td><td>0.6</td></tr><tr><td>Heart failure hospitalisation (see below)</td><td>4.7</td><td>20.2</td></tr><tr><td>Mitral valve surgery</td><td>0.4</td><td>2.1</td></tr><tr><td>Repeat MitraClip</td><td>1.3</td><td>6.2</td></tr></table>
<u>DMR patients only (1 year FU, KM analysis)</u>
Mortality -24.7%
Readmission for HF - 20.5%
Combined – 35.7%

<u>FMR patients only (1 year FU, KM analysis)</u>
Mortality -31.2%
Readmission for HF – 32.6%
Combined – 49.0%%</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td>Healthcare resource use</td><td>Length of stay: Median 2.0 days (IQR 1.0 to 5.0 days) (n = 2676)
Discharge destination:
Home – 85.9%
Extended care – 8.1%
Other – 6.0%</td><td></td><td></td><td></td></tr>
<tr><td colspan="8">Smaller single-armed observational studies (n ≥ 50 DMR specific aetiology)</td></tr>
<tr><td>Braun et al. (2014).

Reported in (Braun et al., 2014)</td><td>Single-armed single-centre prospective observational study.
Germany.</td><td>Consecutive enrolment of 119 patients with severe MR, predominantly DMR.
<u>Characteristics of DMR cohort</u> (n = 72,</td><td>Procedural and 30-day outcomes</td><td><u>DMR patients</u>
Success rate (MR reduction ≥ 1) - 83.3% (60/72).
8 implant not attempted due to unsuitable anatomy.
Of the 12 unsuccessful:
• 2 insufficient TOE images.
• 5 MitraClip would not grasp because of extreme prolapse.</td><td>The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for</td><td>Directly applicable.

Predominantly enrolled DMR patients, and</td><td>This was a small prospective observational study that was well reported. It was single armed and limited to cross sectional and</td></tr>
</table>

Use of MitraClip* in patients with DMR who are at high risk from surgery

<table>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Outcome measures</th><th>Results**</th><th>Quality of Evidence Score***</th><th>Applicability†</th><th>Critical Appraisal Summary</th></tr>
<tr>
<td></td>
<td>Principal aim of study was to analyse outcomes in MitraClip patients with DMR compared with FMR.

<u>Statistics</u>:
Fisher's exact test used to compare categorical variables. The Mann–Whitney-U-test and Wilcoxon test were used for the comparison of continuous variables.
The Log rank test was used to compare overall survival KM analysis).</td>
<td>60.5%)
Mean age 72.2 ± 12.1 (SD) years.
Male: 62.1% (n = 44)

NYHA ≥ 3 – 81.4%
MR ≥3 – 95.8%)
Mean logistic EuroSCORE – 13.8 ± 18.0 (SD).

Compared with FMR patients, DMR patients had significantly higher NYHA class and MR grade, and were of lower surgical risk (p < 0.001).</td>
<td></td>
<td>• 1 removed because of Mitral prolapse.
• 4 patients had < 1 MR grade reduction.</td>
<td rowspan="2">the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data are adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 2).

Total score: 8</td>
<td rowspan="2">reported disaggregated and comparative results.</td>
<td rowspan="2">longitudinal results (rather than comparative).

Patients were recruited consecutively which should limit selection bias.

The relatively small sample size also limited the precision of the results and inferences that can be drawn. The study reported results on an ITT basis which was appropriate.

The study reported data on FMR and DMR separately and limited comparative analysis between these cohorts. However, the groups had important clinical differences at baseline.</td>
</tr>
<tr>
<td>Clinical outcomes (up to 1 year FU)</td>
<td>Table reporting MR grade and NYHA class in DMR patients (up to 1 year FU).
<table>
<tr><th>Follow up time</th><th>MR grade ≤ 2 grades (%)</th><th>NYHA class ≤ 2 classes (%)</th></tr>
<tr><td>Baseline</td><td>0</td><td>18.6</td></tr>
<tr><td>1 month</td><td>83.3</td><td>90.2</td></tr>
<tr><td>6 months</td><td>75</td><td>86.0</td></tr>
<tr><td>12 months</td><td>83.3</td><td>91.1</td></tr>
<tr><td>P value (Baseline vs. 12 months)</td><td>< 0.001</td><td>< 0.001</td></tr>
</table>
Table comparing DMR vs. FMR MR grade at 1 year FU.
<table>
<tr><th>Outcome</th><th>DMR</th><th>FMR</th><th>P value</th></tr>
<tr><td>Persistent reduction of ≥ 1 MR grade (%)</td><td>88.9</td><td>83.3</td><td>0.67</td></tr>
<tr><td>Persistent reduction of ≥ 2 MR grade (%)</td><td>63.9</td><td>16.7</td><td>0.001</td></tr>
<tr><td>Persistent reduction of ≥ 1 NYHA class (%)</td><td>80.0</td><td>75.0</td><td>0.75</td></tr>
<tr><td>Persistent reduction of ≥ 1 NYHA class (%)</td><td>52.8</td><td>44.4</td><td>0.77</td></tr>
</table>
Survival at 12 months:
DMR – 93.1%
FMR – 80.9% (p = 0.04)

Event free survival (freedom from MR 3+ or 4+, mitral valve re-intervention and death):
DMR – 59.7%
FMR – 63.8% (p = 0.73)</td>
</tr>
</table>

Use of MitraClip* in patients with DMR who are at high risk from surgery

<table>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Outcome measures</th><th>Results**</th><th>Quality of Evidence Score***</th><th>Applicability†</th><th>Critical Appraisal Summary</th></tr>
<tr><td></td><td></td><td></td><td>Healthcare resource use</td><td><u>DMR patients</u>
Mitral valve surgery within FU – 13.9% (10/72, 9 MV replacement, 1 MV repair)
Repeat MitraClip – 5.6% (4/72)</td><td></td><td></td><td></td></tr>
<tr><td>Estevez-Loureiro et al. (2013).

Reported in (Estevez-Loureiro et al., 2013b).</td><td>Retrospective observational study using data of patients with DMR with predefined inclusion and exclusion criteria.

Three centres in the UK (Royal Brompton hospital), Denmark and Sweden treated 173 consecutive patients between August 2009 and November 2012.

Retrospective analysis was applied to the DMR subgroup..

The aim of the study was to compare short-term and midterm safety and efficacy of MitraClip treatment between patients with central vs. noncentral DMR.

<u>Statistics</u>:
Categorical data and proportions were compared using chi-square test or Fisher exact test.</td><td>79 patients fulfilled inclusion criteria (had DMR).

Mean age: 79.2 ± 7.9 (SD) years.
Male: 58.2% (n = 46)

<u>NYHA class</u>:
II – 6.3%
III – 83.5%
IV – 10.2%

Mean logistic EuroSCORE – 14.3 ± 10.3 (SD)

<u>MR grade</u>:
2 – 7.6%
3 to 4 – 92.4%</td><td>Procedural and 30-day outcomes</td><td>Procedural success (reduction in MR grade to ≤2): 96.2%
Complications (any): 12.6%
Table reporting complications in overall DMR cohort (n = 79).

<table>
<tr><th>Peri-procedural adverse event</th><th>Proportion (%)</th></tr>
<tr><td>Clip embolisation</td><td>0</td></tr>
<tr><td>Partial clip detachment</td><td>2.5</td></tr>
<tr><td>Prolonged clip entanglement</td><td>0</td></tr>
<tr><td>Chordal rupture</td><td>1.2</td></tr>
<tr><td>Cardiac tamponade</td><td>1.2</td></tr>
<tr><td>Gastro-intestinal bleeding</td><td>2.5</td></tr>
<tr><td>Stroke</td><td>0</td></tr>
<tr><td>Transient atrio-ventricular block</td><td>1.2</td></tr>
<tr><td>Pneumonia</td><td>1.2</td></tr>
<tr><td>Mitral valve surgery</td><td>1.2</td></tr>
<tr><td>Death</td><td>1.2</td></tr>
<tr><td>All complications</td><td>12.6</td></tr>
</table>
</td><td>The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data are adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 2).

Total score: 8</td><td>Directly applicable.

Patients enrolled in the study had exclusively DMR and were at high risk from surgery.

One centre in the study was in the UK.</td><td>This study prospectively enrolled consecutive patients receiving MitraClip and retrospectively analysed those with DMR aetiology.

Although the focus of the study was a comparison of central vs. noncentral DMR, results from the overall DMR cohort were reported making it relevant to the scope.

The relatively small sample size also limited the precision of the results and inferences that can be drawn. Additionally, the range of clinical outcomes reported was limited.

The study was single armed and therefore inherently limited to cross sectional and longitudinal results (rather than comparative).</td></tr>
<tr><td></td><td></td><td></td><td>Clinical outcomes (1 month FU)</td><td>Table reporting changes to MR grade at 1 month.

<table>
<tr><th>MR class</th><th>Baseline (%)</th><th>1 month (%)</th><th>P value</th></tr>
<tr><td>0 to 1</td><td>0</td><td>63.3</td><td rowspan="3"><0.0001</td></tr>
<tr><td>2</td><td>7.6</td><td>32.9</td></tr>
<tr><td>3 to 4</td><td>92.4</td><td>3.8</td></tr>
</table>

Table reporting changes to NYHA class at 6 months.

<table>
<tr><th>NYHA class</th><th>Baseline (%)</th><th>1 month (%)</th><th>P value</th></tr>
<tr><td>I</td><td>0</td><td>21.3</td><td rowspan="4"><0.001</td></tr>
<tr><td>II</td><td>6.3</td><td>62.7</td></tr>
<tr><td>III</td><td>83.5</td><td>14.7</td></tr>
<tr><td>IV</td><td>10.2</td><td>1.3</td></tr>
</table>
</td><td></td><td></td><td></td></tr>
</table>

Use of MitraClip* in patients with DMR who are at high risk from surgery

<table>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Outcome measures</th><th>Results**</th><th>Quality of Evidence Score***</th><th>Applicability†</th><th>Critical Appraisal Summary</th></tr>
<tr><td></td><td>Comparisons of continuous variables were analysed using the unpaired Student t test and the Mann-Whitney U test. KM survival analysis.</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Geis et al. (2018)

Reported in (Geis et al., 2018)</td><td>Retrospective observational study of patients receiving MitraClip to treat DMR caused by chordae rupture.

Single centre (Germany). Patients enrolled between October 2009 and March 2017.

Aim of study was “study was to assess feasibility and clinical effectiveness of the MitraClip device in octogenarians suffering from severe mitral valve regurgitation due to chordae rupture”.

<u>Statistics</u>: Unpaired student's t-test was used to compare continuous data. To compare means among three or more dependent groups one way</td><td>98 patients (all > 80 years age) were included according to following criteria: NYHA class III or IV; severe MR due to prolapse from chordae rupture; ineligible for surgical MV reconstruction/repair as discussed within the “Heart Team”.

Median age: 94 (range 80 to 92) years.
Male: 52% (n = 51)

Mean NYHA stage: 3.5 ± 0.4 (SD).

Mean MR grade: 3.5 ± 0.2 (SD).</td><td>Procedural and 30-day outcomes</td><td>Success rate (defined as a reduction of MV regurgitation to less than mild/moderate [grade 1 or 2]): 91%

Table reporting major adverse events within 30 days.

<table><tr><th>30 day MAE</th><th>Proportion (%)</th></tr><tr><td>Death</td><td>2</td></tr><tr><td>MI</td><td>0</td></tr><tr><td>Stroke</td><td>1</td></tr><tr><td>Major bleeding</td><td>2</td></tr><tr><td>Minor bleed</td><td>5</td></tr><tr><td>Partial clip detachment</td><td>1</td></tr><tr><td>Full clip detachment</td><td>0</td></tr><tr><td>Septicaemia</td><td>1</td></tr><tr><td>Prolonged ventilation (> 12 hours)</td><td>1</td></tr><tr><td>Renal failure</td><td>1</td></tr><tr><td>Pericardia infusion</td><td>0</td></tr><tr><td>Unsuccessful MitraClip procedure</td><td>9</td></tr><tr><td>Need for surgery</td><td>4</td></tr></table></td><td>The research questions, aims and design are clearly stated (score of 1); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data are adequate to support the authors’ interpretation (score of 1); the results are generalisable (score of 1).

Total score: 6</td><td>Directly applicable.

Patients had DMR specifically due to chordae rupture. This may not be fully generalisable to the DMR population as a whole.</td><td>This was a small retrospective observational study subject to the inherent limitations of this study type.

Overall, the study methodology and reporting was relatively poor. Only limited clinical outcome data were reported.

The study was limited to octogenarians with DMR caused by chordae rupture and may not be generalisable to other cohorts in the scope.</td></tr>
<tr><td></td><td></td><td></td><td>Clinical outcomes (1 year FU)</td><td>Reduction in mean MR grade:
Baseline – 3.5 ± 0.2 (SD)
12 months – 1.2 ± 0.3 (SD, p < 0.001)

Reduction in mean NYHA class:
Baseline - 3.5 ± 0.4 (SD).
12 months – 2.0 ± 0.3 (SD, p <0.001).</td><td></td><td></td><td></td></tr>
</table>

<table>
<tr><th colspan="8">Use of MitraClip* in patients with DMR who are at high risk from surgery</th></tr>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Outcome measures</th><th>Results**</th><th>Quality of Evidence Score***</th><th>Applicability†</th><th>Critical Appraisal Summary</th></tr>
<tr><td></td><td>ANOVA measures were performed for statistical comparisons. Bonferroni test was applied whenever multiple comparisons were conducted.</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Lim et al. (2014).

Reported in (Lim et al., 2014)

Data from the same or similar patient cohort also reported in (Glower et al., 2012).</td><td>Post hoc analysis of eligible DMR patients from the prospective EVEREST II HRS (n = 25) and REALISM continued access registry (n = 98) studies, and patients treated under “compassionate use” (n = 4).

The aim of the study was to evaluate the relationship between reduction of MR with MitraClip and improvement in functional status in patients with severe DMR at prohibitive surgical risk and with eligible MV anatomy.

<u>Statistics</u>:
Continuous data comparisons made with paired t test.
KM survival</td><td>127 patients with DMR were included who were defined as being at prohibitive risk of surgery and with eligible MV anatomy, using pre-specified selection criteria.

Mean age: 82.4 ± 8.7 (SD) years.
>75 years: 83.5 (106/127).
Male: 55.1% (70/127).

NYHA class:
I – 2.4%
II – 11.0%
III – 63.8%
IV – 22.8%

Mean STS replacement mortality risk (%) – 13.2 ± 7.3 (SD)

Proportion with STS risk ≥ 8% - 79.5%

MR grade:
2+ - 8.7%
3+ - 56.7%
4+ - 29.9%</td><td>Procedural and 30-day outcomes</td><td>Successful implant – 95.3%
Device not implanted – 4.7% (6 patients):
• 4/6 due to technical reasons (1 due to inability to reduce MR, 1 due to inadequate MV area, 1 due to inability to deliver device due to torturous anatomy [scoliosis], 1 due to right atrial thrombus
• 2/6 due to complications (1 cardiac tamponade and 1 haemodynamic instability)

Mortality at 30 days – 8/127 (6.3%). Reasons for death: septic shock (n = 1); existing comorbidities (n = 2); gastrointestinal bleed n = 1); renal failure and cardiac tamponade (n = 1); MI (n = 1); vascular bleed (n = 1); stoke (n = 1).

