Northern Medical Physics and Clinical Engineering
A Clinical Directorate of The Newcastle upon Tyne Hospitals NHS Foundation Trust

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NICE OBSERVATIONAL DATA UNIT (ODU)

Commissioning through Evaluation (CtE) Percutaneous mitral valve leaflet repair for mitral regurgitation (MitraClip)

FINAL REPORT - DRAFT

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28 February 2018

Project Name:	Commissioning through Evaluation (cardiovascular procedures)
Project Number:	RX085
Start Date:	12 September 2014
Output Date:	28 February 2018

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Commercial in confidence data are redacted

Declared interests of the authors: None

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Executive summary

Mitral valve regurgitation (MR) occurs when the mitral valve loses competency, resulting in retrograde flow of blood from the left ventricle into the atrium, which in turn reduces the efficiency of the heart. There are two principal causes of MR. Degenerative (primary) MR is caused by deterioration of the valve itself, whereas in functional (secondary) MR, the valve itself is structurally normal, but is functionally compromised as the leaflets fail to coapt, usually secondary to left ventricular enlargement. Mitral valve regurgitation leads to worsening heart failure and associated symptoms. In people with MR who are considered at too high risk of open heart surgery, percutaneous leaflet repair with the MitraClip system may be the only treatment option other than palliative medical management.

In order to evaluate the MitraClip procedure, NHS England has set up a multi-centre observational registry using the process of Commissioning through Evaluation (CtE). The registry was designed to include patients who had moderate or severe MR of degenerative or functional aetiology, and for whom conventional surgery was deemed to be an excessively high risk intervention. The registry recorded a range of clinical outcomes with a maximum follow up of 2 years. The aims of the CtE registry were to provide data on the safety, efficacy and costs of MitraClip in a real-world setting, and specifically to answer 11 pragmatic questions concerning these issues. As the registry was single-armed, a parallel literature search was undertaken in order to present the registry findings in the context of published studies in comparable populations, and to assess whether procedural outcomes were consistent with previously reported studies. Information gained from the registry will be used to inform future commissioning.

The MitraClip registry enrolled 272 patients, of whom 199 were eligible for CtE data analyses. The 199 patients included in the CtE analyses had functional (60%) or degenerative (40%) MR with a mean age of 76.2 years. Most patients were men (69%) and most patients (66%) had moderate or severe left ventricular impairment. The majority of patients were recruited electively (84.4%), with 13.6% admitted urgently and 2.0% undergoing the procedure as an emergency. Nearly all patients had moderate or severe MR (grade 3+ or 4+), which was symptomatic in 92% of cases (New York Heart Association [NYHA] class 3 or 4). The mean EuroSCORE II (per cent risk of dying from cardiac surgery) was 6.4 (range 0.67 to 42.46).

The procedural success rate was 85.9% (95% confidence interval 80.3 to 90.4%), with 8.2% of procedures being associated with an in-hospital major complication, including ten deaths (5.1%) and four additional interventions (2.0%). In patients successfully treated, there was an immediate and significant improvement in MR, with a reduction from 100% MR grade ≥3+ to 7% MR grade ≥3+. These peri-procedural outcomes were consistent with observational studies identified in the literature with similar populations, and emphasise the early clinical benefits but also the high mortality associated with this sick cohort.

In the medium term, the MR benefits of MitraClip were largely sustained, with 76% of patients having mild or absent MR (grade ≤2+) at 1 year. This was reflected in significantly improved patient symptoms, with 82% having mild or no symptoms of dyspnoea (NYHA class ≤2), and significant improvements in quality of life (QoL), as measured by EQ-5D. The mortality rate at 1 year was 11.6%. Again, these findings were consistent with those published in observational studies. The CtE registry was unable to provide robust information on the likely demand for MitraClip, its impact on hospital readmission, or long-

term outcomes. However, limited data from published studies suggest cardiac readmissions are relatively high (over 20%) in the first year and that MitraClip may lose efficacy (in terms of MR reduction) at longer follow up times (4 years and above). Planned data linkage of CtE registry data to Hospital Episode Statistics (HES) should provide more insight into outcomes for the cohort.

There was no significant difference in mortality rate, MR grade, NYHA class, and adverse events in patients with degenerative or functional MR aetiologies. Patients receiving MitraClip as an urgent or emergency case had a greater risk of death, with 68.2 dying per 100 person years (PY) compared with 22.1 per 100 PY in the elective cohort ($p = 0.0105$). This increased risk of mortaility was driven by in-hospital mortality. When only post-discharge mortality was considered, there was no significant difference.

A limitation of the CtE registry, common to all device registries, was that it did not report a control arm of optimal medical management without MitraClip. As the EAC was also unable to identify a study with an appropriate and robust control, it is currently unknown how registry patients would have fared without treatment, particularly in terms of mortality.

In conclusion, the CtE registry has reported data that show MitraClip is associated with an immediate reduction in MR. This effect is sustained in the medium term (1 year) and is associated with significant improvements in symptoms and QoL, with 17 of 20 patients surviving for at least 2 years. The longer term complications and benefits of MitraClip are unknown because of a lack of long-term studies with suitable comparators. It is hoped that on-going RCTs will inform these gaps in the evidence.

Any clinical benefits of MitraClip should be considered in the context of an estimated cost for all procedures of £32,560 (range £28,800 to £34,100). Although conclusions cannot be made about the cost effectiveness or cost saving potential of the procedure, work to address the latter is planned for later in 2018, assuming the EAC can access linked data from Hospital Episode Statistics.

Abbreviations

ACC	American College of Cardiologists
ACE-I	Angiotensin-converting enzyme inhibitor
AF	Atrial fibrillation
AKI	Acute kidney injury
ARB	Angiotensin II receptor blockers
BNP	B-type natriuretic peptide
CABG	Coronary artery bypass graft
CCS	Canadian Cardiovascular Society
CG	Clinical guideline
CI	Confidence interval
CPB	Cardiopulmonary bypass
CRT	Cardiac resynchronisation therapy
CSHA	Canadian Study on Health and Ageing
CT	Computed tomography
CtE	Commissioning through Evaluation
CVA	Cerebrovascular accident
DMR	Degenerative mitral valve regurgitation
eGFR	Estimated Glomerular Filtration Rate
EAC	External Assessment Centre
EACTS	European Association for Cardio-Thoracic Surgery
ECG	Electrocardiograph
EQ-5D	EuroQoL 5 dimensions
ESC	European Society of Cardiology
FBC	Full blood count
FMR	Functional mitral valve regurgitation
Fr	French
FU	Follow up
HF	Heart failure
HR	Hazard ratio
IABP	Intra-aortic balloon pump
ICD	Implantable cardioverter defibrillator
ICE	Intracardiac echocardiogram
ICER	Incremental cost-effectiveness ratio
IPG	Interventional procedures guidance
IQR	Inter-quartile range
ITT	Intention to treat
ITU	Intensive therapy unit
LAAO	Left atrial appendage occlusion
LoS	Length of stay
LVEF	Left ventricular ejection fraction
MACCE	Major Adverse Cardiac and Cerebrovascular event
MDS	Minimum data set
MDT	Multi-disciplinary team
MI	Myocardial infarction
MR	Mitral valve regurgitation
MRI	Magnetic resonance imaging
MV	Mitral valve
NHS	National Health Service
NHSE	NHS England
NICE	National Institute for Health and Care Excellence
NICOR	National Institute for Cardiovascular Outcomes Research
NYHA	New York Heart Association
OR	Odds ratio

PCI	Percutaneous coronary intervention
PFO	Patent foramen ovale
PFOC	Patent foramen ovale closure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PVD	Peripheral vascular disease
PY	Person years
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
SD	Standard deviation
SE	Standard error
SE	Systemic embolism
SF-36	Short form 36 [dimensions]
STS	Society of Thoracic Surgeons
TAPSE	Tricuspid annular plane systolic excursion
TIA	Transient ischaemic attack
TOE	Transoesophageal echocardiogram
TR	Tricuspid regurgitation
TTE	Transthoracic echocardiogram
U&E	Urea and electrolytes

Section 1: Introduction

1.1 NHS ENGLAND COMMISSIONING THROUGH EVALUATION – MITRACLIP

NICE provides support to NHS England in Commissioning through Evaluation (CtE):

"NHS England's Commissioning through Evaluation (CtE) programme enables a limited number of patients to access treatments that are not funded by the NHS, but nonetheless show significant promise for the future, while new clinical and patient experience data are collected within a formal evaluation programme."

The work commissioned by NICE ('Project RX085') from Newcastle and York (NY) EAC comprises evaluation of three percutaneous cardiac procedures:

- Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism (NICE IPG349, June 2010). Shortened term used is 'LAAO'.
- Percutaneous Closure of Patent Foramen Ovale to prevent recurrent cerebral embolic events (NICE IPG472, December 2013). Shortened term used is 'PFO Closure'.
- Percutaneous mitral valve leaflet repair for mitral regurgitation (MitraClip) (NICE IPG309, August 2009) [1]. Shortened term used is 'MitraClip'.

A Cardiology CtE Steering Group is established as a subgroup of the NHS England Cardiothoracic Services Clinical Reference Group (CRG). It reports to the Programme of Care Board for Internal Medicine for NHS England. Three Individual Technology Groups report to the CtE Steering Group on the progress of the above three specialised cardiological interventions which form the cardiac CtE programme.

The National Institute for Cardiovascular Outcomes Research (NICOR) was contracted by NY EAC to design and host an on-line registry for MitraClip procedures, to provide a project management function to promote data entry quality and completeness by commissioned CtE provider sites and to link registry data with Hospital Episode Statistics (HES) and Office of National Statistics (ONS) mortality datasets. NICOR and the EAC consulted the MitraClip Individual Technology Group in the design of the MitraClip registry. NICOR were the formal data owner of the registry, and were the applicant to NHS Digital for data linkage with HES and ONS.

NY EAC's objectives in Project RX085 from NICE were to:

- review existing register data fields in each dataset and advise on their suitability for updating and developing NICE guidance;
- advise on the appropriateness of register data fields for each dataset being proposed or considered in relation to clinical and cost effectiveness outcomes to enable NICE to provide NHS England with further data to help inform future commissioning decisions for the procedures;
- establish processes to a) ensure on-going review of the MitraClip dataset quality, completeness and coverage, with action plans for improvements where needed and b) deliver regular evaluative reports that are useful for decision making;
- update the literature searches since publication of each NICE interventional procedures guidance (IPG) in order to identify publications of relevance;

- manage the contract with NICOR and participate in the CtE Steering Group for cardiovascular procedures;
- develop a protocol for analysis of data and consult with key partners (listed above) to gather views on the proposed methodology and proposed outputs;
- produce a final report (not intended for publication) answering the CtE evaluation questions set by NHS England (tabulated below);
- present findings in the form of a publishable paper (to be submitted for peer review for a high impact journal). This should be of a standard to be included as an input in the evidence base of the NICE technology appraisals programme (http://www.nice.org.uk/article/PMG9/chapter/Foreword);
- advise on further research that might be needed to generate clinical and cost effectiveness evidence in line with methods used in NICE evaluation programmes, including suitable study designs for such research.

Outputs required by NICE from NY EAC and delivered prior to this final report were:

- Output One [2] - a report for presentation to the CtE Steering Group on all three procedures, analysing the coverage, quality and completeness of the register to date, and making preliminary recommendations about the definitive dataset to inform NHS England's contracts for the procedures with the specialist centres, and to meet NICE's needs in relation to updating guidance. **Completed 28/11/2014**.
- Output Two [3] - a report for submission to the CtE Steering Group for cardiovascular procedures and collaborating partners proposing: a) a process to ensure on-going review of the database quality, completeness and coverage, with action plans for improvements where needed and b) the format of evaluative reports designed to be useful in informing decision making for guidance development. **Completed 04/02/2015**.
- Output Three [4] - a report for submission to NICE and the CtE Steering Group proposing a draft protocol for analysis of data that describes the methods that will be used to compare effectiveness of each of the procedures between propensity-matched cohorts of patients undergoing the range of treatment options (including cost analysis). This will have been circulated for consultation with key partners (listed above) and adjusted as appropriate prior to presentation to NICE. **Completed 31/03/2015.**

The above three outputs from the project, all of which were shared with the CtE Steering Group and approved by them, are used as source material for the general background and methods sections of this final report from NY EAC to NICE.

The NHS England questions for CtE of MitraClip were originally presented to NICE, discussed with NY EAC, and edited to the final form presented in the Table 1.

Table 1. Percutaneous mitral valve leaflet repair for mitral regurgitation (MitraClip)

Questions from NHS England	Final version of question, as amended by NICE following discussion with EAC
1. Can UK clinical teams undertaking MitraClip reproduce the reduction in mitral regurgitation seen in the early clinical trials?	NICE agrees the question is appropriate
2. Do any reductions in mitral regurgitation lead to reduced symptoms and improved quality of life (compared to pre-procedure)?	Is reduction in mitral regurgitation mediated by MitraClip associated with improvements in quality of life?
3. Is there any evidence of improved survival compared to expected survival from natural history studies or risk models?	Does MitraClip improve survival rates?
4. Is there evidence of reduced frequency of hospital admission following MitraClip?	Does MitraClip reduce the frequency of subsequent hospital admissions?
5. Are the early benefits in reduction in mitral regurgitation maintained in the longer-term? Is there a need for repeat treatment over time (either by a repeat percutaneous procedure or surgery)?	Are the early benefits in reduction in mitral regurgitation maintained in the medium-term? Is there a need for repeat treatment over time (either by a repeat percutaneous procedure or surgery)?
6. How many patients who are not candidates for conventional mitral valve surgery would benefit from a reduction in the degree of mitral regurgitation that could be achieved with successful MitraClip therapy? (i.e. if MitraClip is to become routinely funded, what is the likely clinical need in England?)	What proportion of patients referred to a specialist MitraClip service as defined in the CtE documents were assessed by the MDT as suitable for the intervention? What proportion of the patients considered suitable for the procedures received it and what proportion of them benefitted (refer also to Question 5)?
7. What are the short-term and long-term complications of MitraClip therapy? Is there a risk of longer-term mitral stenosis? Is the frequency of complications sufficiently low to provide a positive risk-benefit ratio?	What are the short and medium term risk of complications from MitraClip use? Answers to Questions 7 and 8 will be considered by the NICE Interventional Procedures Advisory Committee when NICE updates the IP guidance on this procedure.
8. What are the characteristics of patients who are successfully treated compared to those in whom treatment is unsuccessful? Are there subsets of patients who get a particularly advantageous result? Conversely, are there subsets of patients for whom this treatment is not effective? Do patients of different gender or from different ethnic origins respond equivalently?	Are clinical outcomes with MitraClip associated with particular patient characteristics (clinical or demographic)?
9. What is the true procedural cost of MitraClip therapy in the NHS?	What are the full procedural costs of using MitraClip to the NHS?
10. What costs savings might occur in the NHS as a result of MitraClip therapy?	What are the potential cost savings for the NHS arising from patients receiving MitraClip?
11. What is the cost-effectiveness of MitraClip therapy based on UK procedural and follow-up costs?	Is MitraClip cost-effective from the perspective of the NHS?

1.2 DESCRIPTION OF THE PROCEDURE

The MitraClip procedure is described in NICE IPG309:

"Percutaneous mitral valve leaflet repair is undertaken with the patient under general anaesthesia. Under fluoroscopy and transoesophageal echocardiography guidance, a catheter is advanced through the femoral vein to the right atrium and via a transseptal puncture into the left atrium. The mitral leaflets are partially clipped to each other (more than

one clip may be used). Imaging is used to assess whether the reduction in mitral regurgitation is adequate. The clips may be repositioned if necessary."

In the 2009 NICE IP Guidance, evidence on the safety and efficacy of percutaneous mitral valve leaflet repair for mitral regurgitation (MitraClip) was considered inadequate in quality and quantity. Therefore, the procedure should only be used:

- with special arrangements for clinical governance, consent and research for patients who are well enough for surgical mitral valve leaflet repair to treat their mitral regurgitation, or
- in the context of research for patients who are not well enough for surgical mitral valve leaflet repair to treat their mitral regurgitation.

Section 2: Methods

2.1 CTE MITRACLIP PROVIDERS AND PROGRAMME GOVERNANCE

Hospitals providing the CtE procedures in the 3 centres participating in the MitraClip scheme are:

- The University Hospital of South Manchester NHS Foundation Trust (Wythenshawe Hospital)
- University Hospitals Bristol NHS Foundation Trust (Bristol Royal Infirmary)
- Royal Brompton and Harefield NHS Foundation Trust (Royal Brompton Hospital).

The criteria used to select the hospitals for the CtE work considered a number of competing factors and are described in the NHS England Specialised Services Circular (SSC) 1454 for MitraClip [5]. An advisory panel made recommendations to NHS England as to which providers should be selected to be CtE centres. The final selection of centres was undertaken by the regional Medical Directors.

The NHS England Cardiac CtE Clinical Lead for MitraClip is Dr. Mark de Belder, Consultant Cardiologist, South Tees Hospitals NHS Foundation Trust. Dr. de Belder is Chair of the NHS England MitraClip Individual Technology Group. The role of the Group, set out in its Terms of Reference (ToR), is to:

- Work with the EAC and the National Institute for Cardiovascular Outcomes Research (NICOR) on the development of the relevant dataset.
- Define and clarify patient access criteria, where required, within the terms of the published policy statements / specification.
- Ensure that all participating centres are collecting, verifying and uploading data in a timely manner.
- Ensure that all participating centres are collecting follow-up data appropriately.
- Monitor performance of all centres performing procedures as part of CtE and report any concerns to the Steering Group.
- Monitor referrals, patient pathways and waiting times for the relevant procedure at all participating centres (including pathways for patients who do not receive the CtE treatment).

2.2 CTE MITRACLIP COMMISSIONING DETAILS

NHS England commissioned a total of 180 MitraClip procedures in the cardiac CtE scheme. Each of the 3 centres was required to do no more than 40 procedures per financial year. As CtE commenced on 01/10/2014, each centre could do no more than 20 MitraClip procedures in those last 6 months of 2014/15. Funding was made available by NHS England for each centre to do 40 procedures in 2015/16, making 60 procedures per centre in total.

Owing to slower than anticipated roll-out of the programme, centres were permitted, by NHS England Specialised Services Circular SSC 1669 (November 2016), to carry on with their 2015/16 activity plans in financial year 2016/17, up to the contracted number of 180 procedures in total for the MitraClip CtE programme.

2.3 INCLUSION AND EXCLUSION PATIENT SELECTION CRITERIA

According to the NHS England Specialised Services Circular (SSC) 1454 for MitraClip [5], patient selection criteria were:

"Patients with severe grade 3 or 4 mitral regurgitation, deemed by an MDT to be at too high risk or at high risk for conventional mitral valve surgery:

> a. Symptomatic patients (in spite of optimal medical therapy, which includes the appropriate use of device therapy [implantable cardioverter defibrillator (ICD) or cardiac resynchronisation therapy (CRT)]).
> b. Appropriate mitral valve anatomy (mitral valve area ≥4 cm^2, leaflet flail width <15 mm and gap <10 mm; patients with leaflet tethering - coaptation depth >11 mm and length <2 mm – are excluded).
> c. Patient fully informed and consent provided.

Patients with mitral valve disease and heart failure who might be considered eligible for mitral valve replacement or repair or MitraClip can be referred from cardiologists or other specialists in district general hospitals to cardiac surgeons or cardiologists in a specialist cardiac centre. This must be in line with the specialised service specification for cardiology and cardiac surgery. Direct referrals to cardiac centres from primary care and general practice requesting consideration for MitraClip will not be accepted. Selection of patients for a MitraClip procedure must be via the MDT process."

2.4 PRIMARY DATA COLLECTION

2.4.1 Database details and information governance arrangements

NICOR worked with the CtE MitraClip Individual Technology Group and NY EAC to produce the final dataset for MitraClip.

NY EAC produced 'RX085 Output One - Recommendations on three NHS England Commissioning through Evaluation (CtE) registry draft datasets for MitraClip, LAAO and PFO Closure cardiovascular procedures' [2] (November 2014). This identified and appraised new evidence added to the literature base and public domain since the original NICE IP664 overview [6] was published and compared findings against the data fields contained in the draft MitraClip CtE dataset.

The final MitraClip dataset was developed into the online database by NICOR and the latest version may be downloaded as a Microsoft Excel spread sheet (last updated 27/08/2015).

Regarding information governance arrangements, as Data Controller, NICOR's responsibilities were:

- To ensure that a dataset being proposed or used for national data collection has appropriate independent oversight, and that all relevant data will be made available to NICE for use in developing guidance.
- To provide NY EAC with a monthly download of episode level full raw data sets from each registry (out with normal NICOR data sharing policy and following the 'Use of Data' principles agreed with NY EAC). Data cleansing will happen to usual NICOR schedule. Monthly downloads may be aggregated or incremental. The EAC will provide feedback to NICOR on any data quality / completeness issues observed in the monthly raw data downloads.

- To arrange and undertake data linkage with Hospital Episode Statistics (HES) and Office of National Statistics (ONS) mortality data and provide complete data extract(s) to NY EAC in order to check for extra safety and efficacy, clinical effectiveness or resource utilisation information.
- To arrange and maintain appropriate EQ-5D-5L licensing arrangements to cover all projected patient volumes commissioned by NHS England in its CtE programme. This should include all commissioned follow up visits.
- To provide a telephone helpdesk service for answering technical enquiries / requests and for individual registration and access to each registry web portal. Clinical enquiries will need to go to the NICOR project manager and NY EAC may be co-opted to help NICOR respond to clinical or scientific queries.
- To operate within the general principles of Good Clinical Practice (GCP) in research, as outlined in the Research Governance Framework for Health and Social Care 2005.
- To make all necessary applications to comply with information governance requirements. These include but are not restricted to:

    i complete the Information Governance Statement of Compliance process to the satisfaction of the NHS Health and Social Care Information Centre

    ii demonstrate compliance with the Data Protection Act 1998. This is also particularly relevant when data will leave or enter the EU. Appropriate regard needs to be paid to international regulations

    iii complete the Confidentiality Advisory Group application process to comply with the NHS Health Research Authority requirements for Section 251 approval.

2.4.2 Active surveillance

NICOR provided NY EAC with their Minimum Data Standard (MDS) Summary Document for Cardiac CtE **(Confidential)**. Some of the background detail is extracted in the following summary:

"While NICOR undertakes a number of manual and automated data quality control processes, the responsibility for data quality is shared with clinicians and organisations undertaking procedures in the NHS. It is particularly important that data are collected for patients who experience adverse outcomes (such as death, stroke, bleeding) and harm. NICOR aims to further assist organisations in their data submissions by defining a minimum data standard (an acceptable standard for data submissions to be measured against), to provide feedback to the provider organisations on the data quality of their quarterly submissions and to give organisations the opportunity to improve and resubmit the data should improvements be required."

The final NICOR MDS for MitraClip CtE baseline data completeness monitoring contained 21 key fields. Six additional fields were monitored for patient completion of EQ-5D questionnaires and EuroQoL data entry (NICOR field identifiers 4.08 to 4.13). These are summarised in Table 2:

Table 2. Fields in registry used for monitoring of data completeness.

NICOR Field identifier	Data Field
1.03	NHS Number
1.06	Birth date
1.10	Postcode
2.03	Reason for treatment
4.05	New York Heart Association (NYHA) status
4.06	Killip class
4.07	Date EuroQoL form filled
4.08	EuroQoL Mobility
4.09	EuroQoL Self-care
4.10	EuroQoL Usual activities
4.11	EuroQoL Pain / discomfort
4.12	EuroQoL Anxiety / depression
4.13	EuroQoL Health state today
4.15	CSHA
5.02	Severity of mitral valve regurgitation (MR)
5.03	Aetiology of MR
5.64	Logistic EuroSCORE
7.01	Date of admission
7.04	Date and time of procedure
7.06	Responsible consultant
7.27	No of clips successfully deployed
8.01	Device embolisation/detachment
8.12	Mitral valve (MV) surgery
8.26	Pre-discharge mitral regurgitation (echo)
8.29	Successful procedure
9.01	Life status
9.02	Discharge date

The six follow-up MDS fields for MitraClip data completeness monitoring at 6 weeks were:

10.01 Life status
10.05 New York Heart Association (NYHA) status
10.06 Mitral valve regurgitation (MR) severity
10.35 Additional mitral valve (MV) intervention
10.40 Major Adverse Cardiac and Cerebrovascular event (MACCE)
10.41 Date 6 week EuroQoL form filled

The equivalent variables were also monitored for follow up data at 6 months, 12 months and 24 months.

Summary reports were submitted to NICE by NY EAC on a quarterly basis, to a standard reporting template agreed with NHS England for all CtE projects. Key parameters for each CtE provider were:

- Contracted activity to date: the amount of CtE activity the centre should have performed by this point, according to their contract with NHS England.
- Actual activity to date, as identified through both register entries and active surveillance by NICOR collating a 'SurveyMonkey' questionnaire from the CtE providers.
- Number of cases submitted to the NICOR registry to date. This number could be lower than the above actual activity to date, since active surveillance could identify cases that had not yet been registered.
- Number of cases identified through active surveillance but for which data were not yet submitted to the registry (i.e. the difference between the two previous figures).

- Initially, data completeness (%) was calculated for the subset of all MitraClip records where the CtE provider had selected the 'CtE=Yes' check box when submitting the case to the NICOR dataset (this is the 'Number of cases' denominator, below):

  $$\text{Data completeness (\%)} = \frac{\text{Number of completed entries in MDS data fields}}{\text{Number of cases}} \times 100$$

- Later, queries from the CtE providers on this denominator led to refined definitions for Activity, Coverage, Completeness and Follow up (FU) reported. The final defined measures were:
  - Activity: The number of CtE procedures recorded with a procedure date between 01/10/2014 and the date of raw data extract that had an eligible reason for treatment.
  - Coverage: The percentage of patient follow ups reported out of the number of patients reaching the follow up time point in question. A 'reported' follow up had data in any of the MDS follow up fields for the time point in question.
  - Completeness: The percentage of fields with any data out of the number of MDS fields for the time point in question.
  - FU reported: This number included patients reported to have died since the previous follow up visit.

2.4.3 Case eligibility criteria

Inclusion criteria: All pseudonymised NHS procedures recorded in the MitraClip CtE registry conducted between 1st October 2014 to 24th October 2017 for patients with Grade 2 (mild-moderate), Grade 3 (moderate-severe) and Grade 4 (severe) mitral regurgitation with recorded reasons for treatment including surgical turn-down, high risk for surgery (bail-out surgery would be offered) and high-risk for surgery (bail-out surgery would not be offered). A further final data extract was drawn down by NICOR on 13th November 2017, as centres had been asked to complete cause of death against recorded mortality events, where possible.

Exclusion criteria: Patients with rheumatic aetiology (contraindicated for MitraClip), procedures with missing procedure date, discharge date preceding procedure date.

2.4.4 Data cleaning

Detailed methods of variable cleaning are described in *Supplementary Material - Table 1*. Data completeness and summary statistics, in terms of distribution of responses, were conducted for each of the data fields available and used to inform variables used and definition of outcomes during the statistical analysis.

2.4.5 Outcomes indicators

a. Clinical

Primary outcome measures included: device implantation, in-hospital major complications, in-hospital minor complications, new requirement for pacemaker, post-discharge major complications, post-discharge minor complications and mitral regurgitation over time.

Secondary outcome measures included: death, embolisation, requirement for additional intervention, myocardial infarction (MI), pericardial effusion or tamponade requiring intervention, major vascular complication requiring intervention, mitral valve complication, neurological event, cardiogenic shock, major bleed, acute kidney injury (AKI) stage 1/2/3, endocarditis, oesophageal damage, device failure, partial detachment, pericardial effusion or tamponade treated conservatively, thrombus, new moderate or severe mitral stenosis, minor

bleed, minor vascular complication. Detailed definitions of included outcome measures are described in *Supplementary Material – Table 2*.

b. Cost / resource

A bottom-up costing study of each stage in the pathway to insert the MitraClip device was conducted. NY EAC firstly reviewed the draft Excel® costing template provided by the NHS England MitraClip Individual Technology Group. Amendments were agreed with the Chair of the Group and the final template provided to the three NHS England CtE-funded centres with detailed instructions on inputting the resources required to conduct each of three stages in the relevant pathway being:

- Pre-operative assessment;
- Peri-operative procedure;
- Post-operative management.

The findings from the completed templates on resource use were reviewed by all authors and compared with existing clinical pathways. Where possible, outcomes reported in the MitraClip dataset such as number of clips implanted, type of imaging conducted at each stage in the pathway, procedure duration, primary and secondary operator and length of stay were used. Where such information was not available the three clinicians reached a consensus view on the appropriate resources required. Unit costs from NHS national datasets and other English national cost sources were applied to the resources and aggregated to give a total procedural cost. Sensitivity analyses were conducted to provide a high and low range of estimated costs. Full details are provided at Appendix 9, with a summary of results in Tables 7 and 8.

c. Patient experience

From the outset of the cardiac CtE project, it was intended that EQ-5D-5L questionnaires would be issued to all patients at baseline procedure and all subsequent follow-up visits. This was to allow pairwise analysis of results over the follow up period.

2.4.6 Statistical analysis

All scripts for case ascertainment, cleaning, processing and statistical analysis were written in the statistical programming language R [7].

Patient demographics, pre-operative clinical scores and procedural details were compared between the whole, eligible cohort (n = 199) and the subgroup of patients discharged alive and with any information recorded from follow-up appointments at 6 weeks, 6 months, 1 year or 2 years (n = 177). Fisher's exact tests or Mann Whitney U-tests were used as appropriate. Bonferroni correction was used to adjust the level of significance to take into account multiple comparisons.

Exploratory univariate and multivariate analyses were conducted for the defined outcome measures. Univariate analysis was conducted for each outcome measure and up to 36 covariates. Bonferroni correction was used to adjust the level of significance to take into account multiple comparisons (between outcome measure and each covariate of interest). Multivariate analysis used generalised linear modelling with binomial error distribution in order to estimate the effect size of covariates. Numeric covariates were centred on their median before inclusion in multivariate analysis, if appropriate. Binary logistic regression analyses were checked for convergence and over-fitting, and either modified (e.g. by

reducing the number of covariates) or reported as not valid. Coefficients of the covariates were expressed as odds ratios (OR) with 95% confidence intervals.

Crude incidence rates for death, additional mitral valve intervention, and infective endocarditis events recorded during the study period were calculated as the number of events per 100 person years of follow-up. Kaplan-Meier analysis was applied to the time from procedure to the time of the death, and first additional MV intervention and diagnosis of endocarditis. Patients who suffered no events and were alive at the end of the study were considered censored.

Severity of mitral regurgitation was also recorded at each follow-up (6 weeks, 6 months, 1 year, 2 years) and compared to pre-operative severity using Fisher's exact test (paired analysis).

Paired quality of life scores and utilities were compared at each time interval (6 weeks, 6 months, 1 year, 2 years) against pre-operative scores using Fisher's tests or t-tests where appropriate.

2.5 SECONDARY DATA COLLECTION (LITERATURE REVIEW)

The aim of the final MitraClip literature review for CtE was to identify key published studies in patients with mitral valve regurgitation (MR) of any severity or aetiology and summarise results so they align with the requirements of the outputs of NY EAC project RX085, including the 11 questions set by NHS England. A brief summary of the review methods is presented here. A standalone literature review document is available for further information (Willits *et al.*, MitraClip literature review document, November 2017) [8].