Table reporting safety outcomes at 30 days (n = 127).

<table><tr><th>Description of event</th><th>Proportion (%)</th></tr><tr><td>Major bleeding complications</td><td>12.6 (16/27)</td></tr><tr><td>Death</td><td>6.3 (8/127)</td></tr><tr><td>Major vascular complications</td><td>5.5 (7/127)</td></tr><tr><td>Ventilation > 48 hours</td><td>3.1 (4/127)</td></tr><tr><td>Stroke</td><td>2.4 (3/127)</td></tr><tr><td>Renal failure</td><td>1.6 (2/127)</td></tr><tr><td>Atrial-septal defect</td><td>1.6 (2/127)</td></tr><tr><td>Non-cerebral thromboembolism</td><td>1.6 (2/127)</td></tr><tr><td>Gastrointestinal complication requiring surgery</td><td>0.8 (1/127)</td></tr><tr><td>MI</td><td>0.8 (1/127)</td></tr><tr><td>Non-elective surgery for adverse events</td><td>0.8 (1/127)</td></tr><tr><td>Mitral valve stenosis</td><td>0</td></tr><tr><td>Heart block/arrhythmia requiring permanent pace maker</td><td>0</td></tr></table></td><td>The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data are adequate to support the authors’ interpretation (score of 2); the results are generalisable (score of 2).

Total score: 9</td><td>Directly applicable.

Patients exclusively had DMR and were of “prohibitive” risk of surgery. This population is highly generalisable to the scope.</td><td>This was a retrospective analysis of data mainly from a previously published prospective observational study (EVEREST II HRS) and an on-going continued access study (EVEREST II REALISM). Patients were specifically selected for analysis if they were diagnosed with DMR and were considered to be a prohibitive risk from surgery; thus the study was highly generalisable.

The study was of high reporting quality and most of the outcomes relevant to the scope were included for analysis. This included healthcare resource use outcomes and HRQoL.

As this was a single-armed study, outcomes were cross-sectional or</td></tr>
</table>

Use of MitraClip* in patients with DMR who are at high risk from surgery

<table>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Outcome measures</th><th>Results**</th><th>Quality of Evidence Score***</th><th>Applicability†</th><th>Critical Appraisal Summary</th></tr>
<tr>
<td></td>
<td>analysis.
Pairwise comparisons of survival by discharge MR were performed using log-rank tests.
Pairwise comparisons used the chi-square test.
SF-36 data analysed using standard methodology.
Hospitalisation for HF used Poisson regression model.</td>
<td></td>
<td></td>
<td>
<table>
<tr><td>New onset AF</td><td>0</td></tr>
</table>
</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical outcomes (up to 1 year FU)</td>
<td>
Mortality: 23.6% (30/127)

Table reporting safety outcomes at 12 months (inclusive of 30 day data, n = 127).

<table>
<tr><td>Description of event</td><td>Proportion (%)</td></tr>
<tr><td>Major bleeding complications</td><td>15.7 (20/127)</td></tr>
<tr><td>Death</td><td>23.6 (30/127)</td></tr>
<tr><td>Major vascular complications</td><td>7.1 (9/127)</td></tr>
<tr><td>Ventilation > 48 hours</td><td>4.7 (6/127)</td></tr>
<tr><td>Stroke</td><td>2.4 (3/127)</td></tr>
<tr><td>Renal failure</td><td>3.9 (5/127)</td></tr>
<tr><td>Atrial-septal defect</td><td>2.4 (3/127)</td></tr>
<tr><td>Non-cerebral thromboembolism</td><td>1.6 (2/127)</td></tr>
<tr><td>Gastrointestinal complication requiring surgery</td><td>2.4 (3/127)</td></tr>
<tr><td>MI</td><td>0.8 (1/127)</td></tr>
<tr><td>Non-elective surgery for adverse events</td><td>0.8 (1/127)</td></tr>
<tr><td>Mitral valve stenosis</td><td>2.4 (3/127)</td></tr>
<tr><td>Heart block/arrhythmia requiring permanent pace maker</td><td>1.6 (2/127)</td></tr>
<tr><td>New onset AF</td><td>0</td></tr>
</table>

Table reporting changes in MR (%) at discharge and 1 year FU.

<table>
<tr><th>MR grade</th><th>Baseline</th><th>Discharge (n = 121)</th><th>1 year (n = 108)</th></tr>
<tr><td>≤ 1+</td><td>0</td><td>50.4</td><td>23.6</td></tr>
<tr><td>2+</td><td>8.7</td><td>26.8</td><td>29.9</td></tr>
<tr><td>3+</td><td>56.7</td><td>12.6</td><td>8.7</td></tr>
<tr><td>4+</td><td>29.9</td><td>4.7</td><td>2.4</td></tr>
<tr><td>Dead</td><td>0</td><td>0.8</td><td>20.5</td></tr>
</table>

Table reporting changes in NYHA class (%) at 30 days and 1 year FU.

<table>
<tr><th>NYHA class</th><th>Baseline</th><th>30 days</th><th>1 year</th></tr>
</table>
</td>
<td></td>
<td></td>
<td>longitudinal in nature. Because of this, firm conclusions of the relative benefits of treatment compared with other treatment modalities could not be made. However, as the patient population was relatively contraindicated to surgical repair or replacement, it would not be possible to investigate this comparison using experimental methodology on ethical grounds.</td>
</tr>
</table>

Use of MitraClip* in patients with DMR who are at high risk from surgery

<table>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Outcome measures</th><th>Results**</th><th>Quality of Evidence Score***</th><th>Applicability†</th><th>Critical Appraisal Summary</th></tr>
<tr>
<td></td><td></td><td></td><td></td>
<td>
<table>
<tr><td></td><td></td><td>(n = 122)</td><td>(n = 114)</td></tr>
<tr><td>I</td><td>2.4</td><td>2.9</td><td>26.8</td></tr>
<tr><td>I</td><td>11.0</td><td>43.3</td><td>30.7</td></tr>
<tr><td>III</td><td>62 2</td><td>14.2</td><td>7.1</td></tr>
<tr><td>IV</td><td>20.5</td><td>1.6</td><td>1.6</td></tr>
<tr><td>Dead</td><td>0</td><td>7.1</td><td>23.6</td></tr>
</table>

Table reporting QoL scores (SF-36, n = 122 evaluable patients)
<table>
<tr><td>Time point</td><td>QoL score Mean (SD)</td><td>Δ vs baseline Mean</td><td>P value</td></tr>
<tr><td></td><td colspan="3">Physical summary</td></tr>
<tr><td>Baseline</td><td>32.0 (8.7)</td><td></td><td></td></tr>
<tr><td>30 day</td><td>38.7 (10.3)</td><td>6.2</td><td><0.001</td></tr>
<tr><td>6 months</td><td>39.9 (10.4)</td><td>5.9</td><td><0.001</td></tr>
<tr><td>12 months</td><td>39.2 (10.5)</td><td>6.0</td><td><0.001</td></tr>
<tr><td></td><td colspan="3">Mental summary</td></tr>
<tr><td>Baseline</td><td>46.1 (12.5)</td><td></td><td></td></tr>
<tr><td>30 days</td><td>49.5 (11.3)</td><td>3.4</td><td><0.0064</td></tr>
<tr><td>6 month</td><td>52.7 9.7)</td><td>6.1</td><td><0.0004</td></tr>
<tr><td>12 months</td><td>51.8 (10.5)</td><td>5.6</td><td><0.0011</td></tr>
</table>

There were significant improvements in QoL in all domains and at all time-points compared with baseline.
</td>
<td></td><td></td><td></td>
</tr>
<tr>
<td></td><td></td><td></td><td>Healthcare resource use</td>
<td>Mean post-procedural length of stay in ICU – 1.4 ± 1.8 (SD) days.
Mean post-procedural length of hospital stay – 2.9 ± 3.1 (SD) days.

Rate of hospitalisation due to HF:
Before MitraClip - 0.67 (95% CI 0.54 to 0.83) per PY.
After MitraClip - 0.18 (95% CI 0.11 to0.28) per PY.
73% reduction (p <0.0001).
Patients with on-going or untreated severe MR had no reduction in admission due to HF.

3 patients (2.4%) required open MV surgery within 1 year FU.</td>
<td></td><td></td><td></td>
</tr>
<tr>
<td>MARS registry (2016).

Reported in (Tay et al., 2016)</td>
<td>Multicentre retrospective registry with data reported from centres from Australia, China, Indonesia, Malaysia and</td>
<td>163 patients with MR grade ≥ 3+ with aetiology of FMR (n = 88) or DMR (n = 75) were enrolled.

Characteristics of the</td>
<td>Procedural and safety outcomes (30-day)</td>
<td><u>DMR cohort</u>
Procedural success rate – 92% [FMR 95.5%, p = 0.515]
Of 6 patients unsuccessful:
• 4 single leaflet detachment
• 2 difficulty grasping leaflets

30 day mortality rate – 6.7% (5/75, 3 inpatient) [FMR 4.5%, p = 0.555]</td>
<td>The research questions, aims and design are clearly stated (score of 1); the research design is appropriate for the aims and</td>
<td>Directly applicable.

Data from patients with DMR at high risk from surgery</td>
<td>This was a single-armed retrospective study with the attendant limitations this study type confers.

The reporting quality</td>
</tr>
</table>

Use of MitraClip* in patients with DMR who are at high risk from surgery							
Study reference	**Study Design**	**Population characteristics**	**Outcome measures**	**Results****	**Quality of Evidence Score*****	**Applicability†**	**Critical Appraisal Summary**
	Singapore. Patients received MitraClip between February 2011 and March 2014. The aim of this report of the study was to describe and compare the use of the MitraClip therapy in patients with FMR and DMR. <u>Statistics</u>: Comparison of continuous variables performed using the independent t test. Before and after comparison used the paired t test. Categorical variables compared with Chi square test.	<u>DMR cohort</u> (n = 75): Mean age: 72.7 ± 13.5 (SD) years Male: 64% MR grade 3+ - 17.3% MR grade 4+ - 82.7% NYHA class: I – 2.7% II – 36.0% III – 49.3% IV – 12% Mean logistic EuroSCORE – 15.7 ± 15.0 (SD) Mean STS score - 7.2 ± 7.5 (SD) DMR and FMR populations were statistically equivalent except DMR patients had lower risk of prior coronary artery disease, MI, or percutaneous coronary intervention.		DMR deaths: • 2 hypotension from HF • 1 stroke • 1 subarachnoid bleed (post-discharge) • 1 sepsis (post-discharge) 30 day MAE: 14.7% (11/75). [FMR 9.2%, p =0.281]: • 5 deaths • 1 MV operation • 2 ≥ 2 units blood transfusion • 1 prolonged intubation • 1 sepsis	objectives of the research (score of 1); the methods are clearly described (score of 1); the data are adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 2). **Total score: 6**	were reported. This population is highly generalisable to the scope.	of the study was adequate, although there were only limited outcome data reported. There was apparent loss to follow up in the reporting of some outcomes, which was not addressed by the authors. This was a small study, with follow up limited to 30 days. Hence it is not possible to determine the clinical efficacy of MitraClip patients over a meaningful time frame from this study.
			Clinical outcomes (30 days FU)	*MR grade* at 30 days (n = 75) 1+ - 45% 2+ - 25% 3+ - 17% 4+ - 5% Dead - 7% (trend in favour of FMR, p = 0.062) *NYHA class* at 30 days (n = 58) I – 36% II - 47% III - 17% IV+ - 0% (p < 0.001 compared with baseline, p = 0.525 compared with FMR).			
Rudolph et al. (2013) Reported in (Rudolph et al., 2013).	Investigator led, single centre prospective observational study, Germany. Patients recruited consecutively between September 2008 and 31 December 2011 (all patients, n = 270). The aim of the study was to	230 patients with MR grade ≥ 3+ were included in whom FU data were available. DMR – 33% (n = 77) FMR – 67% (n = 153). Characteristics of <u>DMR cohort</u>: Mean age: 77 ± 9 (SD) years. Male: 51% MR grade 3+ - 44%	Procedural and safety outcomes (30-day)	Overall success rate – 88% (202/230) "The 28 patients in whom treatment failed more often had DMR (54% vs. 31% in successfully treated patients, p = 0.020)".	The research questions, aims and design are clearly stated (score of 1); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data are	**Directly applicable** Overall population appears to be generalisable, although possibly at greater risk from surgery than observed in other studies	This was a single-armed prospective study with the inherent limitations of this study type. The aim of the study was primarily to identify prognostic factors in the treatment of MitraClip in patients with DMR and FMR. Some of the
			Clinical outcomes Median FU if successful procedural outcome – 13.3 months (range 0.4 to 37.8 months)	Overall *mortality* during FU – 28% (n = 15 DMR, n = 40 FMR). DMR – 19.5% FMR – 26.1% 1 year *mortality* – 20% 2 year *mortality* – 33% (ns difference between DMR and FMR). DMR survival (from Figure 1): 1 year – 83.8% 2 years – 66.4% (p = ns)			

Use of MitraClip* in patients with DMR who are at high risk from surgery							
Study reference	**Study Design**	**Population characteristics**	**Outcome measures**	**Results****	**Quality of Evidence Score*****	**Applicability†**	**Critical Appraisal Summary**
	assess predictive characteristics for MAE, with particular differentiation between DMR and FMR. Statistics: KM survival analysis. Log rank test, Coc proportional hazards regression analysis. Comparisons of continuous variables performed with Mann–Whitney's U-test or Student's unpaired t-test. Comparisons of categorical variables performed with Fisher's exact test (or Chi square test.	MR grade 4+ - 56% NYHA class: II – 5% III – 68% IV – 27% Median logistic EuroSCORE – 20 (IQR 11 to 39) Median STS mortality score - 4.4 (IQR 2.9 to 8.5) There were significant differences observed between patients with DMR and FMR in LV dysfunction and related physiological parameters.	Median FU if unsuccessful procedural outcome – 5.0 months (range 0.3 to 25.5 months)		adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 1). **Total score: 6**	(median logistic EuroSCORE 20).	outcomes reported reflected low event rates, which is a cause of uncertainty. Thus the results reported did not necessarily support the headline conclusions. This was a particularly high risk cohort of patients that may not be fully generalisable to other populations.
			Healthcare resource use	*HF rehospitalisation* Overall 45% of successful treated patients were re-hospitalised due to HF symptoms over FU period. Freedom from rehospitalisation (from Figure 2) DMR 1 year – 65.1%, 2 years - 59.7% FMR 1 year – 53.6%, 2 year 34.4% (p = ns) *Re-intervention* in 17 patients (8%). 10 MitraClip, 7 MV replacement. Freedom from re-intervention (from Figure 4): DMR 1 year – 88.4% FMR 1 year – 94.7% (p = ns)			
Seeger et al. (2017). Reported in (Seeger et al., 2017)	Prospective observational study set in a single high volume centre (Germany). The aim was to compare short-term outcomes in patients with DMR and FMR using standardised outcome measures (MVARC criteria). Statistics: Categorical	210 patients with severe symptomatic MR (≥ 3+) enrolled, equally with DMR (n = 105) and FMR (n = 105). "Percutaneous repair was decided by a heart team including cardiologists and heart surgeons". Characteristics of DMR cohort: Mean age: 73.6 ± 7.1 (SD) years.	Procedural outcomes	DMR cohort Technical success – 98.1% Mean MR grade after intervention – 1.3 ± 0.6 (SD) Proportion MR grade ≥ 1 improvement – 96.2% Proportion MR grade 0 to 2 – 95.2% Complications: Minor vascular complications – 10.4% New onset AF – 2.9% All the following 0.0%: major vascular complication; major bleeding; partial clip detachment; clip embolization; re-intervention; conversion to surgery; pericardial effusion. No significant differences to FMR in any procedural measure.	The research questions, aims and design are clearly stated (score of 1); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data are adequate to support the	**Directly applicable** The study reported data from patients with DMR and at high risk of surgical intervention.	This was a single-armed prospective study with the inherent limitations of this study type. The study reported disaggregated data from DMR patients at high surgical risk. Limited comparisons were made between these patient groups. The main limitation of the study was that follow up was
			Clinical outcomes (30 day FU)	DMR cohort "Device success" after 30 days – 94.3% 30 day safety (MVARC) – 5.7%			

Use of MitraClip* in patients with DMR who are at high risk from surgery

<table>
<tr><th>Study reference</th><th>Study Design</th><th>Population characteristics</th><th>Outcome measures</th><th>Results**</th><th>Quality of Evidence Score***</th><th>Applicability†</th><th>Critical Appraisal Summary</th></tr>
<tr><td></td><td>variable compared with Pearson's Chi square test. Continuous variables compared with two sample t test of Mann-Whitney U-test.</td><td>Male: 59.1%

Mean NYHA class – 3.2 ± 0.7 (SD)
Proportion NYHA class ≥ III – 79%

Proportion MR grade:
1 – 0%
2 – 0%
3 – 26.7%
4 – 73.3%

Surgical risk – "high risk as defined by STS score".