Firstly, a literature search was performed from March 2009, which was the updated search date of the original NICE IP664 overview that informed NICE IPG309. The NICE search strategies for replication were sourced through documents supplied by NICE and through communication with the Senior Information Manager at NICE Guidance Information Services. The EAC team and NICE agreed that no quality assessment would be made of the NICE strategies and the intention was to use the NICE-designed strategies as supplied. Some minor edits were made (for example, the correction of some search structure and syntax errors identified in the original NICE strategy). Apart from these minor changes, the terms used in the update strategies reflected those used in the original strategies of NICE IPG309.

The scope of the literature review was intended to broadly reflect the population and intervention covered in the CtE registry. The scope, described in PICO (Population, Intervention, Comparator, Outcomes) format, is summarised in the Table 3.

Table 3. Scope of literature review.

Domain	Terms identified from title or abstract	Comment
Population	Patients with mitral regurgitation	Includes degenerative or functional mitral regurgitation.
Intervention	Percutaneous mitral valve leaflet repair	Specifically interested in MitraClip. If unable to ascertain from abstract, retrieve. If other device or procedure, flag.
Comparator	Any or none	Comparative studies preferred but in practice may not be available. Studies with comparisons versus medical management of particular relevance.
Outcomes	Clinical outcomes	Studies reporting only surrogate or non-clinical

Domain	Terms identified from title or abstract	Comment
	Utility and resource use outcomes*	outcomes will be excluded.
Study type	All primary studies Secondary studies* (systematic reviews and meta-analyses) Economic studies*	Non-systematic reviews, editorials and opinion pieces excluded. Abstracts included only if reporting an adverse effect not already known. All RCTs included. Single armed observational studies included if n≥100. Comparative observational studies of any size included if comparator is conservative medical management.
* Systematic reviews and meta-analyses not included in final PRISMA selection but flagged. Economic studies and associated outcomes to be identified for possible future reference.		

Given the timelines of the project and the purpose of the update search, the EAC team and NICE agreed that only the bibliographic databases listed in Table 4 would be searched. In addition, it was agreed that strategies would be limited to results published in English language only, and that conference-related publication types would be excluded from the Embase search.

Where database functionality allowed, results were limited to records added to the database since the date of the last search, using appropriate fields such as the entry date field in MEDLINE. Where database functionality did not allow this, results were limited by publication date, reflecting the pragmatic context of the search.

Table 4. Bibliographic databases searched.

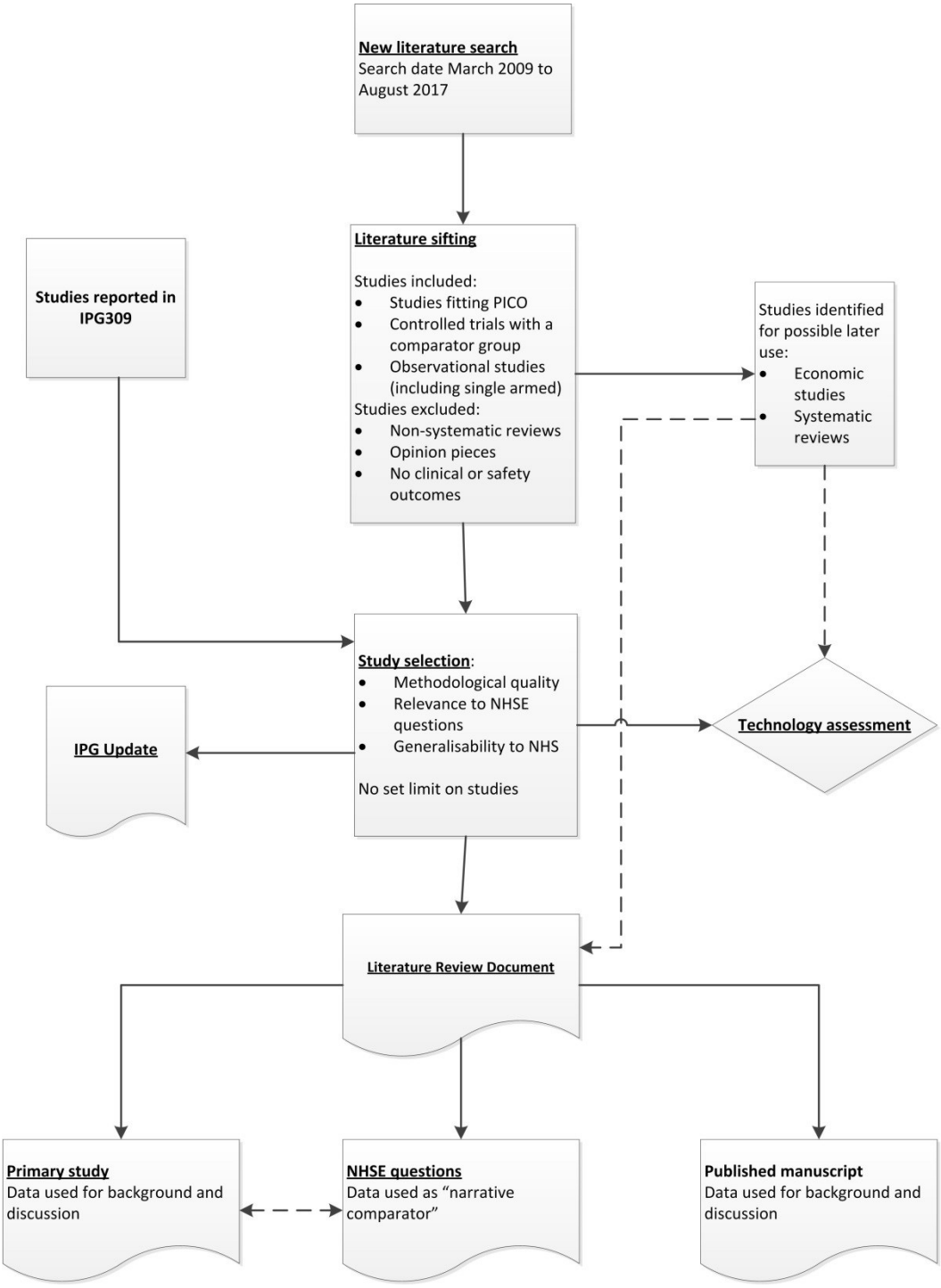
Database / information source	Interface / URL
MEDLINE and MEDLINE In-Process	OvidSP
EMBASE	OvidSP
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library/Wiley Interscience
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library/Wiley Interscience
Database of Abstracts of Reviews of Effects (DARE)	http://www.crd.york.ac.uk/CRDWeb/
Health Technology Assessment Database (HTA)	http://www.crd.york.ac.uk/CRDWeb/
NHS Economic Evaluation Database (EED)	http://www.crd.york.ac.uk/CRDWeb/

Relevant studies were sifted by two reviewers according to the predefined scope, and these studies were then combined with those reported in NICE IPG309. As this approach identified an unmanageable number of studies, a further selection process was employed to identify

studies on the basis of methodological quality and size, with randomised controlled trials (RCTs) and single-armed registry studies with 500 or more participants or cohort studies with a combined total of 100 or more participants selected for full review [8]. Systematic reviews and economic studies were also identified.

Figure 1 is a flow diagram of this pragmatic literature review strategy, including the inclusion and exclusion criteria applied to sifting.

Figure 1. Flow chart illustrating the literature review strategy for MitraClip.



A brief summary of the results of the literature review is presented in the results section of this final CtE report on MitraClip, with full details available in the standalone literature review document [8].

2.6 RESEARCH DESIGN

The study was a procedural registry designed with a maximum 2 years of follow up. The registry was single armed with no comparator or control arm. Data were collected prospectively in accordance with best practice [9, 10].

There remains some uncertainty regarding the efficacy and safety of MitraClip (see Section 3.2 for further details). In particular, there is an issue concerning the generalisability of published comparative trial evidence to this population in the CtE registry, and how effective and safe the procedure is in real-world practice. To help clarify this uncertainty, NHS England has requested that the answers to 11 clinical and economic questions should be addressed, using data reported by the CtE registry and supported by published studies in the literature. These questions have been revised and adjudicated by NICE (see Table 1).

The EAC performed a pragmatic literature review, which identified the key experimental and observational studies performed to date on MitraClip, as described in Section 2.5. As the CtE register was non-comparative, data from the literature has been used as a proxy control for the register.

Table 5 summarises the *a priori* intended methods for answering each question [11]. However, due to issues with data quality and reporting of published literature, the original methods were not always possible. These limitations have subsequently been annotated in the table.

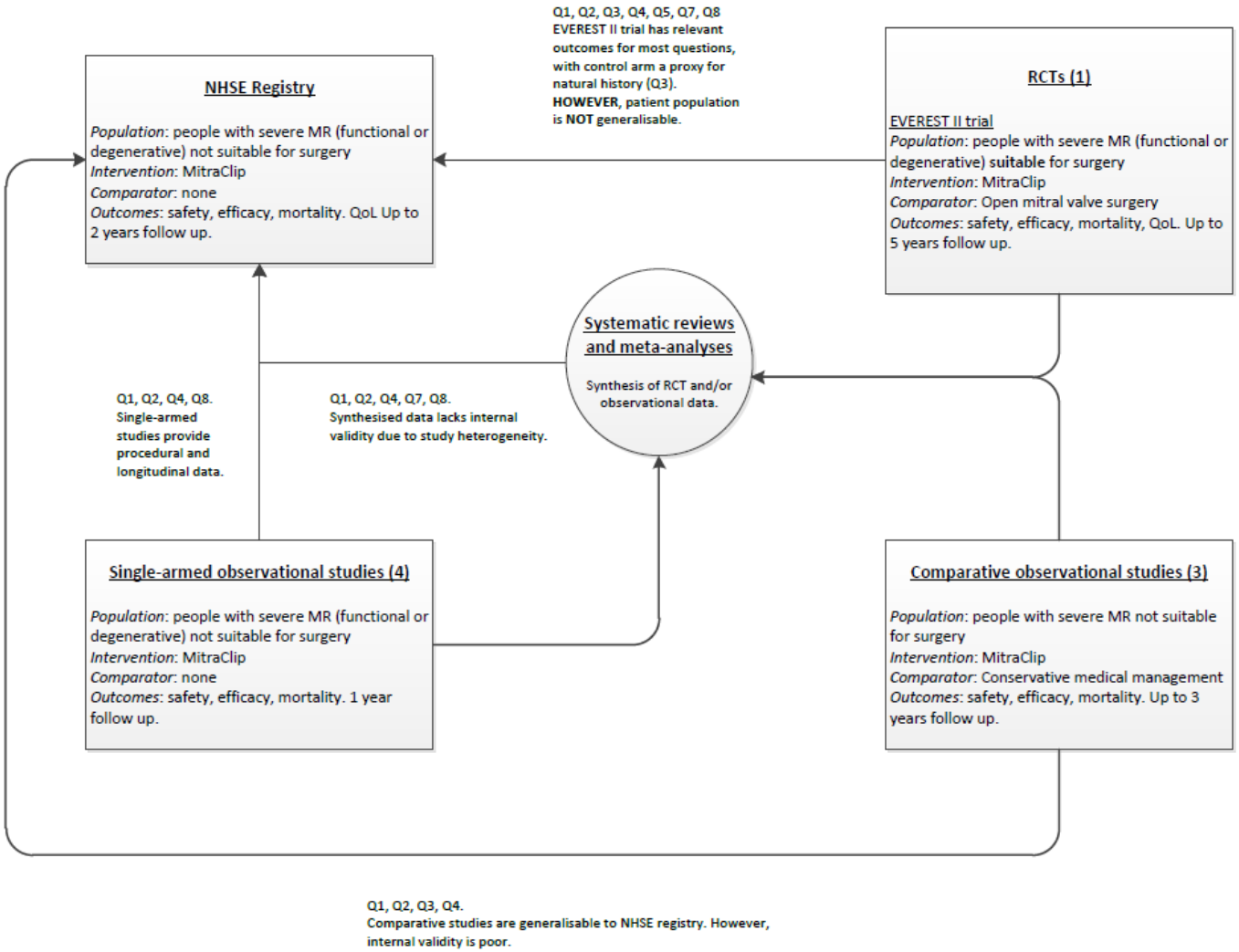
The relationship between the registry and published literature in answering the NHS England questions is illustrated in Figure 2. Inference has been made by comparing point estimates and confidence intervals where available. Additionally, in some instances where the registry was not sufficiently robust to answer the questions, published evidence was used to directly answer questions.

Table 5. Methods used to analyse and report CtE registry data.

Question (NICE modified where applicable)	Can it be answered using registry data?	Key registry data required	Type of analysis	Comment
1) Can UK clinical teams undertaking MitraClip reproduce the reduction in mitral regurgitation seen in the early clinical trials?	Yes, fully.	Change in mitral regurgitation grade.	Pairwise ('before and after') analysis of registry data. Comparison with published RCTs and observational studies.	Registry does not provide comparative data so this will be matched with published data. Depending on the goodness of fit, a narrative summary or statistical analysis may be possible.
2) Is reduction in mitral regurgitation mediated by MitraClip associated with improvements in quality of life?	Yes, fully.	Severity of mitral valve regurgitation. 6 minute walk test. NYHA score. Quality of life.	Pairwise ('before and after') analysis of registry data. Correlation and regression analysis.	Association between reduction in mitral regurgitation and improved quality of life likely to be causal association.
3) Does MitraClip improve survival rates?	Yes, partly.	Mortality rate.	Kaplan-Meier analysis. Comparison with published RCTs and observational studies.	Data from registry limited by low patient enrolment and short follow up.
4) Does MitraClip reduce the frequency of subsequent hospital admissions?	Yes, partly.	Additional mitral valve intervention. MitraClip detachment/embolisation/ retrieval. Electrical device therapy. Other MACCE. [Update: follow up not extended, could feasibly be addressed in future using HES analysis].	Comparison with literature on natural history of mitral valve disease. Control arm of suitable RCTs, observational studies, expert opinion.	Most fields are not core so risk of missing data in registry.
5) Are the early benefits in reduction in mitral regurgitation maintained in the medium-term? Is there a need for repeat treatment over time (either by a repeat percutaneous procedure or surgery)?	Yes, partly.	Severity mitral valve regurgitation. Additional mitral valve intervention.	Kaplan-Meier analysis with extrapolation. Comparison with published literature.	Short, medium, and long (or longer) term time periods require defining and feasibility of longer term analysis will be dependent on contract extension. [Update: follow up not extended, could feasibly be addressed in future using HES analysis].
6) What proportion of patients referred to	Yes, partly.	Decision to treat by MDT.	Proportion of patients	Difficult to unravel selection

Question (NICE modified where applicable)	Can it be answered using registry data?	Key registry data required	Type of analysis	Comment
a specialist MitraClip service as defined in the CtE documents were assessed by the MDT as suitable for the intervention? What proportion of the patients considered suitable for the procedures received it and what proportion of them benefitted?		Severity of mitral valve regurgitation (change over time). NYHA (change over time).	considered by MDT/patient received MitraClip.	process, unknown how many potential candidates do not make the registry at all.
7) What are the short and medium term risk of complications from MitraClip use?	Yes, partly.	Additional mitral valve intervention. MitraClip detachment/embolisation/ retrieval. Electrical device therapy. Other MACCE.	Kaplan-Meier analysis. Comparison with published literature.	Some complications specifically attributable to MitraClip. Risk-benefit ratio of MitraClip will require longer-term studies and/or modelling.
8) Are clinical outcomes with MitraClip associated with particular patient characteristics (clinical or demographic)?	Yes, partly.	Patient characteristics. Efficacy outcomes. Complication outcomes. Mortality.	Subgroup analysis. Bonferroni correction if hypotheses not pre-specified.	Limitations with patient enrolment (power), patient selection and confounding variables (generalisability issues).
9) What are the full procedural costs of using MitraClip to the NHS?	No.	In hospital resources including length of stay, investigations, theatre staff, procedure duration and type of anaesthetic.	Process costing with separate costs for each stage of the clinical pathway.	Procedural costs will be estimated by combining information from the registry and data from sites, collected using a pro forma.
10) What are the potential cost savings for the NHS arising from patients receiving MitraClip?	No.	As 9) plus efficacy post discharge, adverse events and mortality.	Mean and SD for each key event on pathway.	Responses to these questions will be informed by evidence from existing published economic studies. A *de novo* economic analysis, using linked national datasets, to compare annual costs per patient before the procedure and post- procedure is planned but timing depends on accessing the datasets.
11) Is MitraClip cost-effective from the perspective of the NHS?	No.	As 9) plus efficacy post discharge, adverse events and mortality.	Mean and SD for each parameter	

Figure 2. Relationship between NHS England registry clinical data and published evidence identified in the literature review (questions 1 to 8 [Q1 to Q8]).



Section 3: Results

3.1 PRIMARY DATA COLLECTION (CTE DATABASE)

3.1.1 Numbers of patients treated at each centre

A total of 272 MitraClip procedure records were extracted from the registry by NICOR on 13th November 2017. Seventy three did not meet the eligibility criteria, Appendix 1, 57 of which did *not* include eligible reasons for MitraClip treatment (multiple reasons permitted): 8 patient preference, 3 clinician preference, 28 other, and 18 not providing a reason for treatment. A total of 199 MitraClip procedures were eligible for analysis, which included 32 (16.1%) non-CtE commissioned procedures i.e. private procedure or those conducted by non-CtE commissioned centres.

Follow-up information for CtE-commissioned procedures was recorded in 98.7% of eligible MitraClip procedures at 6 weeks, 95.9% at 6 months, 117.7% at 1 year and 29.7% at 2 years, *Supplementary Material – Table 3*. The reason for a figure in excess of 100% follow up at 1 year related to the denominator used for this calculation. The EAC calculated the number of CtE-funded patients reaching 1 year since the date of their successful implant procedure and defined this as the number of patients eligible for follow-up at that time point. On enquiry, NICOR advised the EAC that the follow up pages are locked in the live registry, until the relevant time period has passed since the date of the procedure. However, the centre is then presented with a tab which reads "1st follow up" at 6 weeks post-procedure, "2nd follow up" for 6 months post-procedure, "3rd follow up" for 12 months post-procedure etc. For example, a centre could retrospectively enter 6 month follow up data from local patient notes in the "3rd follow up tab", meaning these entries would be attributed to a 1 year follow up visit, illustrating the potential for human error in this registry design.

3.1.2 Summary statistics of patient and procedural characteristics

The MitraClip registry enrolled 272 patients, of whom 199 were eligible for CtE data analyses (Appendix 1). The 199 patients included in the CtE analyses had functional (60%) or degenerative (40%) MR and a mean age of 76.2 years. Most patients were men (68.8%). Most of these patients were recruited electively (84.4%) with 13.6% admitted urgently and 2.0% undergoing the procedure as an emergency. Nearly all patients had moderate or severe MR (grade 3+ or 4+) that was symptomatic in 92% of cases (New York Heart Association [NYHA] class 3 or 4). The mean EuroSCORE II (risk of dying from cardiac surgery) was 6.4 (standard deviation 5.7). Complete patient demographics and procedural characteristics for the cohort are summarised in Appendix 2 and Appendix 3 respectively. No statistical differences were identified between the whole cohort and those with reported follow-up information for any of the tabulated variables.

3.1.3 Active surveillance (evaluation of coverage)

The data coverage and completeness results for CtE commissioned procedures only, for the 27 MitraClip MDS baseline fields and the 6 specified follow-up fields (to 24/10/2017) are reported in Table 6.

Table 6. Data completeness by CtE-funded provider.

CtE provider	Baseline MDS completeness	Coverage† & completeness‡ at 6 weeks FU	Coverage† & completeness‡ at 6 months FU	Coverage† & completeness‡ at 12 months FU	Coverage† & completeness‡ at 24 months FU
The University Hospital of South Manchester NHS Foundation Trust	97%	100% (42/42) coverage 91.7% FU data completeness	97.6% (40/41) coverage 87.5% FU data completeness	100% (35/35) coverage 61.9% FU data completeness	63.6% (7/11) coverage 54.2% FU data completeness
University Hospitals Bristol NHS Foundation Trust	93%	97.9% (47/48) coverage 79.8% FU data completeness	95.7% (45/47) coverage 61.9% FU data completeness	97.7% (43/44 coverage 32.6% FU data completeness	12.5% (1/8) coverage 78.6% FU data completeness
Royal Brompton and Harefield NHS Foundation Trust	94%	98.6% (72/73) coverage 91.2% FU data completeness	95.8% (68/71) coverage 86.5% FU data completeness	95.8% (68/71) coverage 59.3% FU data completeness	21.1% (4/19) coverage 73.8% FU data completeness
Total	**95%**	163/181 (90.1%) with device implanted, discharged alive and reaching 6 weeks since procedure date. 161/163 (98.8%) with some degree of FU data. **Completeness of FU MDS (versus expected) = 88.0%.**	159/163 (97.5%) with device implanted, still alive at 6 weeks FU and reaching 6 months since procedure date. 153/159 (96.2%) with some degree of FU data. **Completeness of FU MDS (versus expected) = 79.5%.**	153/159 (96.2%) with device implanted, still alive at 6 months FU and reaching 12 months since procedure date. 146/150 (97.3%) with some degree of FU data. **Completeness of FU MDS (versus expected) = 52.1%.**	147/153 (96.1%) with device implanted, still alive at 12 months FU and reaching 24 months since procedure date. 12/38 (31.6%) with some degree of FU data. **Completeness of FU MDS (versus expected) = 88.9%.**

FU Coverage† = Actual no. of MitraClip procedures with some degree of FU data entered / No. of MitraClip procedures eligible for FU for the stated period (%).
NB FU Coverage can only be calculated for cases with a procedure date entered. This is the case for 181/181 (100%) of CtE-funded MitraClip cases in the registry, to 24/10/2017.
FU Completeness‡ = Average completeness of the 6 specified MitraClip MDS-FU data fields (%).

3.1.4 Outcomes

a. Clinical

A total of 182 procedures (91.5%) recorded both admission and discharge dates, showing a median length of stay of 5 nights (inter-quartile range [IQR] 3.3 to 8.0 nights, range 0 to 46 nights). Most of the 199 eligible patients were recruited electively (84.4%) with 13.6% admitted urgently and 2.0% undergoing the procedure as an emergency. Device implantation was conducted in 187 (94.0%) of procedures; reasons for non-use of device included: 3 unable to clip valve at all, 3 procedures ended successfully, 2 ending before completion due to complication, 2 problem with left atrial access, 1 inadequate imaging and 1 inadequate device stability.

In-hospital major complications were reported in 16 patients (8.2%, multiple events permitted) including: 10 deaths, 4 AKI (stage 2/3), 4 requiring additional interventions (comprising 1 percutaneous retrieval of embolised device, 1 bailout/urgent percutaneous coronary intervention (PCI), 1 MV surgery before discharge and 1 conversion to open heart surgery before discharge), 3 major bleeds, 2 myocardial infarctions, 2 cardiogenic shock, 1 embolisation, 1 new neurological event, and 1 oesophageal damage.

In-hospital minor complications were reported in 15 patients (7.6%), including: 7 minor bleeds, 3 new moderate/severe mitral stenosis, 3 pericardial effusion/tamponade treated conservatively, 1 partial detachment, and 1 AKI (stage 1). Frequencies of in-hospital outcomes for all eligible MitraClip patients and post-discharge outcomes for all eligible MitraClip patients with a device implanted are described in Appendix 4. Procedural success (device implanted and no major complications) was achieved in 171 MitraClip procedures (85.9%).

No variables were significantly associated with device implantation, in-hospital major complication, or in-hospital minor complication at the Bonferroni adjusted alpha levels during exploratory univariate or multivariate analysis.

In the 182 procedures (91.5%) which recorded both admission and discharge dates, length of stay was significantly different between elective (median 5 nights, IQR 3 to 7 nights, range 0 to 37 nights) and urgent/emergency cases (24 nights, IQR 8 to 32 nights, range 0 to 46 nights), $p < 0.0001$. In-hospital and outcomes recorded after discharge are described separately for all elective (n = 168) and emergency/urgent (n = 31) cases in Appendix 5.

For those with a MitraClip device implanted (n = 187), follow-up was reported in 170 patients (90.9%). Major complications occurring post-MitraClip procedure discharge were recorded in 25 patients, including: 20 deaths, 4 additional interventions (including 2 surgical MV interventions, 1 percutaneous MV intervention, 1 coronary artery bypass graft (CABG) and 2 strokes. Twenty-two patients reported minor complications, including: 21 with new mitral stenosis and 1 with partial detachment.

Total crude incidence rates of adverse events are described in Appendix 6. A total of 30 deaths have been reported (15.1%). Cause of death was reported in 23 cases (76.7%), and included: 8 multi-organ failure, 1 ventricular fibrillation with severe ventricular impairment, 1 biventricular failure, 1 pulmonary oedema/cardiogenic shock, 1 oesophageal damage, 1 acute renal failure, 1 clip abandoned and patient palliated, 1 peri-prosthetic fracture of knee joint (died in theatre), 1 respiratory arrest, 1 lung cancer, 1 old age, 1 attributed to a

combination of acute kidney injury, heart failure and ischaemic heart disease and 4 not otherwise specified. Kaplan-Meier curves for time to death and additional MV intervention are shown in Appendix 7.

Severity of mitral regurgitation over time is described in Appendix 8. Patients in the CtE registry experienced immediate and dramatic improvements in MR grade, with the proportion of patients with moderate-severe or severe MR (≥3+) reduced from 99.5% to 6.7%, post-procedure. However, after 1 year, some deterioration in mitral valve function was observed, with 24.4% of patients reporting moderate-severe or severe MR.

Improvements in MR were matched by improvements in NYHA scores, with 92.4% of patients reporting a score of NYHA class III or IV at baseline, compared with 17.9% at 1 year. Change in NYHA dyspnoea score over time is described in *Supplementary Material – Table 7*.

b. Cost / resource

Three well-completed MitraClip CtE Excel® costing workbooks were received. These were synthesised, together with information from the LAAO and PFOC pathways and the final dataset from the MitraClip register, to create a list of the resources required at each stage of pathway. In November 2017 these were sent to the three Clinical Leads for review. Following subsequent changes in light of comments received, the NY EAC updated the template and included cost information. Unit costs were taken from published national datasets (primarily NHS Reference Costs [12] and PSSRU [13]). The unit price was provided by the manufacturer as 'commercial in confidence' (Personal communication, Dr Steven Fearn, Health Economics & Reimbursement Manager, Abbott; 4 October 2017) who also advised that manufacturers charge per procedure, not per device. This is a key assumption as the device is the highest cost in the pathway and the registry recorded that the mean number of clips opened was 1.9 per procedure.

The resultant estimated central cost and high and low cost scenarios for a MitraClip procedure conducted in NHS England are shown in Table 7.

Table 7. Central cost and range of cost for a MitraClip procedure.

Pathway stage	Central cost	Low cost	High cost
Pre-operative assessment	£790	£412	£998
Peri-operative procedure	£27,707	£26,681	£28,714
Post-operative management	£4,062	£1,697	£4,407
Total	**£32,560**	**£28,790**	**£34,119**

Table 8 analyses the estimated costs by component and stage for the central case. The device accounts for [redacted]% of the cost, with investigations forming the second largest cost component ([redacted]%), length of stay comprises 8%, staff comprise 5%, consumables and theatre use contribute [redacted]% each to the cost, with outpatient follow-up being 1%.

Table 8. Estimated costs by component by stage for central case.

	Pre-op	Peri-op	Post-op	Total	% of Total
Device		£[redacted]		£[redacted]	[redacted]%
Investigation	£634	£[redacted]	£1,106	£[redacted]	[redacted]%
Staff	£142	£1,590		£1,732	5%
Consumables	£14	£[redacted]		£[redacted]	[redacted]%
Length of stay			£2,765	£2,765	8%

Theatre		£[redacted]		£[redacted]	[redacted]%
Outpatient			£191	£191	1%
Total	**£790**	**£27,707**	**£4,062**	**£32,560**	**100%**

Data from the register show that elective patients have a shorter length of stay at 5.6 days compared with 20.5 days for patients admitted as urgent or emergencies; the mean for all patients was 7.8 days. Applying these lengths of stay gives a cost for an elective patient of £31,790, rising to £37,100 for a non-elective patient.

A full summary of all resources and unit costs is provided in Appendix 9. This also describes the assumptions underpinning the sensitivity analyses.

Hospital resource usage over time is described in *Supplementary Material – Table 9*.

c. Patient experience

Significant improvements in mobility, self-care, usual activities, pain/discomfort and anxiety/depression quality of life (EQ5D) components were observed at varying time points when compared to pre-procedure scores, *Supplementary Material – Table 8*.

Pre-procedure, EQ-5D values were available for 163 patients. At 6 weeks, 136 paired scores were available and these showed a mean gain in utility of 0.18, with 83.1% of patients reporting improved quality of life, 9% no change and 10.3% deterioration. At 6 months, paired data for 113 patients were available. These showed a similar marginal improvement in the utility score of 0.20, with 79.6% of patients reporting improved quality of life, 7.1% no change and 13.3% deterioration. The mean baseline value was 0.55 ± 0.23 (SD); however, the median value of 0.60 was adopted as a measure of central tendency because of the skewed distribution [14].

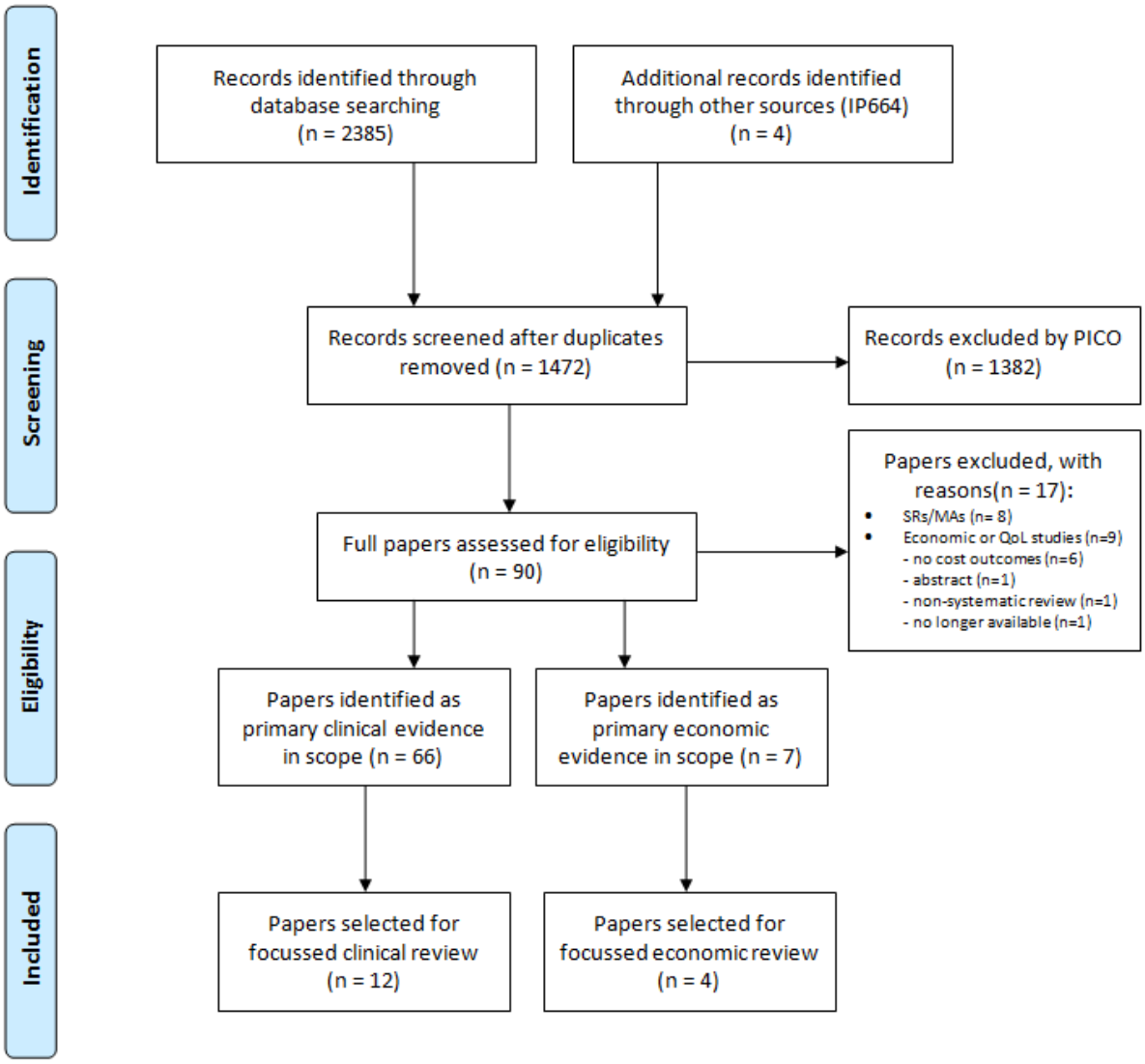
Full EQ-5D results are presented in *Supplementary Material - Table 8*.