No significant differences from FMR cohort except prescribed medication.</td><td></td><td>Mortality – 3.8% (n = 4)
Cause of death: 1 urosepsis, 1 pulmonary embolism, 1 hypoxic respiratory failure, 1 renal failure.

Table reporting change in NYHA class from baseline at 30 days (n = 105).

<table><tr><th>NYHA class</th><th>Baseline</th><th>Discharge</th></tr><tr><td>I</td><td>0.0</td><td>64.4</td></tr><tr><td>II</td><td>10.4</td><td>27.0</td></tr><tr><td>III</td><td>52.8</td><td>8.0</td></tr><tr><td>IV</td><td>35.9</td><td>0.0</td></tr></table></td><td>authors' interpretation (score of 1); the results are generalisable (score of 2).

Total score: 7</td><td></td><td>restricted to 30 days. It was therefore not possible to draw conclusions on the long-term efficacy and safety of MitraClip.</td></tr>
</table>

Abbreviations: ACCESS-EU - ACCESS-Europe A Two-Phase Observational Study of the MitraClip System in Europe; AE – adverse events; AF – atrial fibrillation; ANOVA – analysis of variance; CI – confidence interval; DMR – degenerative mitral valve regurgitation; EQ – Euroqol; EVEREST - Endovascular Valve Edge-to-Edge Repair Study; FMR - functional mitral valve regurgitation; FU – follow up; HR – high risk; HF- heart failure; HRQoL – health-related quality of life; HRS – high risk study; ICU – intensive care unit; IQR – inter-quartile range; ITT – intention to treat; KM – Kaplan Meier; LE – logistic EuroSCORE I; LR – low risk; MAE – major adverse event; LV – left ventricular; MACCE - major adverse cardiac and cerebrovascular events; MARS – MitraClip in the Asia-Pacific Registry; MI – myocardial infarction; MLHFQ - Minnesota Living with Heart Failure questionnaire; MR – mitral valve regurgitation; MV – mitral valve; MVARC – Mitral Valve Academic Research Consortium; ns – not significant; NYHA – New York Heart Association (class); PY – person year; REALISM - (Real World Expanded Multi-center Study of the MitraClip System); SD – standard deviation; SF-36 – short form 36; STS – Society of Thoracic Surgeons; STS-PROM – STS predicted risk of mortality; TIA – transient ischaemic attack; TOE –transoesphageal echocardiograph); TRAMI - Transcatheter Mitral Valve Interventions; TVT – Transcatheter Repair Therapy; US – United States; VARC – Valve Academic Research Consortium; VAS – visual analogue scale.

* All interventions used in single armed studies were percutaneous edge to edge repair of mitral valve using MitraClip.
** Results in italics exactly match those requested in scope.
*** Included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases and sources of confounding inherent to registry and observational studies.
† Applicability score of most relevant subgroup analysed.

7.b. Evidence Summary Table for Clinical studies (comparative).

Use of MitraClip in patients with DMR who are at high risk from surgery								
Study reference	**Study Design**	**Population characteristics**	**Intervention(s)**	**Outcome measures**	**Results**	**Quality of Evidence Score***	**Applicability**	**Critical Appraisal Summary**
EVEREST II HR study†. Reported in (Whitlow et al., 2012)	Multi-centre, prospective observational with retrospectively matched controls (US). Statistics: Intention to treat analysis applied. Categorical data expressed as a compared using the Fisher's exact test, and ordinal data compared using the Bowker test. A Clopper-Pearson exact binomial method was used to determine whether the observed 30-day mortality rate was lower than the 1-sided 95.472% upper CI of the estimated 30-day mortality rate. KM survival analysis was used with the log-rank test to compare the 2 groups. The rate of hospitalization for congestive heart	MitraClip cohort (n = 78) Mean age: 76.7 ± 9.8 (SD) years. Male: 62.8% MR aetiology: DMR – 41.0% FMR – 59.0% MR grade ≤ 2+ - 1.3% NYHA class: I/II – 10.2% III/IV – 89.8% STS suspected mortality risk score – 14.2 ± 8.2% (SD) Comparator cohort (n = 36) Mean age: 77.2 ± 13.0 (SD) years. Male: 50.0% MR aetiology: DMR – 36.1% FMR – 63.9% STS suspected mortality risk score – 14.9 ± 8.5% (SD) No significant difference between	Intervention: percutaneous edge to edge repair of mitral valve using MitraClip. Comparator: cohort of patients who did not receive MitraClip. 86% were managed medically and 14% underwent MV surgery.	Freedom from mortality at 12 months FU.	MitraClip cohort: 75.4% Comparator cohort: 55.3% p = 0.047	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data are adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 0). **Total score: 6**	**Indirectly applicable** Patients in intervention group had mixed DMR and FMR. Patients in comparator group received mixed interventions (medical management and surgery).	This study was of relatively high methodological quality with the prospective cohort being part of the EVEREST group of studies. The study principally reported baseline, cross sectional, and longitudinal data from the prospective cohort who received MitraClip, which was a heterogeneous aetiological case mix. The authors identified a retrospective comparator group, but patient numbers and data in this group were limited. The only comparative outcome reported was mortality after 1 Year. This estimate was subject to selection bias and confounding.

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	failure (CHF) (12-month pre-enrolment and post-discharge) was estimated and compared using a Poisson regression model.	cohorts in any reported variables.						
Swaans et al. (2014) Reported in (Swaans et al., 2014)	Single-centre, prospective observational study with retrospectively identified comparator groups. Aim was to compare survival outcomes in patients with severe MR with 3 different treatment strategies. <u>Statistics</u>: Dichotomous variables were tested by the chi-square test. Comparisons between groups were done by ANOVA, with the least significant difference test as a post-hoc test. Propensity scoring was used on baseline statistics to reduce confounding. LE, age, chronic obstructive pulmonary	MitraClip patients were enrolled consecutively between January 2009 and April 2013 (n = 139). <u>MitraClip patient characteristics</u>: Mean age: 74.6 ± 9.4 (SD) years. Male: 67.6% FMR – 77.0% (n = 107) DMR – 18.0% (n = 25) Mixed – 5.0% (n = 7) NYHA class: II – 11.5% III – 65.5% IV – 23.0% Mean log EuroSCORE – 23.9 ± 16.0% Other comparator groups had significantly different aetiological case mix including significantly larger proportion of DMR in surgically treated patients (p = 0.005), and had lower surgical risk	Intervention (MC): percutaneous edge to edge repair of mitral valve using MitraClip (n = 139). Comparator (HRS): high-risk surgery (n = 53) Comparator (CMM): conservative medical management (n = 59).	Survival outcomes	<u>1 year survival rate</u>: MC – 85.8% HRS – 85.2% CMM - 67.7% <u>2 year survival rate</u>: MC – 75.5% HRS – 77.8% CMM – 52.5% <u>3 year survival rate</u>: MC – 62.3% HRS – 68.5% CMM – 45.8% Following propensity score controlling: MC superior to CMM: (HR 0.41, 95% CI 0.22 to 0.78, P = 0.006) HRS superior to CMM: (HR 0.52, 95% CI 0.30 to 0.88, p = 0.014). MC and HRS not significantly different: (HR 1.25, 95% CI 0.72 to 2.16, p = 0.43)	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data were adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 0). **Total score: 6**	**Indirectly applicable** Only 19% of intervention group had DMR.	This study prospectively enrolled 139 patients receiving MitraClip and compared this cohort with similar cohorts receiving surgery or medical management. The only outcome of interest reported was survival rate (mortality). The groups were not equivalent at baseline, with the MitraClip group exhibiting higher surgical risk as measured by logistic EuroSCORE (23.9 ± 16.1% [SD]) compared with the surgery group (14.2 ± 8.9%) or the conservatively medical management group (18.7 ± 13.2%). This lack of equivalence between groups causes uncertainty in the conclusions. Additionally, this

Use of MitraClip in patients with DMR who are at high risk from surgery								
Study reference	**Study Design**	**Population characteristics**	**Intervention(s)**	**Outcome measures**	**Results**	**Quality of Evidence Score***	**Applicability**	**Critical Appraisal Summary**
	disease, known coronary artery disease, previous MI, history of CABG, history of percutaneous coronary intervention, glomerular filtration rate, LVEF, cardiac resynchronisation therapy in situ, and aetiology of MR were identified as potential confounders Cox proportional hazards model used for comparisons between groups	($p < 0.0001$)						study lacked generalisability as it did not report data exclusively on DMR patients.
Velasquez et al. (2015)† Reported in (Velazquez et al., 2015)	Retrospective observational case series of MitraClip patients propensity matched with similar patients from a hospital database Multicentre centre, US. The study aimed to compare the survival of patients with high-surgical-risk with moderate or severe MR treated with MitraClip or conservative medical management.	MitraClip patients were recruited from EVEREST HRS and REALISM studies (n = 351). Comparator patients were from "Duke high risk" cohort (n = 953) from which patients which matched EVEREST HRS criteria were recruited. Characteristics of propensity matched MitraClip patients (n = 239): Mean age: 73.7 ± 10.5 (SD) years. Age >775 years:	Intervention (MC): percutaneous edge to edge repair of mitral valve using MitraClip (n =239) Comparator (CMM): Duke high-risk patients (conventional medical management) (n = 239)	Mortality at 30 days	<u>30 days</u> MC – 4.2% CMM – 7.2% <u>1 year</u> MC – 22.4% CMM – 32.0%	The research questions, aims and design are clearly stated (score of 2); the research design is appropriate for the aims and objectives of the research (score of 1); the methods are clearly described (score of 2); the data are adequate to support the authors' interpretation (score of 1); the results are generalisable (score of 0). **Total score: 6**	**Indirectly applicable** Only 17.2% of MitraClip cohort had DMR. Only 9.2% of comparator had DMR.	This study enrolled consecutive patients from the EVEREST II HR and REALISM studies, and used propensity matching to compare the outcome of mortality at 1 year with similar patients from a hospital database. Only mortality at 30 days and1 year was This study was at high risk of bias due to its retrospective design and the historical nature of
				KM analysis (12 months FU) MC vs. CMM	"Optimally matched cohorts" (n = 239) Adjusted HR 0.66 (95% CI 0.45 to 0.99) "Best available" matched cohorts" (n = 351) HR = 0.61 (95% CI 0.44 to 0.86; p = 0.005) Total cohort (n = 351 [MC] and 953 [CMM]) HR = 0.67 (95% CI 0.48 to 0.94; p = 0.019)			

Use of MitraClip in patients with DMR who are at high risk from surgery								
Study reference	**Study Design**	**Population characteristics**	**Intervention(s)**	**Outcome measures**	**Results**	**Quality of Evidence Score***	**Applicability**	**Critical Appraisal Summary**
	Statistics: propensity score matching was performed using propensity scores generated from a multivariable logistic regression model including the variables age, sex, history of MI, stroke, chronic obstructive pulmonary disease, renal disease, diabetes mellitus, previous cardiac surgery, current New York Heart Association (NYHA) class III/IV, and LVEF. Wilcoxon rank-sum test was used for continuous variables and Fisher's exact test for categorical variables. KM analysis with Cox proportional hazards model used for survival analysis.	51.0% Male: 59.8% DMR – 17.2% FMR – 88.8% NYHA class III/IV – 78.2% Mean STS valve replacement score 9.93 ± 7.00. Propensity matched comparator patient not equivalent for aetiology (90.8% FMR, p = 0.0144). Equivalent for and STS score (13.8 ±10.9, p = 0.0001) and for all other variables except left ventricular internal dimension (p < 0.0001).						the comparator group. Despite "optimal" propensity matching, there were significant differences in baseline characteristics between the group. Thus results should be interpreted with caution.

Abbreviations: EVEREST - Endovascular Valve Edge-to-Edge Repair Study; FU – follow up; KM – Kaplan Meier; HR – hazard ratio; HRS – high risk study; SD – standard deviation; US – United States.

* Included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases and sources of confounding inherent to registry and observational studies.
† These studies reported data from the EVEREST II studies and have been included due to the comparative analysis used. However, this was also the source of patients used in the analysis by Lim (Table 7.a) (Lim et al., 2014). To avoid double counting of patients, longitudinal data are reported in the Lim study whereas comparative data, using different methodology, are reported here by Whitlow et al. (2012) and Velazquez et al. (2015).

7.c. Evidence Summary Table for Economic studies.