3.2 SECONDARY DATA COLLECTION (LITERATURE REVIEW)

The CtE MitraClip literature search retrieved 1472 potentially relevant articles. Abstracts from these articles were independently assessed for relevance by two EAC researchers. Of these, 1382 were excluded immediately after screening as being not relevant to the scope. Of the remaining 90 records, 17 were excluded for various reasons, including 8 studies that were identified as systematic reviews and/or meta-analyses and 9 studies that reported on economic or QoL outcomes. These were used in the economic evaluation. The remaining 73 records were identified as in scope. Where possible, full papers were retrieved and from these, key studies were identified for full analysis by one researcher (IW for clinical evidence review and JC for economic evidence review). Sixteen papers (12 clinical and 4 economic) were selected for focussed review.

The process of sifting using PRISMA methodology (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [15] is illustrated in Figure 3.

Figure 3. PRISMA schematic of literature search for clinical evidence.



The CtE MitraClip literature search identified 66 publications in scope of the clinical evidence review. Of these, 12 publications pertaining to 8 primary studies were selected for focussed review. Selection was based on study quality, relevance (in particular concerning studies with a relevant comparator), and study size. As a large number of single-armed observational studies were identified, studies of this nature were only selected if they reported data on more than 500 patients.

One of the studies was a randomised controlled trial (RCT) [16]. This study was reported in several publications which included associated registries. This study was selected on the basis of study design and quality. Three of the studies were relatively small prospective observational studies. These studies were selected because they made matched comparisons with the most appropriate comparator, conservative medical treatment. The remaining four studies were observational registries or databases (n > 500).

Thirty-six primary studies identified by the searches were deemed to be technically in scope but were not selected for focussed review. These were primarily observational studies with more than 100 but less than 500 participants, which, due to the existence of several other much larger studies, was subjectively considered as a threshold for selection. In addition to the primary studies, 8 secondary studies (systematic reviews and/or meta-analyses) were

identified; 4 of which were selected for further consideration. The first sift also identified 16 economic or costing studies. Full papers were obtained for 15 of these studies, with 7 meeting the PICO criteria and 4 included in the focussed review.

The RCT identified was the EVEREST II RCT, which reported primary outcomes at 1 year [16] and further follow up at 3 and 5 years [17, 18]. The authors of this study had previously published the EVEREST I registry [19] (which was identified by the NICE IP664 overview [6]) and additionally the EVEREST HRS registry of high risk patients [20]. The EVEREST II RCT randomised relatively low risk patients to receive treatment with MitraClip (n = 184) or open surgery (n = 95). Two pre-specified primary outcomes concerning medium-term efficacy and short-term safety were employed as well as several secondary outcomes. The EAC critically appraised the RCT and considered it was at high risk of performance and detection bias due to the lack of blinding. However, the study was at low risk of selection bias and there was no evidence of selective reporting or attrition bias. In terms of external validity, the study lacked generalisability to the NHS because of the population enrolled, who were relatively well, and the comparator, which was open surgery.

Three comparative observational studies were identified that compared the use of MitraClip with conservative medical management. The prospective EVEREST II HRS study [20] enrolled patients with a high degree of surgical risk and compared them with historical controls. The prospective study by Giannini *et al.* (2016) [21] enrolled patients consecutively and assigned MitraClip to indicated patients and conventional medical management to patients not fulfilling the anatomical criteria; otherwise the groups were closely matched. Propensity matching was performed and the two cohorts (n = 60 each) were compared reporting clinical outcomes. The study by Velazquez *et al.* (2015) [22] identified high-risk patients from the EVEREST studies and propensity matched these with applicable patients receiving conservative management from a hospital database. This study only reported mortality at 1 year as an outcome.

Four large single-armed studies were identified. These were all large European registries and were the German TRAMI registry [23, 24], the ACCESS-EU registry [25], the Pilot European Sentinel Registry [26, 27] and the retrospective study by Rahhab *et al.* (2017) [28]. These studies reported real-life procedural and clinical data on MitraClip and presented subgroup analyses.

In addition to the primary studies, the EAC identified eight systematic reviews of relevance. Four of these studies were selected for further analysis on the basis of methodology, date of search, and included studies. Two of the reviews reported meta-analyses that compared MitraClip with surgical repair [29, 30]. One systematic review and meta-analysis provided a comparative analysis of the efficacy and safety of MitraClip in patients with degenerative and functional MR. The final systematic review focussed on the relative benefits of MitraClip in low and high risk MR populations [31].

The EVEREST II study was a non-inferiority RCT with 12 months follow up [16].The primary efficacy outcome (freedom from death, from surgery for mitral-valve dysfunction, and from grade 3+ or 4+ mitral regurgitation) was achieved in 55% of MitraClip patients compared with 73% in the control (mitral valve surgery) arm, which was statistically inferior (p = 0.007). This suggests that MitraClip is probably not a good option in patients who are well enough to receive open surgery. For patients who are not well enough to undergo open surgery, there is evidence from comparative observational studies that they may benefit from MitraClip, with lower mortality at up to 3 years, and lower rates of readmission to hospital. However,

due the non-experimental methodology employed, these benefits have not been shown definitively. The German TRAMI registry [23, 24], the ACCESS-EU registry [25], the Pilot European Sentinel Registry [26, 27] and the retrospective study by Rahhab *et al.* (2017) [28] reported high procedural success rates in excess of 90%. Longitudinal data reported a mortality rate of between 15 to 20% at 1 year.

Data reported from meta-analyses of studies identified by systematic reviews indicated that, compared with open surgery, there was a trend towards MitraClip having superior short-term mortality (≤ 30 days) and equivalent longer term mortality rates, but that MitraClip was inferior at reducing MR grade. One systematic review did not report any significant difference in outcomes between patients with degenerative or functional MR [32].

The findings from four economic studies (considered to be of medium validity) reported that, although MitraClip could save costs associated with hospital readmission due to congestive heart failure, these did not offset the procedural costs (most of which are associated with the device itself). However, there remain key uncertainties from the clinical evidence base concerning this patient group and the extent of disease progression, and the relationship of this with hospitalisations, life expectancy and patient symptoms. In particularly, there is a lack of evidence concerning the longer-term clinical outcomes in high surgical risk populations. These uncertainties will not be resolved until high-quality, comparative trials are published in this cohort. Newcastle and York EAC is aware that there are three on-going RCTs that may provide these data (see Section 3.3.2).

In conclusion, NY EAC found that there is now a substantial evidence base on the MitraClip system. However, despite this, there remain key uncertainties in the use of MitraClip in populations who are at high-risk of open surgery:

- Evidence from an RCT suggests that, in patients in whom it is a relatively safe option, open surgery is a better option than MitraClip.
- Limited observational evidence suggests that MitraClip may confer benefits in symptom reduction and life expectancy in patients unsuitable for open surgery. Mortality is about 10 to 25% in the first year following MitraClip in this group.
- The costs of MitraClip are likely to outweigh the costs associated with continued conservative medical management. However, because of a lack of direct comparative evidence, particularly concerning longer-term outcomes in a high-risk of surgery group, there is also considerable uncertainty about the cost-effectiveness of MitraClip. Further research is required to acquire clinical data to inform economic analysis that will reduce this uncertainty.

Further details are available in the standalone literature review document by Willits *et al.* (unpublished, November 2017) [8].

3.3 EMERGING NEW EVIDENCE

3.3.1 TVT registry study

The cut-off date for the EAC literature search was August 2017. Since this date, following completion of the RX085 literature review document [8], a new study on MitraClip has been published that has been brought to the EAC's attention. The EAC has briefly reviewed this study and has concluded that, had it been published in time for the literature review document, it would have been included for full review. Additionally, the EAC considers the

data reported by the study is of sufficient importance to be retrospectively included in this report. Consequently, although the study has not been fully appraised, the study is briefly described in this section, and results have been included to inform the NHS England questions (Section 3.4), where relevant.

The study by Sorajja *et al.* (2017, henceforth referred to as the TVT registry) was based on published data from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (STS/ACC TVT) registry [33]. Patients were eligible for inclusion if they had severe (grade 3 or 4) primary (degenerative) MR and were considered to be at prohibitive surgical risk, as measured by STS predictive risk of mortality criteria. The study reported data from all patients registered in the TVT registry who underwent commercially funded therapy with the MitraClip system between the initial U.S. Food and Drug Administration approval (October 2013) and September 2015. Data reported included patient characteristics, procedural outcomes, and clinical and resource use outcomes at up to 1 year follow up. Subgroup comparisons were made between functional and degenerative MR, degree of tricuspid regurgitation, and post-procedural MR grade.

The TVT registry enrolled 2952 patients, 85.9% of whom had a diagnosis of degenerative MR. The broad characteristics of the population are reported in Table 10. The registry reported an acute procedural success rate of 92% and that the large majority of patients were discharged with mild or absent MR (grade ≤2 of 95.5%). There was an overall 30 day mortality rate of 5.2%. The death rate at 1 year was 25.8% and the rate of re-hospitalisation due to heart failure was 20.2%; with repeat mitral valve procedures required in 6.2% of patients. Multivariate subgroup analysis indicated inferior outcomes (mortality and readmission to hospital) associated with functional MR compared with degenerative MR (see Question 8). Tricuspid regurgitation and persistence of MR at discharge were also reported as being associated with significantly increased risk of death and re-hospitalisation at 1 year follow up.

3.3.2 On-going randomised controlled trials

The EAC also identified protocols for four RCTs that are currently on-going [8]. These are summarised in Table 9. Upon completion and publication, these studies will address many of the uncertainties in the extant evidence base.

Table 9. Summary of on-going RCTs on MitraClip (identified from clinicaltrials.gov).

Study characteristics	Setting and Population	Intervention and Comparator	Key outcome(s)*	Comment
COAPT trial [34] Parallel open-label RCT Follow up to 24 months	United States Patients with MR symptomatic of HF Estimated enrolment: 610 subjects	I: MitraClip C: Non-surgical management based on standard hospital clinical practice	Mortality MACCE MR grade QoL Recurrent Heart Failure (HF) hospitalisation Safety endpoints	Started: August 2012 Status: recruiting Estimated primary completion date: September 2019* Sponsor: Abbott Vascular
ReShape-HF2 trial [35] Parallel open-label RCT Follow up 12 months	Europe (Denmark, Germany, Greece, Italy, Poland, Portugal, Spain) Patients with clinically significant functional MR (moderate to severe or severe MR) Estimated enrolment: 420 subjects	I: MitraClip C: Standard medical care	*Composite rate of recurrent heart failure hospitalisations and CV death* MR grade MYHA grade QoL	Started: May 2015 Status: recruiting Estimated primary completion date: July 2018** Sponsor: Institut fuer anwendungsorientierte Forschung und klinische Studien GmbH
MITRA-FR trial [36] Parallel open-label RCT Follow up 12 months	France Patients with severe secondary [functional] mitral regurgitation. Estimated enrolment: 288 subjects	I: MitraClip C: Optimal medical therapy	*All-cause mortality and unplanned hospitalisations for heart failure* MACCE Serious adverse events MR grade QoL	Started: August 2013 Status: unknown Estimated primary completion date: October 2016* Sponsor: Hospices Civils de Lyon
MATTERHORN trial [37] Parallel open-label RCT Follow up 12 months	Germany Patients with moderate-to-severe MR of primarily functional pathology and reduced left ventricular function considered to be at high surgical risk	I: MitraClip C: Mitral valve surgery	*Composite of death, rehospitalisation for heart failure, re-intervention (repeat operation or repeat intervention* Recurrence of grade 3 or 4 MR within 12 months NYHA class	Started: February 2015 Status: recruiting Estimated primary completion date: December 2019* Sponsor: Abbott Vascular

Study characteristics	Setting and Population	Intervention and Comparator	Key outcome(s)*	Comment
	Estimated enrolment: 288 subjects		Length of hospital stay	

Abbreviations: C – comparator; COAPT - Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation Trial; CV – cardiovascular; HF – heart failure; I – intervention; MACCE – Major Adverse Cardiac and Cerebrovascular events; MATTERHORN - Multicenter, Randomised, Controlled Study to Assess Mitral vAlve reconsTrucTion for advancEd Insufficiency of Functional or iscHemic ORigiN trial; MITRA-FR - Multicentre Randomised Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation trial; MR – mitral valve regurgitation; QoL – quality of life; ReShape HF2 - RandomisEd Study of tHe MitrACliP DEvice trial; RCT – randomised controlled trial.

* Primary outcome in italics.
** Final data collection date for primary outcome measure.

3.4 NHS ENGLAND QUESTIONS AND REQUESTS

The aims of the CtE registry were to provide data on the safety, efficacy and costs of MitraClip in the real-world NHS setting and specifically to answer 11 pragmatic questions concerning these issues. In this section, the findings from the CtE registry are used to answer these questions and are presented in the context of published studies in other populations. Table 10 summarises some key characteristics that illustrate the risk profile of patients undergoing MitraClip in the CtE programme, key clinical trials and large observational studies.

Qualitative analysis of the baseline characteristics of the studies highlights that the EVEREST II RCT (2011) [16] was conducted in a younger, healthier population (using surgical risk and NYHA grade as proxies for overall health) than the other studies, including the CtE registry. Patients enrolled into the EVEREST II study were therefore not representative of the patients in the selected observational studies or the CtE registry.

The CtE registry was conducted in a similar population to the observational studies. In general terms, the population of the observational studies was comprised predominantly of men in their mid to late 70s, with functional MR the most common diagnosis (with the notable exception of the large TVT registry [33]). Nearly all patients enrolled in MitraClip studies had moderate or severe MR at baseline, and this was reflected in the observational studies by moderate to severe symptoms of dyspnoea. Finally, the surgical risk reported in the CtE registry was consistent with those reported in other observational studies; that is, the surgery was not an appropriate option in most of these patients.

Table 10. Summary of patient characteristics in the CtE registry and published literature.

Study	Mean age ± SD (years)	Sex (% male)	Aetiology	MR grade (% ≥ 3+)	NYHA grade (% ≥ III)	Urgency	Surgical risk ± SD*
CtE registry	76.2 ±10.5	68.8	FMR: 60% DMR: 40%	100.0	92.4	Elective: 84.4% Urgent: 13.6% Emergency: 2.0%	Mean ES: 20.1 ± 15.6 Mean ES2: 6.4 ± 5.7
EVEREST II RCT** (2011) [16]	67.3 ± 12.8	62	FMR: 27% DMR: 77%	96	52	Elective: 100%	NR
EVEREST II HR study ***(2012) [20]	76.7 ± 9.8	62.8	FMR: 41.0% DMR: 59.0%	98.7	89.7	Elective: 100%	Mean STS: 14.2 ± 8.2
Giannini (2016) [21]	75 ± 8	67	FMR: 100%	95	75	Elective: 100%	Mean ES: 17 (IQR 11 to 28) Mean ES2: 6 (IQR 4 to 120
Velazquez (2015) [22]	75.7 ± 10.5	61.0	FMR: 70.1% DMR: 29.9%	100	84.9	Elective: 100%	NR
TRAMI registry (2012) [23]	Median 75 (IQR 70 to 80)	59	FMR: 67% DMR: 33%	100**	93	Elective: 91% Emergency: 9%	Median ES: 23 (IQR 12 to 38)
ACCESS-EU study (2013) [25]	73.7 ± 9.6	63.8	FMR: 69% DMR: 31%	100	84.9	NR	Mean ES: 23.0 ± 18.3
European Pilot Sentinel study (2014) [26]	73.7 ± 9.7	63.1	FMR: 72% DMT: 28%	93.3**	85.5	NR	Mean ES: 24.7 ± 16.7
Rahhab (2017) [28]	Median 76 (IQR 69 to 82)	59	FMR: 72% DMR: 17%	99	NR	NR	NR
TVT registry (2017) [33]	Median 82 (IQR 74 to 86)	55.8	FMR: 8.6% DMR: 85.9% Mixed: 8.9% Post-inflammatory: 0.7% Other/indeterminate: 2.8%	93.0	85.0	NR	Median STS for MV repair: 6.1 (IQR 3.7 to 9.9) Median STS for MV replacement: 9.2 (6.0 to 14.1)

Abbreviations: DMR – degenerative MR; ES – Logistic EuroSCORE; ES2 – Logistic EuroSCORE II; FMR – functional MR; IQR – inter-quartile range; MR – mitral valve regurgitation; MV – mitral valve; NR – not reported; SD – standard deviation; STS – Society of Thoracic Surgeons (score).

*

* EuroScore II is a risk-stratification model that estimates the mortality risk following cardiac surgery [38]. It has replaced the EuroSCORE and logistic EuroSCORE algorithms which overestimate the risk of death from cardiac surgery [39]. The STS calculator is a US algorithm that provides similar estimates of risk of surgical mortality [40].
** Data reported from MitraClip arm. No significant differences were reported between MitraClip and surgery arms.
*** MR graded as I (mild), II (moderate), and III (severe). Value refers to proportion of patients who were grade II or III.

3.4.1 Question One

> "Can UK clinical teams undertaking MitraClip reproduce the reduction in mitral regurgitation seen in the early clinical trials?"

The mechanism of action of percutaneous repair of the mitral valve using MitraClip, through which clinical and patient benefits are derived, is to reduce MR. The severity of MR has been measured in the registry by categorisation into MR grades (of none, 1+, 2+, 3+, or 4+) [41], which have been dichotomised into grades of ≤MR 2+ and ≥MR 3+, which broadly speaking demarcates patients with absent or mild MR from patients with moderate or severe MR. Summary data reporting MR grades of this nature has been used extensively in the published literature allowing for direct comparisons with other relevant studies (see EAC Literature Review for further detail [8]).

All except one of the patients recruited into the CtE registry were in the ≥MR 3+ category at baseline. This was in full concordance with the inclusion criteria which specified "Patients with severe grade 3 or 4 mitral regurgitation" [5]. Following the MitraClip procedure, there was an immediate clinical and statistically significant impact on MR, with 93% of patients being classified as ≤MR 2+ on discharge from hospital. This effect was only slightly diminished at later time points, with 76%, 81%, 76%, and 90% being classified as ≤MR 2+ at 6 week, 6 months, 12 months and 24 months follow up respectively.

The distribution of MR grades of patients in the registry is illustrated in Figure 4. Dichotomised MR grades are illustrated in Figure 5. As can be seen, there is an immediate and substantial improvement in MR grade associated with the MitraClip procedure. Figure 6 plots how the MR grade of individual patients changed over the course of follow up. Nearly all patients are observed to move down at least one MR grade at discharge. Subsequent to this, most patients remained at the lower grade of MR, but a minority also moved up one or more classes.

A comparison of dichotomised MR grades of patients in the CtE registry compared with data from published studies is reported in Table 11. Only one of these studies, the EVEREST II trial [17, 19], was an RCT with controlled comparative data. This study, performed in a population at lower surgical risk than those enrolled in the CtE registry, reported similar efficacy in terms of MR grade reduction for MitraClip and open surgery, and both were similar to the CtE registry. The observational studies that included a medical management arm did not report longitudinal MR data on the comparator [20-22]. However, single armed observational studies all reported similar MR outcomes to the CtE registry [23, 25-28]. That is, there was an immediate and significant reduction in MR grade at discharge (typically with over 90% of patients achieving mild or absent MR). At 12 months follow up, around 20% of patients in the observational studies had moderate or severe MR, indicating that most patients had sustained mitral valve integrity.

Figure 4. Proportional distribution of MR grades at baseline and following the MitraClip procedure observed in the CtE registry. Numbers above bars report raw data count.

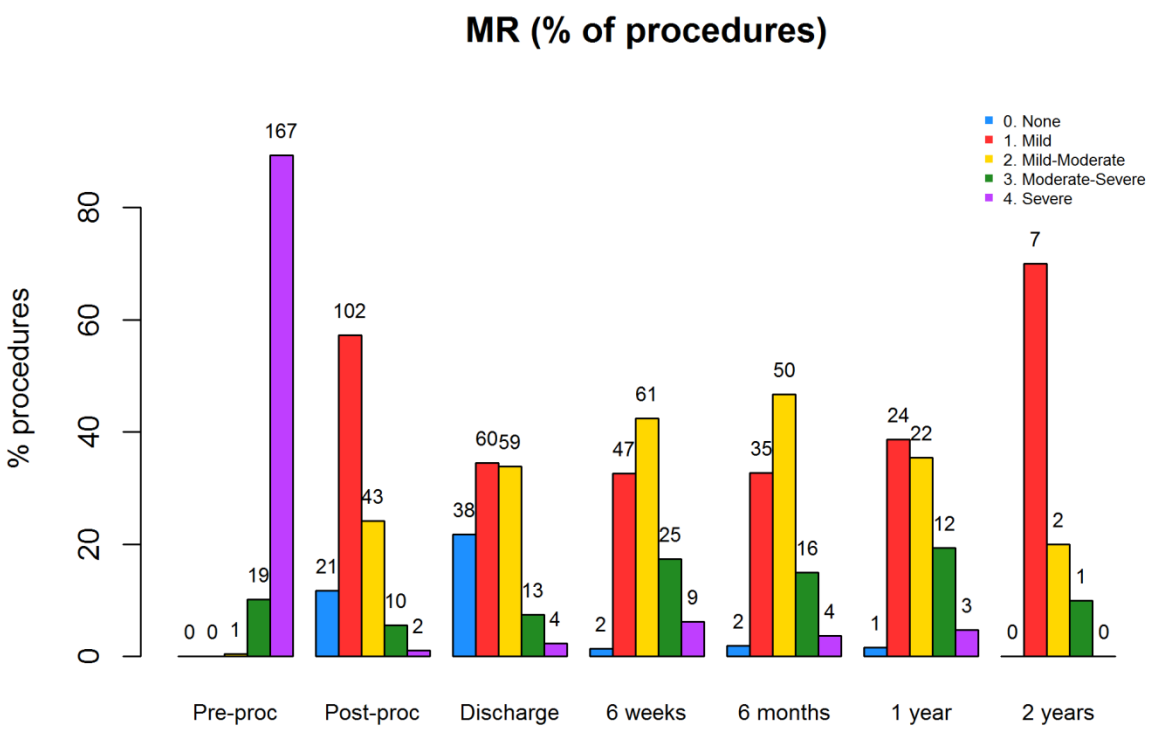


Figure 5. Dichotomised proportional MR grades at baseline and following the MitraClip procedure. Numbers above bars report raw data count.

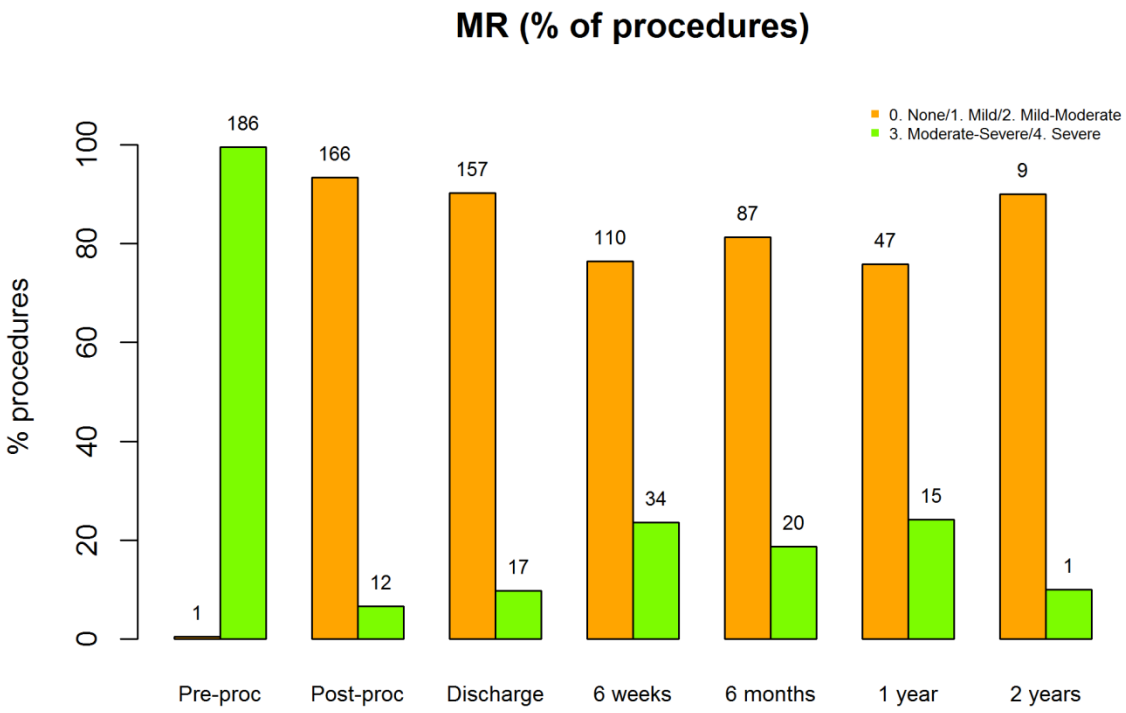


Figure 6. Graphical representation of individual patients moving between MR grades at follow up periods.

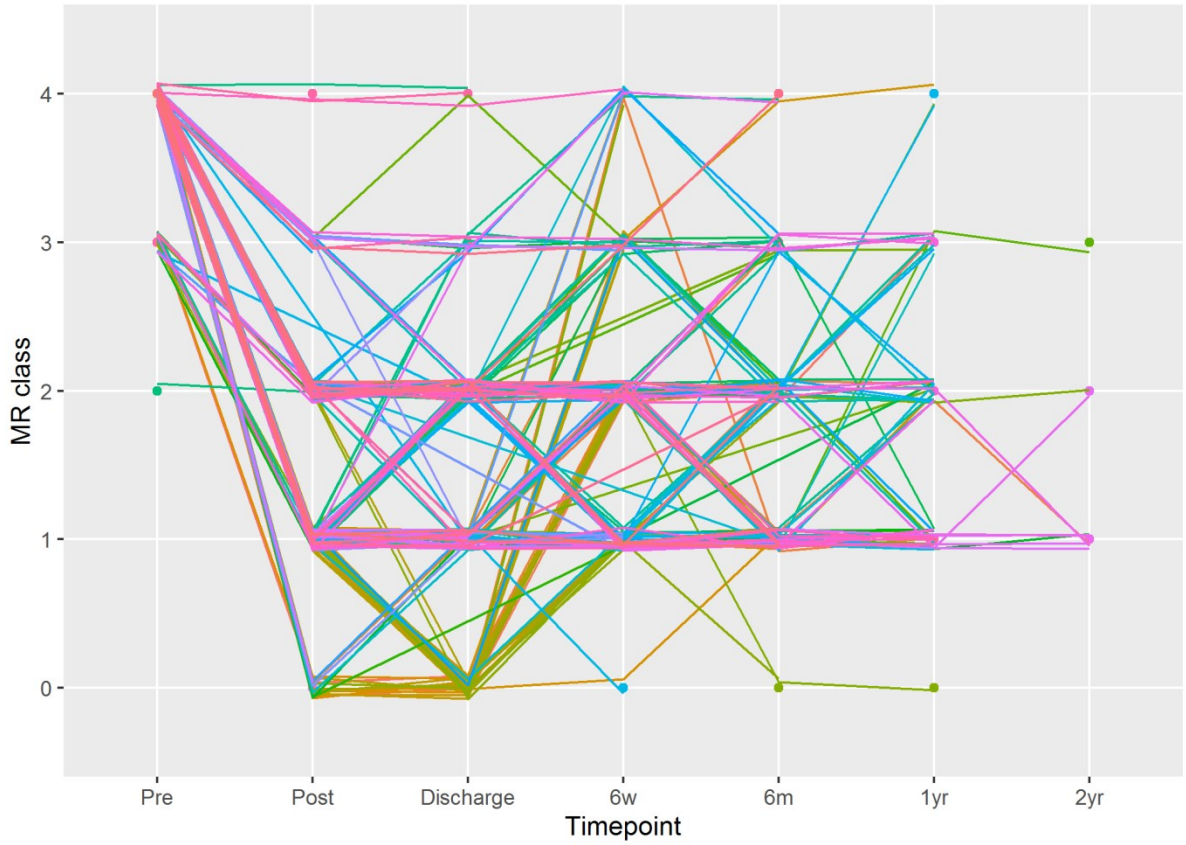


Table 11. Severity of MR reported in the CtE registry and selected published literature before and after the MitraClip procedure.

Study		Proportion of patients with significant MR (MR grade of 3+ or 4+ or equivalent) (%)				
		Baseline	**Post-procedure**	**6 weeks**	**6 months**	**12 months**
CtE registry		100	7	24	19	24
EVEREST II RCT [17, 19]*	MitraClip arm (n = 194)	96				21
	Surgery arm (n = 95)	93				20
EVEREST HR study [20]		98.7				22.2
TRAMI registry [23, 24]**		99	3			
ACCESS-EU study [25]		97.7	7.8			21.1
Pilot European Sentinel Registry [26, 27]**		99.3	27.2			
Netherlands study [28]		99	6			
TVT registry*** [33]		93.0	7.0			5.1

Abbreviations: MR – mitral valve regurgitation (grade).
* Five year follow up reported as significant MR of 12% in MitraClip arm and 2% in surgery arm.
** In these instances, MR grade was classified as none, mild, moderate or severe. The EAC classified moderate or severe MR as significant.
Shaded areas report absence of data reported.
*** The TVT registry was identified after the cut off dates for the literature search and has *not* been critically appraised (see Section 3.3.1).

Although the EVEREST II study reported that MitraClip was as effective as surgery at reducing MR, differences (in favour of surgery) were reported in some comparative observational studies. For instance, in the study by Alozie *et al.* (2017) [42], none of the surgically treated patients had residual post-operative MR (MR grade 2 or 3), compared with 23.8% of patients treated with MitraClip ($p < 0.001$). Similarly, the study by Taramasso *et al.* (2012) [43] reported freedom from MR grade ≥3+ at 1 year was 79.1 ± 8% (SD) for MitraClip, compared with 94 ± 2% for surgery ($p = 0.01$). The study by De Bonis (2016) [44] reported freedom from MR grade ≥3+ at 4 years follow up was 75 ± 7.6% (SD) in the MitraClip group, compared with 94 ± 3.3% in the surgical cohort ($p = 0.04$). This is discussed further in Question Five.