Study reference	Study Design	Population and characteristics	Intervention and comparator	Methods of analysis	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
UK Study (Mealing et al., 2013)	Cost utility analysis	Patients with severe MR (MR 3 to 4+) and unfit for surgery due to high surgical risk profile. Data taken from EVEREST II HRS study(n = 78 in the MitraClip arm and 36 in the MM arm). (Whitlow et al., 2012)	Intervention: percutaneous edge to edge repair of mitral valve using MitraClip. Comparator: "All comparator group patients were treated according to standard of care over the 12-month period, with 86% managed medically and 14% undergoing mitral valve surgery".	A short term (30 day) Markov model linked to a long-term (5 year) Markov model. In 30 days state are health states for surgery, MitraClip procedure, ICU/general ward, home and death. In long-term model events are home, MitraClip procedure and death. NHS perspective and discounting at 3.5% applied. Model also captures change in NYHA class at baseline and to 24 months for MitraClip arm from EVEREST II HRS; thereafter no change is assumed. In MM arm baseline distribution is maintained for lifetime. Mortality at 12 months from EVEREST II HRS and extrapolated using Weibull curves for both arms. Subsequent MitraClip procedures, other cardiac related	Cost were at 2011 prices. Cost for MitraClip was £20,000. Other unit prices from BNF and NHS Reference costs. Utilities were from the literature and by NYHA classes and by ward (ICU and general wards). At 2 years additional QALYs with MitraClip were 0.48; additional costs £25,565, giving incremental cost/QALY of £52,947. At 5 years additional QALYs with MitraClip were 1.22; additional costs £27,000, giving incremental cost/QALY of £22,200. At 10 years ICER was £14,800. Cost drivers were lifetime procedure costs £20,500, short term LoS £3,800 and higher drug costs £1,400) as live longer. Probability MitraClip cost effective at £30,000 per QALY was 93%. Results were sensitive to time horizon, utility for NYHA class II and cost of MitraClip. Lifetime survival 5.1 years with MitraClip versus 1.9 years with MM.	The research questions, aims and design are clearly stated (score of 2). The research design is appropriate for the aims and objectives of the research (score of 2). Methods are well-described particularly in the supplementary materials (score 2). Assumptions and data used are transparent and provide sufficient information to give confidence that these support the authors' interpretation/conclusions (score 1). Results likely to generalise to NHS perspective (score 1) **Total score: 8**	This was a cost utility analysis with a payer perspective from the UK NHS and PSS using H R-QoL scoring and a discount rate relevant to NICE. One possible limitation was that the clinical data used to inform the clinical inputs was derived from a US study. However, overall generalisability was good. **Directly applicable.**	MitraClip was cost effective at 10 years compared with medical management in this high risk population (patients with mixed mitral valve pathology a high risk of surgery). Authors noted several limitations including small sample size).. Also not clear if 36 would be eligible for MitraClip so may not be valid comparator. Other issues included absence of long-term data, follow-up at 12 months only in survivors in MitraClip arm plus extrapolation of methods. A possible omission was that there was no endpoint for hospitalisation from bleeds.

Study reference	Study Design	Population and characteristics	Intervention and comparator	Methods of analysis	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
				surgery, length of stay (LoS), major stroke, and HF hospitalisation from clinical study for MitraClip arm. MM arm included HF admissions and LoS only.				
(Vemulapalli et al., 2017)	"Before and after" cost comparison.	FMR and DMR at high surgical risk (surgical mortality risk of ≥12%) in the EVEREST II High-Risk Registry & REALISM Continued-Access Registry plus had to match to Medicare records for 12 months pre and post procedure (n = 403 patients, mean age 80, 60% male, mean baseline LVEF 50%, 58% had grade 3+/4+ MR).	Intervention: percutaneous edge to edge repair of mitral valve using MitraClip. Comparator: Data from 12 months prior to MitraClip treatment.	The following outcomes were measured before and after treatment with MitraClip: Intervention: percutaneous edge to edge repair of mitral valve using MitraClip. All-cause death, stroke, MI, heart failure (HF), and bleeding hospitalizations were identified and analysed within patient.	All-cause hospitalisation in the year prior to MitraClip was 1,853.6/1,000 PY and decreased to 1,435.0/1,000 PY, (HR 0.82 (95% CI 0.73 to 0.92, p = .001). 70.5% had all-cause hospitalizations (mainly for HF) in year prior to MitraClip vs 55.3% in 12 months post MitraClip. Rates of hospitalizations for bleeds or procedures increased from 198.5/1,000 PY before the procedure to 297.9/1,000 PYs in post 12 months (HR = 1.72, 95% CI 1.28 to 2.32, p = 0.001). Hospitalization for stroke & MI was rare and not significantly different in the year before and after MitraClip. In the sensitivity analysis of those who survived 12 months after MitraClip, similar event ratios except bleeds not statistically significant change. LoS: the rate of days hospitalized for all causes increased from 9,384.6/1,000 PY to 10,311.5/1,000 PY in the	The research questions, aims and design are clearly stated (score of 2). The research design is appropriate for the aims and objectives of the research (score of 2). Methods are well-described particularly in the supplementary materials (score 1). Assumptions and data used are transparent and provide sufficient information to give confidence that these support the authors' interpretation/conclusions (score 1). Results likely to generalise to NHS perspective (score 0) **Total score:6**	Clinical data was derived from a study in a US setting and costs were reported in US dollars. **Indirectly applicable**	The main issue was that the definition of cost was limited to hospital admissions only and excluded costs of Mitraclip and related procedure. Low external validity due to costs not UK (for instance, the use Medicare .expenditures) Additionally, clinical evidence was informed by a study that was undertaken in a US healthcare setting. Abbott Vascular funded work.

Study reference	Study Design	Population and characteristics	Intervention and comparator	Methods of analysis	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
					year pre-MitraClip vs post MitraClip (HR= 1.36, 95% CI 1.29-1.42, P b .001). Most common cause was HF, which decreased from 3,878.4/1,000 PY pre-MitraClip to 2,257.1/1,000 PY post- MitraClip (HR = 0.68, 95% CI 0.62-0.75, p = 0.001). The rate of hospital days attributable to stroke (HR= 2.65, 95% CI 1.28-5.48, p = .009) and bleeds (HR = 3.11, 95% CI 2.79-3.48, p = 0 .001) increased post-MitraClip but lower for MI.			

Abbreviations: EVEREST - Endovascular Valve Edge-to-Edge Repair Study; HR-QoL – health-related quality of life; HF – heart failure; HR – hazard ratio; HRS – high risk study; ICU – intensive care unit; LoS - Length of stay; LVEF – left ventricular ejection fraction; MM – medical management; MR – mitral valve regurgitation; MI - myocardial infarction; NHS National Health Service; NYHA – New York Heart Association; PSS – personal social services; PY – person year.

8. Grade of evidence tables

Use of MitraClip in patients with DMR who are at high risk from surgery					
Outcome Measure	**Study and reference**	**Quality of Evidence Score (out of 10)***	**Applicability****	**Grade of Evidence**	**Summary of evidence from studies**
Procedural and technical success rate (Critical)	ACCESS-EU study (Reichenspurner et al., 2013)	8	Direct	A	Overall success rate - 94.9%
	Braun et al. (2014) (Braun et al., 2014)	8	Direct		Success rate (defined as successful MR reduction ≥ 1) - 83.3%
	Estevez-Loureiro et al. (2013)(Estevez-Loureiro et al., 2013b)	8	Direct		Procedural success - 96.2%
	Geis et al. (2018) (Geis et al., 2018)	6	Direct		Success rate (defined as a reduction of MV regurgitation to less than mild/moderate [grade 1 or 2]): 91%
	Lim et al. (2014) (Lim et al., 2014)	9	Direct		Successful implant - 95.3%
	MARS registry (2016) (Tay et al., 2016): 6	6	Direct		Procedural success rate – 92%
	Netherlands registry".(Rahhab et al., 2017)	5	Indirect		Device success - 91% Technical success - 95%
	Pilot European Sentinel registry (Nickenig et al., 2014)	9	Direct		Procedural success - 93.7%
	Rudolph et al. (2013) (Rudolph et al., 2013)	6	Direct		Overall success rate – 88%
	Seeger et al. (2017) (Seeger et al., 2017)	7	Direct		Technical success – 98.1%
	TRAMI registry (Baldus et al., 2012):	5	Indirect		Procedural success: 97%
	TVT registry (Sorajja et al., 2017a):	9	Direct		Successful procedure: Post-implant MR grade ≤ 2, no mortality, and no cardiac surgery – 91.8% Post-implant MR grade 1, no mortality, and no cardiac surgery – 60.9%
Overall summary of evidence for procedural and technical success rate	All the single-armed observational studies (N = 12) reported some metric of technical or procedural success, ranging from "an overall success rate" of 88% (Rudolph et al., 2011), to a "procedural success rate" of 97% (Baldus et al., 2012). However, definitions of success using MitraClip varied. In general, the more strict the definition (for instance technical success incorporating measurable MR grade reduction), the lower the rate reported. Overall the technical and procedural success of attaching MitraClip inpatients with DMR is high, with an estimate between 90 to 95% being reasonable.				
	ACCESS-EU study (Reichenspurner et	8	Direct	A	Death (30 days) – 6.0%

Use of MitraClip in patients with DMR who are at high risk from surgery					
Outcome Measure	**Study and reference**	**Quality of Evidence Score (out of 10)***	**Applicability****	**Grade of Evidence**	**Summary of evidence from studies**
Procedural and 30 day mortality rate (Critical)	al., 2013)				
	Estevez-Loureiro et al. (2013)(Estevez-Loureiro et al., 2013b)	8	Direct		Peri-procedural death – 1.2%
	Geis et al. (2018) (Geis et al., 2018)	6	Direct		Death (30 days) – 2%
	Lim et al. (2014).(Lim et al., 2014)	9	Direct		Death (30 days) – 6.3%
	MARS registry (2016) (Tay et al., 2016):	6	Direct		Death (30 days) – 6.7%
	"Netherlands registry" (Rahhab et al., 2017)	5	Indirect		Intra-procedural death - 0.3%
	Pilot European Sentinel Registry (Nickenig et al., 2014)	9	Direct		Procedural and in-hospital death – 4.9%
	Seeger et al. (2017) (Seeger et al., 2017)	7	Direct		Death (30 days) – 3.8%
	TRAMI registry (Baldus et al., 2012)	5	Indirect		In-hospital mortality rate – 2.4%
	TVT registry	9	Direct		In-hospital mortality rate – 2.7%
Overall summary of evidence for procedural and 30 day mortality rate	Procedural and short-term mortality (measured as in-hospital or at 30 days) was reported by most of the included observational studies (N = 10). The procedural death rate was very low, as reported in a large retrospective analysis (0.3%) (Rahhab et al., 2017), with peri-procedural mortality reported at 1.2% (Estevez-Loureiro et al., 2013b). However, the reported in-hospital mortality rate was considerably greater (around 2.5%) and the rate increased at 30 days, to around 6.5%. These figures should be considered bearing in mind the uncertainty caused by low absolute event numbers. Additionally they should be considered in the context these patients are by definition at high surgical risk. EuroSCORE and STS estimates of mortality were invariably higher than the observed mortality rates.				
Procedural, in-hospital and 30 day AE rates (Critical)	ACCESS-EU study (Reichenspurner et al., 2013)	8	Direct	A	Total AE at 30 days – 14.3%
	Braun et al. (2014) (Braun et al., 2014)	8	Direct		16.7% of procedures "unsuccessful"
	Estevez-Loureiro et al. (2013) (Estevez-Loureiro et al., 2013b).	8	Direct		All complication rate (30 days) – 12.6%
	MARS registry (2016) (Tay et al., 2016)	6	Direct		30 day MAE – 14.7%
	TRAMI registry (Baldus et al., 2012)	5	Indirect		MACCE – 3.1%
Overall summary of evidence for in-hospital and 30 day AE rates	Only studies which reported overall (aggregate) AE rates have been included (N = 5). Differences in definitions and terminology make direct comparisons of AE rates between studies difficult. However, the overall AE rate, which includes relatively unserious AE, appears to be around 12 to 15%. More serious events, which include death, are less common.				
Reduction in MR grades (Critical)	ACCESS-EU study (Reichenspurner et al., 2013)	8	Direct	A	Freedom from MR ≥ 2 – 74.6%
	Braun et al. (2014) (Braun et al., 2014)	8	Direct		Proportion MR reduction ≤ 2 grades: 1 month 83.3%; 6 months – 75%; 12 months – 83.3% ($p < 0.001$ compared with baseline).
	Estevez-Loureiro et al. (2013)(Estevez-Loureiro et al., 2013b)	8	Direct		Proportion MR grade at 6 months: 0 to 1 – 63.3%; 2 – 32.9%; 3 to 4 – 3.8%.
	Geis et al. (2018) (Geis et al., 2018)	6	Direct		Reduction in mean MR grade at 12 months – 1.2 ± 0.3 (SD, $p < 0.001$)

Use of MitraClip in patients with DMR who are at high risk from surgery					
Outcome Measure	**Study and reference**	**Quality of Evidence Score (out of 10)***	**Applicability****	**Grade of Evidence**	**Summary of evidence from studies**
	Lim et al. (2014) (Lim et al., 2014)	9	Direct		Proportion MR grade at 12 months: ≤ 1+ - 23.6%; 2+ - 29.9%; 3+ - 8.7%; 4+ - 2.4%; (Dead – 20.5%)
	MARS registry (2016) (Tay et al., 2016): 6	6	Direct		Proportion MR grade at 30 days: ≤ 1+ - 45%; 2+ - 25%; 3+ - 17%; 4+ - 0%; (Dead – 7%)
	"Netherlands registry".(Rahhab et al., 2017)	5	Indirect		MR reduction (post implant): 1 class: 9%; 2 classes: 51%; 3 classes: 33%; (≥1 class: 94%)
	Pilot European Sentinel registry (Nickenig et al., 2014)	9	Direct		Proportion MR grade at 12 months: none/mild – 57.4%; moderate – 36.1%; severe – 6.6%.
Overall summary of evidence reduction in MR grades	Eight studies reported post-implant data on MR grade compared with baseline. Results between studies are not always comparable because of non-standardised measurement and classification of MR. However, all the studies that included this outcome in DMR patients reported large statistically and clinically significant reductions in MR grade following treatment with MitraClip.				
Reduction in deaths (Critical)	EVEREST II HR study (Whitlow et al., 2012)	6	Indirect	C	Freedom from death at 12 months: MitraClip – 75.4% Comparator (86% CMM, 14% surgery) – 55.3%
	Swaans et al. (2014) (Swaans et al., 2014)	6	Indirect		<u>1 year survival rate:</u> MC – 85.8% HRS – 85.2% CMM - 67.7% <u>2 year survival rate:</u> MC – 75.5% HRS – 77.8% CMM – 52.5% <u>3 year survival rate:</u> MC – 62.3% HRS – 68.5% CMM – 45.8% MitraClip superior to CMM: (HR 0.41, 95% CI 0.22 to 0.78, p = 0.006) MitraClip and surgery not significantly different: (HR 1.25, 95% CI 0.72 to 2.16, p = 0.43)
	Velazquez et al. (2015) (Velazquez et al., 2015)	6	Indirect		<u>Mortality at 30 days:</u> MC – 4.2% CMM – 7.2% <u>Mortality at 1 year:</u> MC – 22.4% CMM – 32.0% "Optimally matched cohorts" (n = 239) Adjusted HR 0.66 (95% CI 0.45 to 0.99)
Overall summary of evidence	The comparative evidence for reduction in deaths associated with MitraClip (compared with medical management or high risk surgery) was derived from three observational studies which prospectively				

Use of MitraClip in patients with DMR who are at high risk from surgery					
Outcome Measure	**Study and reference**	**Quality of Evidence Score (out of 10)***	**Applicability****	**Grade of Evidence**	**Summary of evidence from studies**
reduction in deaths	enrolled MitraClip patients and compared these with historical controls. There are four important limitations with these analyses. Firstly, these studies reported on a case mix of patients with DMR and FMR (but with FMR predominating). Secondly, despite the use of propensity matching, the patient cohorts differed in some important respects at baseline. Thirdly, this methodology is inherently subject to particular confounding and bias. Finally, two of these studies (Whitlow et al., 2012, Velazquez et al., 2015) used patient data that have been reported in another study (Lim et al., 2014). These studies reported significant reductions in patient mortality over a follow up period of up to 3 years compared with CMM (but not surgery. Thus it is feasible that MitraClip may reduce mortality in selected patients.				
Proportion of deaths at follow up (Critical)	ACCESS-EU study (Reichenspurner et al., 2013)	8	Direct	A	Mortality rate at 1 year – 17.1%
	Braun et al. (2014) (Braun et al., 2014)	8	Direct		Survival at 12 months – 93.1% (Mortality rate – 16.9%)
	Lim et al. (2014) (Lim et al., 2014)	9	Direct		Mortality at 12 months – 23.6%
	Pilot European Sentinel registry (Nickenig et al., 2014)	9	Direct		Mortality at 12 months – 16.3%%
	Rudolph et al. (2013) (Rudolph et al., 2013)	6	Direct		Survival rate: 1 year – 83.8% (mortality rate – 16.2%) 2 years – 66.4% (mortality rate 33.6%)
	TRAMI registry (Baldus et al., 2012):	5	Indirect		Mortality at 12 months - 19.8% (95% CI 17.2 to 22.8%)
	TVT registry (Sorajja et al., 2017a):	9	Direct		Mortality at 12 months 24.7%
Overall summary of evidence of proportion of deaths at follow up	Seven studies reported mortality or survival rates at 1 year or more. The results were relatively consistent. At 1 year, mortality ranged from 16.3% to 24.7%. One study reported the mortality rate at 2 years was 35.6%, over double of that reported at 1 year (Rudolph et al., 2013). The relatively high mortality rate in these DMR patients highlights the high levels of comorbidity in this patient group.				
Improvements in symptoms: NYHA class (Critical)	ACCESS-EU study (Reichenspurner et al., 2013)	8	Direct	A	NYHA class I or II at 12 months – 80.8%
	Braun et al. (2014) (Braun et al., 2014)	8	Direct		Reduction ≤ 2 NYHA classes: 1month 90.2%; 6 months – 90.2%; 12 months – 91.1% ($p < 0.001$ compared with baseline).
	Estevez-Loureiro et al. (2013)(Estevez-Loureiro et al., 2013b)	8	Direct		NYHA class at 6 months: I – 21.3%; II – 62.7%;III – 14.7%; IV – 1.3%.
	Geis et al. (2018) (Geis et al., 2018):	6	Direct		Reduction in mean NYHA class: Baseline - 3.5 ± 0.4 (SD); 12 months – 2.0 ± 0.3 (SD, $p < 0.001$).
	Lim et al. (2014) (Lim et al., 2014):	9	Direct		NYHA class at 12 months: I – 26.8%; II – 30.7%; III – 7.1%; IV – 1.6%; (Dead – 23.6%)
	MARS registry (2016) (Tay et al., 2016):6	6	Direct		NYHA class at 30 days: I – 36%; II – 47%; III – 17%; IV – 0%; ($p < 0.001$ compared with baseline).
	"Netherlands registry".(Rahhab et al.,	5	Indirect		NYHA reduction (post implant): no reduction: 7%; 1 class - 9%; 2 classes - 51%; 3 classes - 33%; ≥1 class - 94%.

Use of MitraClip in patients with DMR who are at high risk from surgery					
Outcome Measure	**Study and reference**	**Quality of Evidence Score (out of 10)***	**Applicability****	**Grade of Evidence**	**Summary of evidence from studies**
	2017)				
	Pilot European Sentinel registry (Nickenig et al., 2014)	9	Direct		NYHA class at 12 months: I – 36.8%; II – 47.1%; III – 14.7%; IV – 1.5%
	Seeger et al. (2017) (Seeger et al., 2017)	7	Direct		NYHA class at discharge: I – 64.4%; II – 27.0%; III – 8.0; IV – 0.0%
	TRAMI registry (Baldus et al., 2012):	5	Indirect		NYHA class at 12 months: I/II – 63.3% III/IV – 36.7%
Overall summary of evidence of improvements in NYHA class	Change to NYHA class is an important measurement of patient health, and changes to this were reported by most the observational studies (N = 10). These longitudinal results show unequivocally that treatment with MitraClip was associated with statistical and clinical improvement in NYHA class.				
Changes to HR-QoL (Critical)	Lim et al. (2014) (Lim et al., 2014)	9	Direct	B	SF-36 scores (n = 122 evaluable patients) Physical summary: Baseline - 32.0 (8.7) 30 days - 38.7 (10.3) 6 months - 39.9 (10.4) 12 months - 39.2 (10.5) ($p < 0.0001$ all time points compared with baseline) Mental summary Baseline - 46.1 (12.5) 30 days - 49.5 (1.3) 6 months - 52.7 (9.7) 12 months - 51.8 (10.5) ($p < 0.0001$ all time points compared with baseline) There were significant improvement in QoL in all 8 individual domains and nearly all time-points compared with baseline.
Overall summary of evidence of changes to HRQoL	One study reported HR-QoL using SF-36 methodology. This study reported significant longitudinal improvements associated with MitraClip in all 12 domains (namely physical function, role physical, bodily pain, general health, vitality, social function, role emotional, and mental health index) at all time points (with the exception of role emotional at 30 days, $p = 0.234$).				
Re-intervention rate (Critical)	Braun et al. (2014) (Braun et al., 2014)	8	Direct	B	Event free survival (freedom from MR 3+ or 4+, mitral valve re-intervention and death) – 59.7%
	Lim et al. (2014) (Lim et al., 2014):	9	Direct		3 patients (2.4%) required open MV surgery within 1 year FU.
	Pilot European Sentinel Registry (Nickenig et al., 2014)	9	Indirect		Re-intervention at 1 year - 3.8% (additional MitraClip implantation in 2.9%, surgical MV repair in 0.7%, and MV replacement in 0.2%). Difference between FMR vs. DMR ns.
	Rudolph et al. (2013) (Rudolph et al., 2013)	6	Direct		Re-intervention rate - 8% (n = 17, 10 MitraClip, 7 MV replacement). Freedom from re-intervention (from Figure 4): DMR 1 year – 94.7% (FMR 1 year – 88.4%, p = ns)
Overall summary of evidence for re-intervention rate	There is limited from 2 studies that the re-intervention rate in MitraClip patients with DMR is between 2 to 5% in the first year. Most re-interventions are repeat procedures with MitraClip , although surgery for MV repair or replacement also occurs.				

Use of MitraClip in patients with DMR who are at high risk from surgery					
Outcome Measure	**Study and reference**	**Quality of Evidence Score (out of 10)***	**Applicability****	**Grade of Evidence**	**Summary of evidence from studies**
Impact on admissions for Heart Failure (Critical)	Lim et al. (2014) (Lim et al., 2014):	9	Direct	A	Rate of hospitalisation due to HF: Before MitraClip - 0.67 (95% CI 0.54 to 0.83) per PY. After MitraClip - 0.18 (95% CI 0.11 to0.28) per PY. 73% reduction ($p < 0.0001$).
	Rudolph et al. (2013) (Rudolph et al., 2013)	6	Direct		Overall 45% of successful treated patients were re-hospitalised due to HF symptoms over FU period (13.3 months, range 0.4 to 37.8 months).
	TVT registry (Sorajja et al., 2017a):	9	Direct		Readmission for HF (12 months) - 20.5%
Overall summary of evidence for Impact on admissions for Heart Failure	One large registry reported that the readmission rate for HF in patients with DMR was around 20% (meaning one in five are readmitted) in the first year . On study reported the rate was higher (45%) over a slightly longer period (Sorajja et al., 2017a). Data from patients participating in the EVEREST studies suggested treatment with MitraClip was associated with an decrease in HF admission rates (Lim et al., 2014).				
Length of stay in hospital (Important)	ACCESS-EU study (Reichenspurner et al., 2013)	8	Direct	A	*Mean hospital stay* (acute) Overall DMR: 2.4±3.1 days HR DMR: 2.5±3.8 days LR DMR: 2.4±2.8 days *Mean hospital stay* (overall) HR DMR: 7.2 ±4.3 days LR DMR: 6.5±5.4 days
	Lim et al. (2014) (Lim et al., 2014)	9	Direct		Mean post-procedural length of stay in ICU – 1.4 ± 1.8 (SD) days. Mean post-procedural length of hospital stay – 2.9 ± 3.1 (SD) days.
	TVT registry (Sorajja et al., 2017a):	9	Direct		Length of stay: Median 2.0 days (IQR 1.0 to 5.0 days)
Overall summary of evidence for Impact on admissions for length of stay in hospital	Data from three observational studies report that the average length of stay for a patient with DMR receiving MitraClip is between 2 and 3 days. Distributional data suggest that the length of stay is much longer for some patients. These studies were not conducted in the UK and it is unclear how generalisable these data are.				
Discharge destination (Important)	ACCESS-EU study (Reichenspurner et al., 2013)	8	Direct	A	"A significantly larger proportion of low-risk patients were discharged home with or without home health care than of high-risk patients (83.1 and 71.9%, respectively)".
	TVT registry (Sorajja et al., 2017a):	9	Direct		Discharge destination: Home – 85.9% Extended care – 8.1% Other – 6.0%
Overall summary of evidence for discharge destination	Data from two studies suggest that over 80% of patients discharged after treatment with MitraClip are sent home. However, these studies were not conducted in the UK and it is unclear how generalisable these data are.				
Rate of repeat MitraClip procedure (Important)	Braun et al. (2014) (Braun et al., 2014)	8	Direct	B	Repeat MitraClip – 5.6% (4/72)
	Rudolph et al. (2013) (Rudolph et al., 2013)	6	Direct		10 patients had repeat MitraClip in the FU period (4.3%)
Overall summary of evidence for rate of repeat MitraClip	There is relatively weak evidence from 2 studies that between 4 and 6% of patients with DMR receiving MitraClip may require a repeat MitraClip procedure. These studies were not conducted in the UK and it is unclear how generalisable these data are.				

Use of MitraClip in patients with DMR who are at high risk from surgery					
Outcome Measure	**Study and reference**	**Quality of Evidence Score (out of 10)***	**Applicability****	**Grade of Evidence**	**Summary of evidence from studies**
procedure					
Cost effectiveness (unspecified)	Cost utility analysis (2013) (Mealing et al., 2013)	8	Direct	B	ICER at 2 years - £52,947. ICER at 5 years - £22,200 ICER at 10 years - £14,800 Probability cost effective at 5 years WTP threshold of £20,000 – 37% Probability cost effective at 5 years WTP threshold of £30,000 – 93%
Overall summary of evidence for cost effectiveness	Limited evidence from one study indicated that MitraClip is likely to be cost-effective after 5 years onwards using a WTP threshold of £30,000. However, this study was subject to considerable uncertainty concerning its clinical inputs and extrapolated timeframe.				
Cost saving from avoidance of hospitalisation (Unspecified)	"Before and after" study (Vemulapalli et al., 2017)	6	Indirect	C	All-cause hospitalisation in the year prior to MitraClip - 1,853.6/1,000 PY All-cause hospitalisation in the year after MitraClip - 1,435.0/1,000 PY HR 0.82 (95% CI 0.73 to 0.92, p = 0.001).
Overall summary of cost-saving from avoidance of hospitalisation	There is weak evidence from one US study that MitraClip reduces the number of hospital readmissions and the costs associated with this.				

Abbreviations: ACCESS-EU - ACCESS-Europe A Two-Phase Observational Study of the MitraClip System in Europe; AE – adverse events; AF – atrial fibrillation; CI – confidence interval; DMR – degenerative mitral valve regurgitation; EVEREST - Endovascular Valve Edge-to-Edge Repair Study; FMR - functional mitral valve regurgitation; FU – follow up; HR – high risk; HF- heart failure; HR-QoL – health-related quality of life; HRS – high risk study; ICER – incremental cost-effectiveness ratio; ICU – intensive care unit; IQR – inter-quartile range; KM – Kaplan Meier; LR – low risk; MAE – major adverse event; LV – left ventricular; MACCE - major adverse cardiac and cerebrovascular events; MARS – MitraClip in the Asia-Pacific Registry; MI – myocardial infarction; MR – mitral valve regurgitation; MV – mitral valve; ns – not significant; NYHA – New York Heart Association (class); PY – person year; REALISM - (Real World Expanded Multi-center Study of the MitraClip System); SD – standard deviation; SF-36 – short form 36; STS – Society of Thoracic Surgeons; STS-PROM – STS predicted risk of mortality; TRAMI - Transcatheter Mitral Valve Interventions; TVT – Transcatheter Repair Therapy; US – United States; WTP – willingness to pay.

* Included studies were generally well reported (hence highly scored), but this scoring system does not take into account biases and sources of confounding inherent to registry and observational studies.
** Applicability score in this instance means whether the large majority of the patient population had DMR (direct applicability) rather than a case mix of DMR and FMR (indirect applicability).

9. Literature Search Terms

Search strategy *Indicate all terms to be used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	**Inclusion criteria** Patients with severe (defined as grade 3+ and 4+), symptomatic, mitral regurgitation assessed as at high risk for conventional mitral valve repair surgery (assessed by a Heart Team and classified as having a high surgical risk using the Society of Thoracic surgeons calculator, or Euroscore surgical risk scores, and frailty assessment etc Studies that include patients with mixed aetiology of mitral regurgitation (MR) are only included if data are reported separately for the degenerative (DMR) population of interest to NHS England and the DMR cohort size is n ≥ 50 subjects. **Exclusion criteria** Studies exclusively in FMR populations are excluded.
I – Intervention Which intervention, treatment or approach should be used?	**Inclusion criteria** Percutaneous mitral valve leaflet repair for mitral regurgitation (i.e. transcatheter mitral valve repair using MitraClip). **Exclusion criteria** Studies that combine MitraClip with other interventions (e.g. LAAO).
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	**Inclusion criteria** Medical management or surgical repair/replacement (but see exclusion criteria). Single arm observational studies with n ≥ 500 will have no comparator. **Exclusion criteria** Studies that include mitral valve repair or mitral valve replacement surgery as a comparator are not excluded at first sift, but full papers are retrieved and checked to see whether a high risk group was reported in the surgical cohort, as described in the Population Inclusion Criteria.
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-	*Critical to decision-making:* • Reduction in MR grade • Reduction in deaths • Improved survival

term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	• Improvement in symptoms, quality of life and NYHA Grade from III/IV to I/II. • Duration/durability of above • Procedural complications • Re-intervention rate • Impact on admissions for Heart Failure *Important to decision-making:* • Length of stay in hospital • Discharge destination • Rate of second/ repeat valve device procedures
Assumptions / limits applied to search	
Inclusion Criteria	**Study design:** • Randomised controlled trials (RCTs) • Comparative cohort studies • Single armed observational studies where n ≥ 500 • Economic evaluations Any systematic reviews published in the last three years that are identified are screened for references. Only English-language studies published in the last 10 years are eligible for inclusion. For cost-effectiveness studies, only those which are generalisable to the UK or countries with similar healthcare provision to the UK.
Exclusion Criteria	**Study design:** Case reports, case series, non-peer reviewed publications, conference abstracts and communications.