Evidence from systematic reviews reflects that of the constituent studies. For instance, the systematic review by Vakil *et al.* (2014) reported that the mean MR at baseline of the included studies was 3.56 (± 0.1 SD). Following the MitraClip procedure, this reduced to 1.8 (± 0.1) [31]. The systematic review by Takagi *et al.* (2017) [29] compared percutaneous repair with MitraClip with surgical repair. It reported freedom from recurrent MR (≥3+) at 1 year was 84.0% for MitraClip compared with 97.3% for surgery. At 3 years, the respective figures were 75.0% and 96.0%. This difference was significant, with a pooled hazard ratio (HR) for moderate or severe MR recurrence of 4.80 (95% confidence interval [CI] 2.58 to 8.93; $p = 0.00001$) for MitraClip.

Conclusion

Evidence reported from the CtE registry shows that percutaneous mitral valve leaflet repair using the MitraClip system results in immediate and dramatic improvements in mitral valve function, as measure by MR grade. Immediately following the procedure, the proportion of patients with moderate-severe or severe MR (≥3+) reduced from 99.5% to 6.7%. This large effect is consistent with all the studies identified in the literature. However, after 1 year there is evidence that there is some deterioration in mitral valve function, with 24.4% of patients reporting moderate-severe or severe MR. Again, this is fully consistent with the published literature.

The EAC did not identify any studies that compared MitraClip with optimal medical management and reported MR outcomes, but it would be assumed that no improvement is possible without physical intervention. The EVEREST II RCT reported that reduction in MR grade was similar for both MitraClip and surgery patients. However, this is contradicted by several observational studies which have reported surgery is superior to MitraClip in reducing MR, especially in the longer term.

3.4.2 Question Two

"Is reduction in mitral regurgitation mediated by MitraClip associated with improvements in quality of life?"

Quality of life (QoL) has been captured in the registry using the validated EQ-5D-5L (EuroQoL 5 dimension 5 levels) system [45] favoured by NICE. This reports data of personal wellbeing in five domains: mobility, self care, usual activities, pain and/or discomfort, and anxiety and/or depression. Five point scores from these domains are used to calculate a single utility score measuring from negative values (indicating wellbeing worse than death), zero (death), to one (perfect health). It also comprises a visual analogue scale (VAS) which can be used as a validatory measure. Quality of life data were captured at baseline, 6 weeks, 6 months, 12 months, and 24 months. Changes in QoL were analysed statistically using paired analysis, and summary data were also presented.

The New York Heart Association (NYHA) classification system is a measurement of dyspnoea (symptom of heart failure), which is closely related to physical QoL, and as such can be considered a surrogate outcome. An NYHA class I represents no limitation of physical activity, and class IV represents inability to conduct any activity without physical discomfort [46]. The NYHA scale is particularly useful as it is widely reported in studies of mitral valve dysfunction.

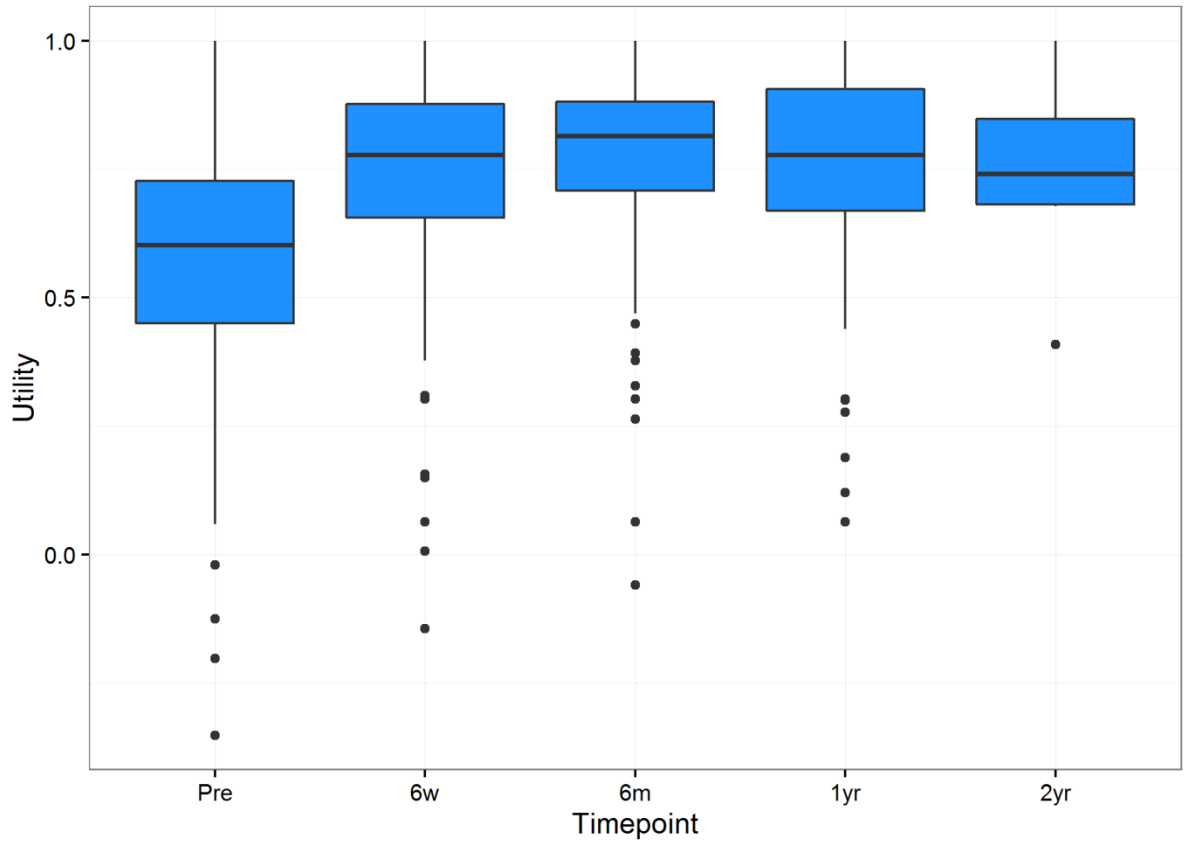
Quality of life

The utility scores for patients who received MitraClip in the registry and reported EQ-5D outcomes at baseline and follow up (paired data) is reported in Table 12, with additional detail in *Supplementary Material – Table 8*. It can be seen that there is a significant improvement observed in utility measured at 6 weeks, and this improvement is sustained throughout the course of the study (although significance is lost at 2 years because of limited follow up). This upward trend and plateau is illustrated in Figure 7.

Table 12. Utility scores of patients in CtE registry over time (paired data).

Time point	Paired (with baseline) median utility score (Q1, Q3 quartiles) Number of participants n	Paired (with baseline) mean utility score (SD)	Mean change in utility score (SD)	Statistical significance compared with baseline (paired test)
Baseline (reference)	0.6 (0.45, 0.72) 163	0.55 (0.23)	Reference	Reference
6 weeks	0.78 (0.66, 0.88) 136	0.75 (0.21)	0.18 (0.23)	$p < 0.0001$
6 months	0.81 (0.71, 0.88) 113	0.77 (0.20)	0.20 (0.24)	$p < 0.0001$
1 year	0.78 (0.67, 0.90) 48	0.73 (0.24)	0.15 (0.22)	$p < 0.0001$
2 years	0.74 (0.68, 0.85) 7	0.75 (0.18)	0.21 (0.24)	$p = 0.059$

Figure 7. Changes in utility scores over time (paired data) observed in the CtE registry.

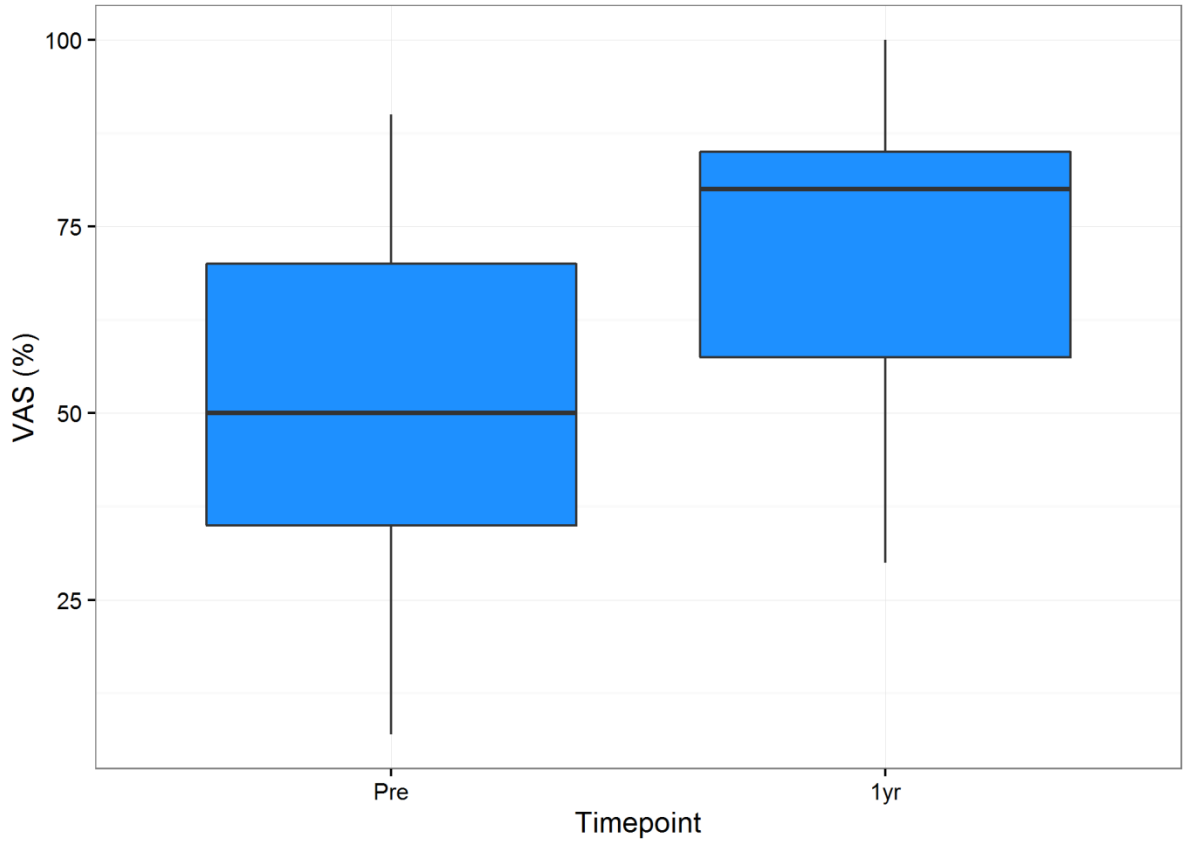


Analysis of individual EQ-5D domains showed trends for improvement at all time points, which were mostly significant up to 1 year (Table 13). Additionally, there were more patients reporting improved rather than deteriorating utility compared to baseline at all follow up time points. Improvements in utility were matched by changes in the visual analogue score (VAS) [47], which was measured as 50 mm (IQR 25 to 65 mm) at baseline, and 70 mm (50 to 80 mm), 70 mm (60 to 80 mm) and 80 mm (57.5 to 85 mm) at 6 weeks, 6 months and 12 months respectively. This change at 1 year is illustrated in Figure 8.

Table 13. Statistical improvement from baseline in each EQ-5D domain reported in the CtE registry.

Time point	Statistical improvement compared with baseline*				
	Mobility	**Self care**	**Usual activities**	**Pain/discomfort**	**Depression/anxiety**
6 weeks	Yes p < 0.0001	Yes p < 0.0001	Yes p < 0.0001	Yes p = 0.0001	Yes p < 0.0001
6 months	Yes p < 0.0001	Yes p = 0.0001	Yes p < 0.0001	Yes p < 0.0001	Yes p = 0.0001
12 months	Yes p = 0.016	No p = 0.391	Yes p = 0.0001	Yes p = 0.0009	Yes p = 0.0061
24 months	No p = 0.254	No p = 1.000	No p = 0.45	Yes p = 0.0128	No p = 1.000
* Paired comparison with baseline data using Fisher's Exact test.					

Figure 8. VAS at baseline and 1 year.



There are only limited data on QoL associated with MitraClip reported in the literature. The EVEREST II study [16] measured QoL using Short Form-36 (SF-36) at pre-procedure (baseline), 30 days, and 12 months. It reported significant positive changes in both mental and physical components associated with MitraClip at these time points. In contrast, there was a significant decrease in the physical component at 30 days associated with surgery. However, physical and mental components were significantly improved with surgery after 12 months. The generalisability of these results should be treated with caution because the EVEREST II trial recruited a healthier population than the CtE registry. However, similar improvements in QoL (SF-36) were observed in the EVEREST II HR observational study [20], and the TRAMI registry reported significant improvements in utility at 12 months as measured by EQ-5D-3L and VAS [23].

The systematic review by Vakil *et al.* (2014) [31] reported an increase in the physical component of QoL, as measured by SF-36, from 32.5 ± 1.3 standard error (SE) at baseline to 40.1 ± 2.0 at follow up (3 studies). For the mental component, the change was from 44.3 ± 0.5 to 52.2 ± 2.6. The significance of these changes was not stated.

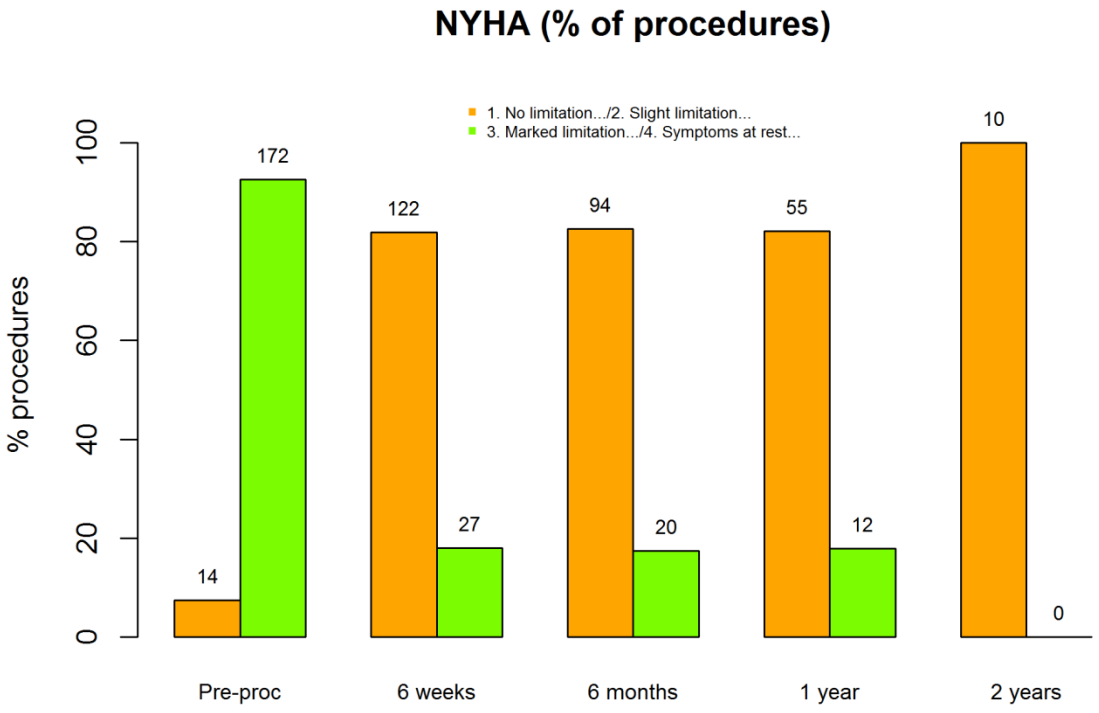
NYHA

NYHA dyspnoea scores observed by the CtE registry are reported in Table 14. Scores are dichotomised such that I and II represents patients with no or moderate limitations to activity, whereas III and IV represents marked or extreme limitation and discomfort. As can be seen, the MitraClip procedure is associated with an immediate improvement of NYHA scores at 6 weeks, which persists for up to 2 years and which is significant. This improvement is represented graphically in Figure 9.