10. Search Strategy

The literature search was designed to identify RCTs, observational studies and economic evaluations on percutaneous mitral valve repair using MitraClip in patients with severe degenerative mitral regurgitation.

The strategy was developed for MEDLINE (OvidSP interface) and is presented in Figure 0.1. The main structure of the strategy comprised five concepts:

- mitral regurgitation (search lines 1-3);
- percutaneous mitral valve repair (search lines 4 – 18);
- RCTs (search lines 22 – 30);
- observational studies (search lines 31 – 47);
- economic evaluations (search lines 48 – 64).

The strategy also searched on 'mitraclip' terms in a stand-alone search line (search line 67).

The strategy was devised using a combination of subject indexing terms and free text search terms in the title, abstract and keyword heading word fields. The search terms were identified through discussion within the research team, scanning background literature, browsing database thesauri and use of the PubMed PubReminer tool (http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi).

The search terms for the RCTs concept were based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision, Ovid format).

The search terms for the observational study concept were based on the filter developed by the Scottish Intercollegiate Guidelines Network (SIGN) to identify observational studies (search lines 31 – 43). The SIGN filter was developed by SIGN to retrieve studies most likely to meet their methodological critieria. The SIGN filter was expanded by the addition of registry and observational study subject heading terms, and free text terms on registry studies (search lines 44 – 47).

The search terms for the economic evaluations concept were based on the strategy developed by the University of York Centre for Reviews and Dissemination for identification of economic evaluations in Ovid MEDLINE.

Animal studies were excluded from MEDLINE using a standard algorithm (search line 69). The strategy also excluded studies indexed as news, comment, editorial, letter or case report publication types, and records with the phrase 'case report' in the title (search line 70). The strategy was restricted to studies published in the English language in the last 10 years (from 2008 to date), as per the eligibility criteria (search line 72).

The MEDLINE strategy was translated appropriately for other databases. Full strategies (including search dates) for all sources searched are included in Appendix A.

Figure 0.1: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1 Mitral Valve Insufficiency/ (20741)
2 ((mitral or mitralis or cardiac valv$ or heart valv$ or bicuspid or left atrioventricular) adj5 (regurgitat$ or incompetenc$ or insufficien$)).ti,ab,kf. (19252)
3 or/1-2 (28356)
4 Mitral Valve/su and (Minimally Invasive Surgical Procedures/ or Heart Valve Prosthesis Implantation/ or Endovascular Procedures/ or Cardiac Catheterization/ or Surgical Instruments/) (3721)
5 (percutaneous$ adj3 (surg$ or repair$ or clos$ or reconstruc$ or correct$ or approach$ or technique$ or procedure$ or intervention$ or device$ or implant$ or treat$ or therap$)).ti,ab,kf. (58887)

6 (percutaneous$ adj3 (catheter-based or transcatheter$ or trans-catheter$)).ti,ab,kf. (1050)
7 (percutaneous$ adj3 (mitral or mitralis or cardiac valv$ or heart valv$ or bicuspid or left atrioventricular)).ti,ab,kf. (2020)
8 pmvr.ti,ab,kf. (56)
9 ((catheter-based or transcatheter$ or trans-catheter$) adj3 (surg$ or repair$ or clos$ or reconstruc$ or correct$ or approach$ or technique$ or procedure$ or intervention$ or device$ or implant$ or treat$ or therap$)).ti,ab,kf. (12937)
10 tmvr.ti,ab,kf. (87)
11 ((catheter-based or transcatheter$ or trans-catheter$) adj3 (mitral or mitralis or cardiac valv$ or heart valv$ or bicuspid or left atrioventricular)).ti,ab,kf. (1110)
12 ((minimal$ invasive or less invasiv$ or non invasiv$ or reduced invasive) adj3 (surg$ or repair$ or clos$ or reconstruc$ or correct$ or approach$ or technique$ or procedure$ or intervention$ or device$ or implant$ or treat$ or therap$)).ti,ab,kf. (59696)
13 ((minimal$ invasive or less invasiv$ or non invasiv$ or reduced invasive) adj3 (catheter-based or transcatheter$ or trans-catheter$)).ti,ab,kf. (186)
14 ((minimal$ invasive or less invasiv$ or non invasiv$ or reduced invasive) adj3 (mitral or mitralis or cardiac valv$ or heart valv$ or bicuspid or left atrioventricular)).ti,ab,kf. (552)
15 (clip or clips).ti,ab,kf. (16503)
16 "edge-to-edge".ti,ab,kf. (1094)
17 alfieri$.ti,ab,kf. (113)
18 or/4-17 (148244)
19 3 and 18 (3921)
20 Mitral Valve Insufficiency/su and (Minimally Invasive Surgical Procedures/ or Heart Valve Prosthesis Implantation/ or Endovascular Procedures/ or Cardiac Catheterization/ or Surgical Instruments/) (3114)
21 or/19-20 (5293)
22 randomized controlled trial.pt. (455803)
23 controlled clinical trial.pt. (92241)
24 randomized.ab. (405843)
25 placebo.ab. (187283)
26 drug therapy.fs. (2000820)
27 randomly.ab. (286950)
28 trial.ab. (421497)
29 groups.ab. (1774854)
30 or/22-29 (4162081)
31 Epidemiologic studies/ (7631)
32 exp case control studies/ (902190)
33 exp cohort studies/ (1720094)
34 Case control.tw. (106472)
35 (cohort adj (study or studies)).tw. (151156)
36 Cohort analy$.tw. (6075)
37 (Follow up adj (study or studies)).tw. (44678)
38 (observational adj (study or studies)).tw. (79252)
39 Longitudinal.tw. (201018)
40 Retrospective.tw. (418612)
41 Cross sectional.tw. (271886)
42 Cross-sectional studies/ (259606)
43 or/31-42 (2533475)
44 Registries/ (72949)

45 observational study/ or Observational Studies as Topic/ (47686)
46 (register or registers or registry or registries).ti,ab,kf. (154434)
47 or/43-46 (2649564)
48 Economics/ (26972)
49 exp "Costs and cost analysis"/ (213038)
50 Economics, dental/ (1891)
51 exp "Economics, hospital"/ (22702)
52 Economics, medical/ (8939)
53 Economics, nursing/ (3978)
54 Economics, pharmaceutical/ (2742)
55 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (654310)
56 (expenditure$ not energy).ti,ab. (25111)
57 value for money.ti,ab. (1399)
58 budget$.ti,ab. (25266)
59 or/48-58 (795933)
60 ((energy or oxygen) adj cost).ti,ab. (3640)
61 (metabolic adj cost).ti,ab. (1197)
62 ((energy or oxygen) adj expenditure).ti,ab. (21916)
63 or/60-62 (25857)
64 59 not 63 (789981)
65 30 or 47 or 64 (6543282)
66 21 and 65 (2146)
67 (mitraclip$ or mitralclip$ or mitra clip$ or mitral clip$ or mitraclipnt$ or mitralclipnt$ or mitra clipnt$ or mitral clipnt$).ti,ab,kf. (805)
68 66 or 67 (2664)
69 exp animals/ not humans/ (4434788)
70 (news or comment or editorial or letter or case reports).pt. or case report.ti. (3512845)
71 68 not (69 or 70) (2160)
72 limit 71 to (english language and yr="2008 -Current") (1381)
73 remove duplicates from 72 (1374)

Key to Ovid symbols and commands

$	Unlimited right-hand truncation symbol
ti,ab,kf	Searches are restricted to the Title, Abstract, and Keyword Heading Word fields
.tw	Searches are restricted to all the fields which contain text words
adjN	Retrieves records that contain terms (in any order) within a specified number (N) of words of each other
/	Searches are restricted to the Subject Heading field
exp	The subject heading is exploded
pt.	Search is restricted to the publication type field
or/4-17	Combines sets 4 to 17 using OR

The literature searches were conducted in a range of relevant bibliographic databases (Table 10.1). These resources are appropriate to the context outlined in NHS England Guidance on conducting evidence reviews for Specialised Services Commissioning Products.

We also checked the reference lists of four relevant systematic reviews published since May 2015 (Tan et al., 2017, Takagi et al., 2017, Iliadis et al., 2017, Chiarito et al., 2018) for any eligible studies that may have been missed by the database searches.

No further relevant studies were identified.

The databases and information sources searched are shown in Table 0.1.

Table 0.1: Databases and information sources searched

Resource	Interface / URL
MEDLINE, MEDLINE In-Process and MEDLINE(R) Daily Epub Ahead of Print	Ovid SP
Embase	OvidSP
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library / Wiley
Database of Abstracts of Reviews of Effects (DARE)	Cochrane Library / Wiley
Health Technology Assessment Database (HTA)	Centre for Reviews and Dissemination
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library / Wiley
NHS EED	Cochrane Library / Wiley
CEA Registry	http://healtheconomics.tuftsmedicalcenter.org/cear4/Home.aspx
National Guidelines Clearinghouse	http://www.guideline.gov/index.aspx
Guidelines International Network: International Guideline Library	http://www.g-i-n.net/library/international-guidelines-library
National Institute for Health and Care Excellence	https://www.nice.org.uk/

Searching a number of databases produces a degree of duplication in the results. To manage this issue, the titles and abstracts of bibliographic records were downloaded and imported into EndNote bibliographic management software and duplicate records were removed using several algorithms.

Literature Search Results

The searches were undertaken between 21 and 22 March 2018 and they identified 2,836 records (Table 0.2). Following deduplication 1914 records were assessed for relevance.
A rapid first pass of the 1914 records was undertaken to exclude:

- Animal studies
- Studies involving children
- Case reports
- Conferences
- Reports in languages other than English
- Older and non-systematic reviews

Following this 1639 records were screened at title and abstract level.

Table 0.2: Literature search results

Resource	Number of records identified
MEDLINE, MEDLINE In-Process and MEDLINE(R) Daily Epub Ahead of Print	1,374
Embase	1,242
Cochrane Central Register of Controlled Trials (CENTRAL)	171
Database of Abstracts of Reviews of Effects (DARE)	11
Health Technology Assessment Database (HTA)	20
Cochrane Database of Systematic Reviews (CDSR)	3
NHS Economic Evaluation Database (NHS EED)	0
CEA Registry	7
National Guidelines Clearinghouse	3
Guidelines International Network: International Guideline Library	0
National Institute for Health and Care Excellence	5
Records found via review reference checking	**0**
Total number of records retrieved	**2,836**
Total number of records after deduplication	**1,914**

11. Evidence selection

- Total number of publications reviewed: 1914 titles and abstracts.
- Total number of publications considered relevant: 121 records were identified as potentially relevant and full papers were obtained and screened for relevance.
- Total number of publications selected for inclusion in this briefing: 39. 37 publications were included for clinical effectiveness and adverse events (reporting on a total of 15

studies) and 2 publications were included for economic data (reporting on a total of 2 studies).

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ZUERN, C. S., BAUER, A., LUBOS, E., BOEKSTEGERS, P., PULS, M., BARDELEBEN, R. S. V., OUARRAK, T., BUTTER, C., EGGEBRECHT, H., NICKENIG, G., ZAHN, R., SENGES, J. & MAY, A. E. 2015. Influence of non-cardiac comorbidities on outcome after percutaneous mitral valve repair: results from the German transcatheter mitral valve interventions (TRAMI) registry. *Clinical Research in Cardiology,* 104**,** 1044-53.

Appendix A: Full Search Strategies

A.1: Source: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Interface / URL: OvidSP
Database coverage dates: 1946 to present
Search date: 21 March 2018
Retrieved records: 1,374
Search strategy:

1 Mitral Valve Insufficiency/ (20741)
2 ((mitral or mitralis or cardiac valv$ or heart valv$ or bicuspid or left atrioventricular) adj5 (regurgitat$ or incompetenc$ or insufficien$)).ti,ab,kf. (19252)
3 or/1-2 (28356)
4 Mitral Valve/su and (Minimally Invasive Surgical Procedures/ or Heart Valve Prosthesis Implantation/ or Endovascular Procedures/ or Cardiac Catheterization/ or Surgical Instruments/) (3721)
5 (percutaneous$ adj3 (surg$ or repair$ or clos$ or reconstruc$ or correct$ or approach$ or technique$ or procedure$ or intervention$ or device$ or implant$ or treat$ or therap$)).ti,ab,kf. (58887)
6 (percutaneous$ adj3 (catheter-based or transcatheter$ or trans-catheter$)).ti,ab,kf. (1050)
7 (percutaneous$ adj3 (mitral or mitralis or cardiac valv$ or heart valv$ or bicuspid or left atrioventricular)).ti,ab,kf. (2020)
8 pmvr.ti,ab,kf. (56)
9 ((catheter-based or transcatheter$ or trans-catheter$) adj3 (surg$ or repair$ or clos$ or reconstruc$ or correct$ or approach$ or technique$ or procedure$ or intervention$ or device$ or implant$ or treat$ or therap$)).ti,ab,kf. (12937)
10 tmvr.ti,ab,kf. (87)
11 ((catheter-based or transcatheter$ or trans-catheter$) adj3 (mitral or mitralis or cardiac valv$ or heart valv$ or bicuspid or left atrioventricular)).ti,ab,kf. (1110)
12 ((minimal$ invasive or less invasiv$ or non invasiv$ or reduced invasive) adj3 (surg$ or repair$ or clos$ or reconstruc$ or correct$ or approach$ or technique$ or procedure$ or intervention$ or device$ or implant$ or treat$ or therap$)).ti,ab,kf. (59696)
13 ((minimal$ invasive or less invasiv$ or non invasiv$ or reduced invasive) adj3 (catheter-based or transcatheter$ or trans-catheter$)).ti,ab,kf. (186)
14 ((minimal$ invasive or less invasiv$ or non invasiv$ or reduced invasive) adj3 (mitral or mitralis or cardiac valv$ or heart valv$ or bicuspid or left atrioventricular)).ti,ab,kf. (552)
15 (clip or clips).ti,ab,kf. (16503)
16 "edge-to-edge".ti,ab,kf. (1094)
17 alfieri$.ti,ab,kf. (113)
18 or/4-17 (148244)
19 3 and 18 (3921)

20 Mitral Valve Insufficiency/su and (Minimally Invasive Surgical Procedures/ or Heart Valve Prosthesis Implantation/ or Endovascular Procedures/ or Cardiac Catheterization/ or Surgical Instruments/) (3114)
21 or/19-20 (5293)
22 randomized controlled trial.pt. (455803)
23 controlled clinical trial.pt. (92241)
24 randomized.ab. (405843)
25 placebo.ab. (187283)
26 drug therapy.fs. (2000820)
27 randomly.ab. (286950)
28 trial.ab. (421497)
29 groups.ab. (1774854)
30 or/22-29 (4162081)
31 Epidemiologic studies/ (7631)
32 exp case control studies/ (902190)
33 exp cohort studies/ (1720094)
34 Case control.tw. (106472)
35 (cohort adj (study or studies)).tw. (151156)
36 Cohort analy$.tw. (6075)
37 (Follow up adj (study or studies)).tw. (44678)
38 (observational adj (study or studies)).tw. (79252)
39 Longitudinal.tw. (201018)
40 Retrospective.tw. (418612)
41 Cross sectional.tw. (271886)
42 Cross-sectional studies/ (259606)
43 or/31-42 (2533475)
44 Registries/ (72949)
45 observational study/ or Observational Studies as Topic/ (47686)
46 (register or registers or registry or registries).ti,ab,kf. (154434)
47 or/43-46 (2649564)
48 Economics/ (26972)
49 exp "Costs and cost analysis"/ (213038)
50 Economics, dental/ (1891)
51 exp "Economics, hospital"/ (22702)
52 Economics, medical/ (8939)
53 Economics, nursing/ (3978)
54 Economics, pharmaceutical/ (2742)
55 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (654310)
56 (expenditure$ not energy).ti,ab. (25111)
57 value for money.ti,ab. (1399)
58 budget$.ti,ab. (25266)
59 or/48-58 (795933)
60 ((energy or oxygen) adj cost).ti,ab. (3640)
61 (metabolic adj cost).ti,ab. (1197)

62 ((energy or oxygen) adj expenditure).ti,ab. (21916)
63 or/60-62 (25857)
64 59 not 63 (789981)
65 30 or 47 or 64 (6543282)
66 21 and 65 (2146)
67 (mitraclip$ or mitralclip$ or mitra clip$ or mitral clip$ or mitraclipnt$ or mitralclipnt$ or mitra clipnt$ or mitral clipnt$).ti,ab,kf. (805)
68 66 or 67 (2664)
69 exp animals/ not humans/ (4434788)
70 (news or comment or editorial or letter or case reports).pt. or case report.ti. (3512845)
71 68 not (69 or 70) (2160)
72 limit 71 to (english language and yr="2008 -Current") (1381)
73 remove duplicates from 72 (1374)

A.2: Source: Embase

Interface / URL: OvidSP
Database coverage dates: 1974 to 2018 March 20
Search date: 21 March 2018
Retrieved records: 1,242
Search strategy:

1 mitral valve regurgitation/ (37392)
2 ((mitral or mitralis or cardiac valv$ or heart valv$ or bicuspid or left atrioventricular) adj5 (regurgitat$ or incompetenc$ or insufficien$)).ti,ab,kw. (28095)
3 or/1-2 (43986)
4 mitral valve/su and (minimally invasive surgery/ or heart valve replacement/ or endovascular surgery/ or heart catheterization/ or surgical equipment/) (559)
5 (percutaneous$ adj3 (surg$ or repair$ or clos$ or reconstruc$ or correct$ or approach$ or technique$ or procedure$ or intervention$ or device$ or implant$ or treat$ or therap$)).ti,ab,kw. (95126)
6 (percutaneous$ adj3 (catheter-based or transcatheter$ or trans-catheter$)).ti,ab,kw. (1515)
7 (percutaneous$ adj3 (mitral or mitralis or cardiac valv$ or heart valv$ or bicuspid or left atrioventricular)).ti,ab,kw. (3179)
8 pmvr.ti,ab,kw. (133)
9 ((catheter-based or transcatheter$ or trans-catheter$) adj3 (surg$ or repair$ or clos$ or reconstruc$ or correct$ or approach$ or technique$ or procedure$ or intervention$ or device$ or implant$ or treat$ or therap$)).ti,ab,kw. (21664)
10 tmvr.ti,ab,kw. (137)
11 ((catheter-based or transcatheter$ or trans-catheter$) adj3 (mitral or mitralis or cardiac valv$ or heart valv$ or bicuspid or left atrioventricular)).ti,ab,kw. (1939)

12 ((minimal$ invasive or less invasiv$ or non invasiv$ or reduced invasive) adj3 (surg$ or repair$ or clos$ or reconstruc$ or correct$ or approach$ or technique$ or procedure$ or intervention$ or device$ or implant$ or treat$ or therap$)).ti,ab,kw. (91351)
13 ((minimal$ invasive or less invasiv$ or non invasiv$ or reduced invasive) adj3 (catheter-based or transcatheter$ or trans-catheter$)).ti,ab,kw. (263)
14 ((minimal$ invasive or less invasiv$ or non invasiv$ or reduced invasive) adj3 (mitral or mitralis or cardiac valv$ or heart valv$ or bicuspid or left atrioventricular)).ti,ab,kw. (850)
15 (clip or clips).ti,ab,kw. (24305)
16 "edge-to-edge".ti,ab,kw. (1334)
17 alfieri$.ti,ab,kw. (174)
18 or/4-17 (227597)
19 3 and 18 (5630)
20 mitral valve regurgitation/su and (minimally invasive surgery/ or heart valve replacement/ or endovascular surgery/ or heart catheterization/ or surgical equipment/) (1340)
21 or/19-20 (6468)
22 randomized controlled trial/ (493678)
23 controlled clinical study/ (457027)
24 22 or 23 (672688)
25 random$.ti,ab. (1282693)
26 randomization/ (77395)
27 intermethod comparison/ (231416)
28 placebo.ti,ab. (268854)
29 (compare or compared or comparison).ti. (462494)
30 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (1708162)
31 (open adj label).ti,ab. (62867)
32 ((double or single or doubly or singly) adj blind).ti,ab. (188274)
33 ((double or single or doubly or singly) adj blinded).ti,ab. (19171)
34 ((double or single or doubly or singly) adj blindly).ti,ab. (280)
35 double blind procedure/ (147686)
36 parallel group$1.ti,ab. (21436)
37 (crossover or cross over).ti,ab. (91609)
38 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. (276813)
39 (assigned or allocated).ti,ab. (325460)
40 (controlled adj7 (study or design or trial)).ti,ab. (288825)
41 (volunteer or volunteers).ti,ab. (221508)
42 human experiment/ (400883)
43 trial.ti. (245572)
44 or/25-43 (4080150)
45 44 or 24 (4226399)
46 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (7355)

47 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) (178994)
48 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. (14456)
49 (Systematic review not (trial or study)).ti. (92645)
50 (nonrandom$ not random$).ti,ab. (14389)
51 "Random field$".ti,ab. (1785)
52 (random cluster adj3 sampl$).ti,ab. (1050)
53 (review.ab. and review.pt.) not trial.ti. (650257)
54 "we searched".ab. and (review.ti. or review.pt.) (24482)
55 "update review".ab. (88)
56 (databases adj4 searched).ab. (23961)
57 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (949093)
58 Animal experiment/ not (human experiment/ or human/) (1956238)
59 or/46-58 (2924188)
60 45 not 59 (3798303)
61 Clinical study/ (154256)
62 Case control study/ (123383)
63 Family study/ (25451)
64 Longitudinal study/ (109856)
65 Retrospective study/ (625118)
66 Prospective study/ (433487)
67 Randomized controlled trials/ (141873)
68 66 not 67 (429100)
69 Cohort analysis/ (354578)
70 (Cohort adj (study or studies)).mp. (220643)
71 (Case control adj (study or studies)).tw. (111343)
72 (follow up adj (study or studies)).tw. (57461)
73 (observational adj (study or studies)).tw. (121875)
74 (epidemiologic$ adj (study or studies)).tw. (95687)
75 (cross sectional adj (study or studies)).tw. (157554)
76 or/61-65,68-75 (2020547)
77 register/ (108434)
78 observational study/ (134174)
79 (register or registers or registry or registries).ti,ab,kw. (236687)
80 or/76-79 (2223753)
81 Health Economics/ (35643)
82 exp Economic Evaluation/ (270747)
83 exp Health Care Cost/ (259893)
84 pharmacoeconomics/ (7810)
85 (econom$ or cost or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (869488)
86 (expenditure$ not energy).ti,ab. (33721)
87 (value adj2 money).ti,ab. (2060)

88 budget$.ti,ab. (32636)
89 or/81-88 (1112690)
90 (metabolic adj cost).ti,ab. (1289)
91 ((energy or oxygen) adj cost).ti,ab. (3852)
92 ((energy or oxygen) adj expenditure).ti,ab. (27611)
93 or/90-92 (31757)
94 89 not 93 (1106165)
95 60 or 80 or 94 (6250527)
96 21 and 95 (1926)
97 (mitraclip$ or mitralclip$ or mitra clip$ or mitral clip$ or mitraclipnt$ or mitralclipnt$ or mitra clipnt$ or mitral clipnt$).ti,ab,kw. (1683)
98 96 or 97 (3109)
99 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5830562)
100 (conference abstract or conference paper or conference proceeding or conference review or editorial or letter or note).pt. or case report.ti. (6187059)
101 98 not (99 or 100) (1693)
102 limit 101 to (english language and yr="2008 -Current") (1303)
103 remove duplicates from 102 (1242)

A.3: Source: Cochrane Central Register of Controlled Trials (CENTRAL)
Interface / URL: Cochrane Library / Wiley
Database coverage dates: Issue 2 of 12, February 2018
Search date: 21 March 2018
Retrieved records: 171
Search strategy:

#1 [mh ^"Mitral Valve Insufficiency"] 329
#2 ((mitral or mitralis or cardiac next valv* or heart next valv* or bicuspid or "left atrioventricular") near/5 (regurgitat* or incompetenc* or insufficien*)) 889
#3 #1 or #2 889
#4 [mh ^"Mitral Valve"/SU] and ([mh ^"Minimally Invasive Surgical Procedures"] or [mh ^"Heart Valve Prosthesis Implantation"] or [mh ^"Endovascular Procedures"] or [mh ^"Cardiac Catheterization"] or [mh ^"Surgical Instruments"]) 93
#5 (percutaneous* near/3 (surg* or repair* or clos* or reconstruc* or correct* or approach* or technique* or procedure* or intervention* or device* or implant* or treat* or therap*)) 9811
#6 (percutaneous* near/3 ("catheter-based" or transcatheter* or trans-catheter*)) 40
#7 (percutaneous* near/3 (mitral or mitralis or cardiac next valv* or heart next valv* or bicuspid or "left atrioventricular")) 113
#8 pmvr 8

#9 (("catheter-based" or transcatheter* or trans-catheter*) near/3 (surg* or repair* or clos* or reconstruc* or correct* or approach* or technique* or procedure* or intervention* or device* or implant* or treat* or therap*)) 1632
#10 tmvr 5
#11 (("catheter-based" or transcatheter* or trans-catheter*) near/3 (mitral or mitralis or cardiac next valv* or heart next valv* or bicuspid or "left atrioventricular")) 98
#12 ((minimal* next invasive or less next invasiv* or non next invasiv* or "reduced invasive") near/3 (surg* or repair* or clos* or reconstruc* or correct* or approach* or technique* or procedure* or intervention* or device* or implant* or treat* or therap*)) 6319
#13 ((minimal* next invasive or less next invasiv* or non next invasiv* or "reduced invasive") near/3 ("catheter-based" or transcatheter* or trans-catheter*)) 5
#14 ((minimal* next invasive or less next invasiv* or non next invasiv* or "reduced invasive") near/3 (mitral or mitralis or cardiac next valv* or heart next valv* or bicuspid or "left atrioventricular")) 40
#15 (clip or clips) 1331
#16 "edge-to-edge" 25
#17 alfieri* 148
#18 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 18571
#19 #3 and #18 239
#20 [mh ^"Mitral Valve Insufficiency"/SU] and ([mh ^"Minimally Invasive Surgical Procedures"] or [mh ^"Heart Valve Prosthesis Implantation"] or [mh ^"Endovascular Procedures"] or [mh ^"Cardiac Catheterization"] or [mh ^"Surgical Instruments"]) 59
#21 (mitraclip* or mitralclip* or mitra next clip* or mitral next clip* or mitraclipnt* or mitralclipnt* or mitra next clipnt* or mitral next clipnt*) 77
#22 #19 or #20 or #21 273
#23 #19 or #20 or #21 Publication Year from 2008 to 2018, in Trials 171

A.4: Source: Database of Abstracts of Reviews of Effect (DARE)
Interface / URL: Cochrane Library / Wiley
Database coverage dates: Issue 2 of 4, April 2015
Search date: 21 March 2018
Retrieved records: 11
Search strategy:

#1 [mh ^"Mitral Valve Insufficiency"] 329
#2 ((mitral or mitralis or cardiac next valv* or heart next valv* or bicuspid or "left atrioventricular") near/5 (regurgitat* or incompetenc* or insufficien*)) 889
#3 #1 or #2 889
#4 [mh ^"Mitral Valve"/SU] and ([mh ^"Minimally Invasive Surgical Procedures"] or [mh ^"Heart Valve Prosthesis Implantation"] or [mh ^"Endovascular Procedures"] or [mh ^"Cardiac Catheterization"] or [mh ^"Surgical Instruments"]) 93

#5 (percutaneous* near/3 (surg* or repair* or clos* or reconstruc* or correct* or approach* or technique* or procedure* or intervention* or device* or implant* or treat* or therap*)) 9811
#6 (percutaneous* near/3 ("catheter-based" or transcatheter* or trans-catheter*)) 40
#7 (percutaneous* near/3 (mitral or mitralis or cardiac next valv* or heart next valv* or bicuspid or "left atrioventricular")) 113
#8 pmvr 8
#9 (("catheter-based" or transcatheter* or trans-catheter*) near/3 (surg* or repair* or clos* or reconstruc* or correct* or approach* or technique* or procedure* or intervention* or device* or implant* or treat* or therap*)) 1632
#10 tmvr 5
#11 (("catheter-based" or transcatheter* or trans-catheter*) near/3 (mitral or mitralis or cardiac next valv* or heart next valv* or bicuspid or "left atrioventricular")) 98
#12 ((minimal* next invasive or less next invasiv* or non next invasiv* or "reduced invasive") near/3 (surg* or repair* or clos* or reconstruc* or correct* or approach* or technique* or procedure* or intervention* or device* or implant* or treat* or therap*)) 6319
#13 ((minimal* next invasive or less next invasiv* or non next invasiv* or "reduced invasive") near/3 ("catheter-based" or transcatheter* or trans-catheter*)) 5
#14 ((minimal* next invasive or less next invasiv* or non next invasiv* or "reduced invasive") near/3 (mitral or mitralis or cardiac next valv* or heart next valv* or bicuspid or "left atrioventricular")) 40
#15 (clip or clips) 1331
#16 "edge-to-edge" 25
#17 alfieri* 148
#18 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 18571
#19 #3 and #18 239
#20 [mh ^"Mitral Valve Insufficiency"/SU] and ([mh ^"Minimally Invasive Surgical Procedures"] or [mh ^"Heart Valve Prosthesis Implantation"] or [mh ^"Endovascular Procedures"] or [mh ^"Cardiac Catheterization"] or [mh ^"Surgical Instruments"]) 59
#21 (mitraclip* or mitralclip* or mitra next clip* or mitral next clip* or mitraclipnt* or mitralclipnt* or mitra next clipnt* or mitral next clipnt*) 77
#22 #19 or #20 or #21 273
#23 #19 or #20 or #21 Publication Year from 2008 to 2018, in Other Reviews 11

A.5: Source: Cochrane Database of Systematic Reviews (CDSR)
Interface / URL: Cochrane Library / Wiley
Database coverage dates: Issue 3 of 12, March 2018
Search date: 21 March 2018
Retrieved records: no records
Search strategy:

#1 [mh ^"Mitral Valve Insufficiency"] 329
#2 ((mitral or mitralis or cardiac next valv* or heart next valv* or bicuspid or "left atrioventricular") near/5 (regurgitat* or incompetenc* or insufficien*)):ti,ab,kw 832
#3 #1 or #2 832
#4 [mh ^"Mitral Valve"/SU] and ([mh ^"Minimally Invasive Surgical Procedures"] or [mh ^"Heart Valve Prosthesis Implantation"] or [mh ^"Endovascular Procedures"] or [mh ^"Cardiac Catheterization"] or [mh ^"Surgical Instruments"]) 93
#5 (percutaneous* near/3 (surg* or repair* or clos* or reconstruc* or correct* or approach* or technique* or procedure* or intervention* or device* or implant* or treat* or therap*)):ti,ab,kw 8898
#6 (percutaneous* near/3 ("catheter-based" or transcatheter* or trans-catheter*)):ti,ab,kw 36
#7 (percutaneous* near/3 (mitral or mitralis or cardiac next valv* or heart next valv* or bicuspid or "left atrioventricular")):ti,ab,kw 112
#8 pmvr:ti,ab,kw 8
#9 (("catheter-based" or transcatheter* or trans-catheter*) near/3 (surg* or repair* or clos* or reconstruc* or correct* or approach* or technique* or procedure* or intervention* or device* or implant* or treat* or therap*)):ti,ab,kw 924
#10 tmvr:ti,ab,kw 5
#11 (("catheter-based" or transcatheter* or trans-catheter*) near/3 (mitral or mitralis or cardiac next valv* or heart next valv* or bicuspid or "left atrioventricular")):ti,ab,kw 98
#12 ((minimal* next invasive or less next invasiv* or non next invasiv* or "reduced invasive") near/3 (surg* or repair* or clos* or reconstruc* or correct* or approach* or technique* or procedure* or intervention* or device* or implant* or treat* or therap*)):ti,ab,kw 5366
#13 ((minimal* next invasive or less next invasiv* or non next invasiv* or "reduced invasive") near/3 ("catheter-based" or transcatheter* or trans-catheter*)):ti,ab,kw 5
#14 ((minimal* next invasive or less next invasiv* or non next invasiv* or "reduced invasive") near/3 (mitral or mitralis or cardiac next valv* or heart next valv* or bicuspid or "left atrioventricular")):ti,ab,kw 38
#15 (clip or clips):ti,ab,kw 1129
#16 "edge-to-edge":ti,ab,kw 24
#17 alfieri*:ti,ab,kw 2
#18 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 16074
#19 #3 and #18 214
#20 [mh ^"Mitral Valve Insufficiency"/SU] and ([mh ^"Minimally Invasive Surgical Procedures"] or [mh ^"Heart Valve Prosthesis Implantation"] or [mh ^"Endovascular Procedures"] or [mh ^"Cardiac Catheterization"] or [mh ^"Surgical Instruments"]) 59
#21 (mitraclip* or mitralclip* or mitra next clip* or mitral next clip* or mitraclipnt* or mitralclipnt* or mitra next clipnt* or mitral next clipnt*):ti,ab,kw 71
#22 #19 or #20 or #21 247
#23 #19 or #20 or #21 Publication Year from 2008 to 2018, in Cochrane Reviews (Reviews and Protocols) 0

A.6: Source: NHS Economic Evaluation Database (NHS EED)

Interface / URL: Cochrane Library / Wiley

Database coverage dates: Issue 2 of 4, April 2015

Search date: 21 March 2013

Retrieved records: 3

Search strategy:

#1 [mh ^"Mitral Valve Insufficiency"] 329

#2 ((mitral or mitralis or cardiac next valv* or heart next valv* or bicuspid or "left atrioventricular") near/5 (regurgitat* or incompetenc* or insufficien*)) 889

#3 #1 or #2 889

#4 [mh ^"Mitral Valve"/SU] and ([mh ^"Minimally Invasive Surgical Procedures"] or [mh ^"Heart Valve Prosthesis Implantation"] or [mh ^"Endovascular Procedures"] or [mh ^"Cardiac Catheterization"] or [mh ^"Surgical Instruments"]) 93

#5 (percutaneous* near/3 (surg* or repair* or clos* or reconstruc* or correct* or approach* or technique* or procedure* or intervention* or device* or implant* or treat* or therap*)) 9811

#6 (percutaneous* near/3 ("catheter-based" or transcatheter* or trans-catheter*)) 40

#7 (percutaneous* near/3 (mitral or mitralis or cardiac next valv* or heart next valv* or bicuspid or "left atrioventricular")) 113

#8 pmvr 8

#9 (("catheter-based" or transcatheter* or trans-catheter*) near/3 (surg* or repair* or clos* or reconstruc* or correct* or approach* or technique* or procedure* or intervention* or device* or implant* or treat* or therap*)) 1632

#10 tmvr 5

#11 (("catheter-based" or transcatheter* or trans-catheter*) near/3 (mitral or mitralis or cardiac next valv* or heart next valv* or bicuspid or "left atrioventricular")) 98

#12 ((minimal* next invasive or less next invasiv* or non next invasiv* or "reduced invasive") near/3 (surg* or repair* or clos* or reconstruc* or correct* or approach* or technique* or procedure* or intervention* or device* or implant* or treat* or therap*)) 6319

#13 ((minimal* next invasive or less next invasiv* or non next invasiv* or "reduced invasive") near/3 ("catheter-based" or transcatheter* or trans-catheter*)) 5

#14 ((minimal* next invasive or less next invasiv* or non next invasiv* or "reduced invasive") near/3 (mitral or mitralis or cardiac next valv* or heart next valv* or bicuspid or "left atrioventricular")) 40

#15 (clip or clips) 1331

#16 "edge-to-edge" 25

#17 alfieri* 148

#18 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 18571

#19 #3 and #18 239

#20 [mh ^"Mitral Valve Insufficiency"/SU] and ([mh ^"Minimally Invasive Surgical Procedures"] or [mh ^"Heart Valve Prosthesis Implantation"] or [mh ^"Endovascular Procedures"] or [mh ^"Cardiac Catheterization"] or [mh ^"Surgical Instruments"]) 59
#21 (mitraclip* or mitralclip* or mitra next clip* or mitral next clip* or mitraclipnt* or mitralclipnt* or mitra next clipnt* or mitral next clipnt*) 77
#22 #19 or #20 or #21 273
#23 #19 or #20 or #21 Publication Year from 2008 to 2018, in Economic Evaluations 3

A.7: Source: Health Technology Assessment (HTA)
Interface / URL: Centre for Reviews and Dissemination
Database coverage dates: from inception to date
Search date: 21 March 2018
Retrieved records: 20
Search strategy:

1 MeSH DESCRIPTOR Mitral valve insufficiency 50
2 ((mitral or mitralis or cardiac valv* or heart valv* or bicuspid or left atrioventricular) NEAR5 (regurgitat* or incompetenc* or insufficien*)) 74
3 #1 OR #2 74
4 MeSH DESCRIPTOR Mitral Valve WITH QUALIFIER SU 32
5 MeSH DESCRIPTOR Minimally Invasive Surgical Procedures 260
6 MeSH DESCRIPTOR Heart Valve Prosthesis Implantation 139
7 MeSH DESCRIPTOR Endovascular Procedures 160
8 MeSH DESCRIPTOR Cardiac Catheterization 148
9 MeSH DESCRIPTOR Surgical Instruments 88
10 #5 OR #6 OR #7 OR #8 OR #9 744
11 #4 AND #10 17
12 (percutaneous* NEAR3 (surg* or repair* or clos* or reconstruc* or correct* or approach* or technique* or procedure* or intervention* or device* or implant* or treat* or therap*)) 1070
13 (percutaneous* NEAR3 (catheter-based or transcatheter* or trans-catheter*)) 8
14 (percutaneous* NEAR3 (mitral or mitralis or cardiac valv* or heart valv* or bicuspid or left atrioventricular)) 16
15 (pmvr) 0
16 ((catheter-based or transcatheter* or trans-catheter*) NEAR3 (surg* or repair* or clos* or reconstruc* or correct* or approach* or technique* or procedure* or intervention* or device* or implant* or treat* or therap*)) 144
17 (tmvr) 0
18 ((catheter-based or transcatheter* or trans-catheter*) NEAR3 (mitral or mitralis or cardiac valv* or heart valv* or bicuspid or left atrioventricular)) 8
19 ((minimal* invasive or less invasiv* or non invasiv* or reduced invasive) NEAR3 (surg* or repair* or clos* or reconstruc* or correct* or approach* or technique* or procedure* or intervention* or device* or implant* or treat* or therap*)) 688

20 ((minimal* invasive or less invasiv* or non invasiv* or reduced invasive) NEAR3 (catheter-based or transcatheter* or trans-catheter*)) 0
21 ((minimal* invasive or less invasiv* or non invasiv* or reduced invasive) NEAR3 (mitral or mitralis or cardiac valv* or heart valv* or bicuspid or left atrioventricular)) 6
22 (clip or clips) 54
23 (edge-to-edge) 2
24 (alfieri*) 4
25 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 1905
26 #3 AND #25 30
27 MeSH DESCRIPTOR Mitral Valve Insufficiency WITH QUALIFIER SU 19
28 #10 AND #27 10
29 (mitraclip* or mitralclip* or mitra clip* or mitral clip* or mitraclipnt* or mitralclipnt* or mitra clipnt* or mitral clipnt*) 17
30 #26 OR #28 OR #29 38
31 (#30 IN HTA) FROM 2008 TO 2018 20

A.8: Source: CEA Registry

Interface / URL: http://healtheconomics.tuftsmedicalcenter.org/cear4/Home.aspx
Database coverage dates: 1976 to 2017
Search date: 21 March 2018
Retrieved records: 7
Search strategy:

The freely available Basic search interface was used. The interface is simple and does not allow creating complex searches with Boolean operators. The system seems to perform automatic truncation. Only the most specific search terms were used. Retrieved records were downloaded from PubMed to allow importing into Endnote.

mitral regurgitation - 7 results (6 results downloaded, 1 excluded as as before 2008)
mitral insufficiency – no results
mitral valve – 6 results (1 result downloaded, 2 excluded as before 2008, 3 excluded as duplicates)
transcatheter mitral – 2 results (excluded as duplicates)
trans-catheter mitral – no results
catheter-based mitral – no results
percutaneous mitral – 1 result (excluded as a duplicate)
pmvr - 1 result (excluded as a duplicate)
tmvr – no results
mitraclip – 4 results (excluded as duplicates)
mitralclip – no results
mitra clip – no results

mitral clip – no results
edge-to-edge - 1 result (excluded as a duplicate)
Alfieri – no results

A.9: Source: National Guidelines Clearinghouse
Interface / URL: https://www.guideline.gov/
Database coverage dates: not available on the website
Search date: 22 March 2018
Retrieved records: 3
Search strategy:

The default search option was used. The system seems to perform a full-text search of the whole guideline. Results were screened and relevant guidelines were downloaded as pdf files.

mitral regurgitation – 8 results screened, 1 result downloaded
mitral insufficiency – 5 results screened, no downloads
mitral valve – 12 results screened, 2 results downloaded
percutaneous mitral – 8 results screened, no downloads
transcatheter mitral – 4 results screened, no downloads
trans-catheter mitral – no results
catheter-based mitral – 8 results screened, no downloads
valve – 13 results screened, no downloads
mitraclip – 1 result screened, excluded (mitraclip mentioned in the COI statement)
mitralclip – no results
mitra clip – no results
mitral clip – no results

A.10: Source: Guidelines International Network: International Guideline Library
Interface / URL: http://www.g-i-n.net/library/international-guidelines-library
Database coverage dates: not available on the website
Search date: 22 March 2018
Retrieved records: no records
Search strategy:

mitral regurgitation – 1 result screened, excluded based on language (in Spanish)
mitral insufficiency – 1 result screened, excluded based on language (in Spanish)
mitral valve – 1 result screened, excluded based on language (in Spanish)
percutaneous mitral – no results
transcatheter mitral – no results
trans-catheter mitral – no results
catheter-based mitral – no results

valve – 15 results screened, no downloads
mitraclip – 1 result screened, excluded based on language (in Spanish)
mitralclip – no results
mitra clip – no results
mitral clip – no results

A.11: Source: National Institute for Health and Care Excellence
Interface / URL: https://www.nice.org.uk/
Database coverage dates: not available on the website
Search date: 22 March 2018
Retrieved records: 5
Search strategy:

The default search option on the initial page was used to run the searches. The results were limited to Guidance using the "Filter results by…" option.

mitral regurgitation – 12 results screened, 5 downloaded
mitral insufficiency – 3 results screened, no downloads
mitral valve – 19 results screened, 5 excluded as duplicates, no downloads
percutaneous mitral – 13 results screened, 5 excluded as duplicates, no downloads
transcatheter mitral – 4 results screened, 2 excluded as duplicates, no downloads
trans-catheter mitral – 2 results screened, 2 excluded as duplicates, no downloads
catheter-based mitral – 12 results screened, 5 excluded as duplicates, no downloads
mitraclip – no results
mitralclip – no results
mitra clip – 1 result, excluded as duplicate
mitral clip – 1 result, excluded as duplicate

Appendix B: Quality assessment of included economic studies

Cost utility analysis (Mealing et al., 2013)	
Each quality item is scored as follows: **Yes= 2; In part = 1; No= 0**	**Score**
1. Are the research questions/aims and design clearly stated?	**2**
2. Is the research design appropriate for the aims and objectives of the research?	**2**
3. Are the methods clearly described?	**2**
4. Is the data adequate to support the authors' interpretation/conclusions?	**1**
5. Are the results generalizable?	**1**
Total	**8/10**

Source: Department of Health. The National Service Framework for Long Term Conditions. March 2005. Available at https://www.gov.uk/government/publications/quality-standards-for-supporting-people-with-long-term-conditions

"Before and after" costing study (Vemulapalli et al., 2017)	
Each quality item is scored as follows: **Yes= 2; In part = 1; No= 0**	**Score**
1. Are the research questions/aims and design clearly stated?	**2**
2. Is the research design appropriate for the aims and objectives of the research?	**2**
3. Are the methods clearly described?	**1**
4. Is the data adequate to support the authors' interpretation/conclusions?	**1**
5. Are the results generalizable?	**0**
Total	**6/10**

Source: Department of Health. The National Service Framework for Long Term Conditions. March 2005. Available at https://www.gov.uk/government/publications/quality-standards-for-supporting-people-with-long-term-conditions