Table 14. NYHA class at baseline and follow up reported in the CtE registry.

Time point	NYHA class I or II % (frequency, n)	NYHA class III or IV % (frequency, n)	Statistical significance compared with baseline*
Pre-procedure (baseline)	7.5 (14)	92.4 (172)	N/A
6 weeks	81.9 (122)	18.1 (27)	p < 0.0001
6 months	82.5 (94)	17.5 (20)	p < 0.0001
1 year	82.1 (55)	17.9 (12)	p < 0.0001
2 years	100 (10)	0 (0)	p < 0.0001
* Fisher's Exact test (paired data).			

Figure 9. NYHA class at baseline and follow up reported in the CtE registry. Numbers above bars report raw data count.



The CtE results for improvements in NYHA class are consistent with those seen in the published literature, as reported by Table 15. At 12 months, all the studies that included NYHA class as an outcome reported statistically significant results compared with baseline. Similar results were observed in other retrospective [48-50] and prospective [51-55] observational studies.

Table 15. Comparison of CtE registry NYHA data with published literature.

Study		Proportion of patients with NYHA class III/IV at baseline (%)	Proportion of patients with NYHA class III/IV at 12 months follow up (%)	Absolute change from baseline (%)
CtE registry		92.4	17.9	74.5
EVEREST II [19]	MitraClip arm	52	2	50
	Surgery arm	47	13	34
EVEREST HR study [20]		74.1	25.9	48.2
TRAMI study [23]		93	37	56
ACCESS-EU study [25]		84.9	28.6	56.3
European Sentinel study [26]		84.1	25.8	58.3

Conclusion

The CtE registry reported significant improvements in QoL, as measured by utility and VAS, at all follow up time points compared with baseline. Baseline EQ-5D index scores were similar to those reported for 75 year old people with heart failure in the literature [56]. There were statistically significant improvements in all domains of EQ-5D at 6 months. These results were consistent with results reported in the EVEREST II RCT [57] and two observational studies [20, 23] which measured QoL at baseline and 12 months. The use of MitraClip was also associated with an immediate and sustained (up to 2 years) improvement in NYHA class, with the large majority of patients experiencing resolution from moderate or severe dyspnoea to mild or absent dyspnoea. Similar improvements in NYHA class were also widely demonstrated in the published literature.

3.4.3 Question Three

"Does MitraClip improve survival rates?"

The CtE registry was unable to directly answer this question because it did not have a comparator group (of patients who did not receive MitraClip). The mean age of patients in the CtE registry was 76.2 years (± 10.5 SD). The age-specific mortality rate of people aged 75 to 79 years of age is 3.4% [58]; this value can be considered as a "background" annualised incidence of death in the general population; however it is not representative of the population receiving MitraClip in the registry, who were generally in much poorer health (as indicated by their high EuroSCORE values, see Section 3.1.2). However, indirect comparisons with limited published data have been made (see below).

Ten patients died in-hospital; these deaths can be considered to be directly attributable to the procedure (see Section 3.1.4 for individual recorded causes of death). This resulted in an in-hospital death rate of 5.0% (95% CI 2.4 to 9.0%). The death rate at 30 days (12 individuals) was slightly higher at 6.0% (95% CI 3.2 to 10.3%). A further 20 patients were recorded as dying during follow up of up to 2 years, giving an overall death rate of 15.1% (95% CI 10.4 to 20.8%). The death rate at 1 year was 11.6% (95% CI 7.5% to 16.8%). However, the annualised death rate using time to event analysis, derived from a total of 111.2 recorded person years (PY), was 27.0 (95% CI 18.2 to 38.5%) per 100 PY. This ostensibly higher rate was likely due to early deaths associated with the procedure and censoring of patients at later time points. Kaplan-Meier analysis of this data is reported in Appendix 7.

The rate of death reported in the registry is compared with those in the published literature in Table 16. Four of the studies reported comparative data. The EVEREST II study was an RCT which compared MitraClip with surgery [16]. However, participants in this trial were significantly healthier than those enrolled into the CtE registry, which were patients "deemed by an MDT to be at too high risk or at high risk for conventional mitral valve surgery" [5]. The three observational studies used optimal medical management as the comparator. These comparator groups were derived from retrospective [20, 22] or prospective [21] cohorts and were subject to considerable confounding and potential for bias. The remaining studies were single armed observation studies which enrolled similar populations to that of the CtE registry and thus provide a relevant comparison of clinical performance.

The rate of in-hospital death, or death within 30 days, was 6% in the CtE registry, which is broadly comparable with results reported for MitraClip in the observational studies, which ranged from 0% to 7.7%. Longer-term follow up mortality data was most comprehensively reported at 12 months. The 1 year rate of death of 11% in the CtE registry was within the expected range as reported in published studies, which were between 6% and 24.6%. The 1 year mortality rate was significantly lower in the MitraClip cohorts than medical management cohorts in the studies where it was reported. In the study by Giannini *et al*., which prospectively matched patients undergoing medical management, 10.3% died after 1 year in the MitraClip cohort compared with 35.7% in the medical management cohort [21]. This study also reported a mortality rate of 38.6 % and 65.1% at 3 years for MitraClip and medical management respectively (HR 2.31 [95% CI 1.30 to 4.09, p = 0.007]).

For comparison, the EAC did not identify any epidemiological studies that reported on patients closely equivalent to those enrolled in the CtE registry. However, a meta-analysis of individual data of UK patients with heart failure (n = 39,372) reported a death rate of 40.2% after a median follow up of 2.5 years [59].

Table 16. Comparison of mortality data reported by the CtE registry and published literature.

Study			Mortality rate (%)				Comment
			30 days (unless otherwise stated)	1 year	2 years	Longer follow up	
CtE registry			6.0	11.6	15.1		Annualised mortality rate: 27.0 (95% CI 18.2 to 38.5) per 100 PY
Comparative studies	EVEREST II RCT [16, 17]	MC arm	1	6	11	21 (5 years)	No significant difference at 1 year (p=1.00)
		Surgery arm	2	6	11	27 (5 years)	
	EVEREST II HR study [20]	MC cohort (prospective)	7.7	24.6			MC associated with significantly reduced mortality at 1 year (p=0.047)
		MM/surgery cohort (retrospective)		44.7			
	Giannini (2016) [21]	MC cohort	0.0	10.3	28.8	38.6 (3 years)	HR (MM vs. MC at 3 years): 2.31 (95% CI 1.30 to 4.09, p=0.007)
		MM cohort	1.7	35.7	48.3	65.1 (3 years)	
	Velazquez (2015) [22]	MC cohort	4.2	22.4			Adjusted HR (MC vs. MM at 1 year) 0.66 (95% CI 0.45 to 0.99; p=0.043)
		MM cohort (historical)	7.2	32.0			
Single armed studies	TRAMI registry [23, 24]		2.0 (in-hospital) 4.5 (30 days)	20.3			
	ACCESS EU study [25]		3.4	17.3			
	Pilot European Sentinel Registry [26, 27]		2.9 (procedural)	15.3			
	TVT registry [33]*		5.2	25.8			

Abbreviations: CI – confidence intervals; HR – hazard ratio; MC – MitraClip; MM – medical management; PY – person years.
Shaded areas indicate data not available.
* The TVT registry was identified after the cut off dates for the literature search and has not been critically appraised (see section 3.3.1).

The EVEREST II RCT did not report significant differences in overall mortality rate between MitraClip and surgery [16]. One observational study that compared these treatment modalities found that surgery was associated with an increased risk of death at 30 days, but over time this changed, such that at 1 year the risk of death was higher in the MitraClip cohort. Longer-term data from the study by De Bonis *et al.* (2016) [60] found no significant difference in mortality rates between MitraClip and surgery at 4 years, with a survival rate of 77% ± 5.6% for surgery compared with 74% ± 5.1% for MitraClip (p = 0.2).

Regarding synthesised data, the systematic review by Takagi *et al.* (2017) compared mortality rates in patients treated with MitraClip with open surgery [29]. The authors reported that MitraClip was associated with a significantly lower short-term (≤ 30 days) mortality rate (1.5% vs. 3.1%, relative risk [RR] 0.54 [95% CI 0.27 to 1.08, p = 0.08]). However, there was no significant difference in survival rate over the longer term (> 6 months), with 91.5% of MitraClip patients surviving compared with 92.7% of surgery patients, giving a reported HR of 1.17 (95% CI 0.77 to 1.77, p = 0.46). The systematic review by Philips *et al.* (2014) similarly reported an increased early death rate associated with surgery, with 3% (95% CI 3 to 4%) of deaths occurring at ≤ 30 days in the MitraClip cohorts, compared with 16% (95% CI 13 to 20%) in the surgery cohort. This study reported that the 1 year mortality rate associated with MitraClip was 13.0 % (95% CI 9 to 18.3%). Synthesised data from the study by Vakil *et al.* (2014) [31] reported a procedural death rate of 0.1%, a 30-day death rate of 4.2%, and a longer-term death rate (mean 310 days follow up) of 15.8%.

Conclusion

The CtE registry reported an in-hospital mortality rate of 5.0% (95% CI 2.4% to 9.0%) and a 1 year mortality rate of 11.6% (95% CI 7.5% to 16.8%). These data appear consistent with results from observational studies performed in patients with similar characteristics. However, there is a lack of published evidence comparing this mortality rate with optimal medical management. The EAC identified three observational studies that included optimal medical management as a historic or matched control which all indicated MitraClip reduces mortality in those patients *who survive the procedure*. However, interpretation of these studies is limited by bias and confounding. Studies that have compared MitraClip with surgery, including the EVEREST II RCT [16], have indicated that MitraClip is a safer procedure in the short-term, with fewer death-related procedural complications, but the evidence that either MitraClip or surgery is superior at reducing longer-term mortality is equivocal. It is likely the reason for this uncertainty is because adequately powered studies of sufficient methodological rigour have not been performed; that is, current research is prone to type II error.

The EAC notes that the company that manufactures MitraClip have made the following statement (EAC italics) [61]:

> "The major clinical benefits of MitraClip are reduction of MR to ≤2+ resulting in reduced hospitalisations, improved quality of life, reverse LV remodeling and symptomatic relief in patients who have no other therapeutic option. *No mortality benefit following MitraClip therapy has been demonstrated*".

The EAC would therefore conclude that, at present, there is an absence of good evidence that supports the hypothesis that MitraClip reduces patient mortality rates compared with alternative management strategies.

3.4.4 Question Four

"Does MitraClip reduce the frequency of subsequent hospital admissions?"

This question cannot be adequately answered by the CtE registry alone as there are no comparator data on patients receiving optimal medical management. Additionally, although readmission to hospital was a (non-required) field, data reported from this is unlikely to be reliable, because patients being readmitted would not have their data routinely entered into the registry.

Surgery for mitral valve dysfunction was a component of the primary composite outcome of the EVEREST II RCT [16]. The authors reported 20% of the MitraClip patients required repeat surgery after 12 months, compared with 2% in the surgery arm ($p < 0.001$). Thus, one fifth of patients were effectively crossed over to the other arm of the trial and reported as treatment failures; this is the principal reason that MitraClip was found to be inferior compared with surgery in the primary outcome. This effect persisted at 5 years follow up, with 28% of MitraClip patients requiring surgical intervention, compared with 9% of patients initially requiring surgery ($p = 0.003$). However, in patients who were event-free at 12 months, there was no significant difference (6% in both arms, $p = 0.99$). It should be noted however that repeat (open) surgery would not be an option for most of the population enrolled into the CtE registry.

One prospective comparative observational study reported data on readmission to hospital due to cardiac disease in patients receiving MitraClip or optimal medical management [21]. The authors reported in the MitraClip cohort that the rate of freedom from readmission for cardiac disease was 98.2% at 30 days, 76.5% at 1 year, 71.5% at 2 years, and 57.2% at 3 years. This compared with 96.4%, 66.9%, 48.2%, and 36.5% for time points at 30 days and 1, 2, or 3 years respectively for the medical management cohort. This difference was significant in favour of MitraClip, with a HR of 1.86 (95% CI 1.05 to 3.29, Log-rank test $p = 0.04$).

Three single armed studies in high-risk patients were identified in the literature that reported outcomes relating to readmission. The TRAMI registry [23, 24] reported a high rehospitalisation rate of 64.3% at 12 months follow up, with 14.1% of the registry cohort being readmitted for reasons related to cardiac decompensation, 17.8% for other cardiac reasons, and the remaining patients (25.8%) having non-cardiac reasons for readmission. The Pilot European Sentinel Registry reported a readmission rate of 22.8% at 12 months follow up [62]. In contrast, the EVEREST II HR study reported that no patients required readmission for "reoperation for failed MV surgical repair or replacement" or "urgent or emergent cardiovascular surgery for adverse event" at 30 days or 12 months.

The TVT registry, which was published after the EAC literature review was completed, reported data on readmission to hospital for heart failure in a cohort of 2,952 patients with mainly degenerative MR. The overall incidence of readmission for heart failure at 1 year was 20.5%. The rate of rehospitalisation with heart failure was significantly associated with MR of functional aetiology ($p = 0.008$).

Hospital readmission data are summarised in Table 17.

Table 17. Proportion of patients requiring re-intervention or re-admission following MitraClip procedure.

Study		Readmission (or proxy) rate (%)		Definition/comment
		Early	12 months	
CtE registry		10.4 (between discharge and 6 weeks)	9.3 (in addition to 6 week data)	Data considered unlikely to be reliable.
EVEREST II RCT (2011) [16]	MC	2 (≤ 30 days)	20	"Early" data is "Reoperation for failed surgical repair or replacement" or "Urgent or emergency cardiovascular surgery for adverse event". 12 month data is "Surgery for mitral-valve dysfunction: first mitral-valve surgery in the MC group and the rate of reoperation for mitral-valve dysfunction in the surgery group".
	Surgery	4 (≤ 30 days)	2	
Giannini (2016) [21]	MC	1.8 (≤ 30 days)	23.5	Readmission to hospital for cardiac indication.
	MM	3.6 (≤ 30 days)	33.1	
TRAMI registry [23, 24]		3.5 (peri-procedural)	64.3	"Early" data is procedural indicating "surgery for failed percutaneous intervention".
Pilot European Sentinel Registry [62]		0.7 (peri-procedural)	22.8	"Early" data reported as "Vascular complication requiring intervention".
EVEREST II HR study [20]		0	0	
TVT registry [33]		6.2	20.5	"Early" data reported as repeat transcatheter mitral valve repair.
Abbreviations: MC – MitraClip; MM – medical management.				

Conclusion

There is no reliable evidence from the CtE registry concerning the relative rate of readmission in patients following the MitraClip procedure. Evidence from the EVEREST II RCT [16] suggests that about one fifth of patients require open surgery following the MitraClip procedure, with the majority happening in the first year. However, this study was conducted in a population well enough to tolerate surgery. Evidence from observational studies indicated that the rate of readmission for MitraClip patients is high in the first year, ranging from approximately 20 to 60%.

It is hoped that this question will be fully answered through linkage with Hospital Episode Statistics (HES) data in future.

3.4.5 Question Five

> "Are the early benefits in reduction in mitral regurgitation maintained in the medium-term? Is there a need for repeat treatment over time (either by a repeat percutaneous procedure or surgery)?"

The efficacy of MitraClip in reducing MR is discussed in Question One. The benefits of this reduction, in terms of improvements to QoL and reducing symptomatic dyspnoea, are discussed in Question Two. Reductions in MR grade and related health benefits were sustained for the duration of the CtE registry (up to 2 years).

The CtE registry recorded that four people required an additional intervention (three having a surgical intervention and one having a repeat percutaneous intervention to retrieve an embolised device). This is probably an underestimate because of incomplete reporting (see Question Four).

The EVEREST II RCT follow up at 3 years [18] and 5 years [17] reported that reduction in MR grade was sustained in the longer-term. At 5 years, 87.7% of patients had ≤MR 2+; this compared with 98.2% of patients who had surgery (p = 0.02). However patients enrolled into the EVEREST II RCT were not representative of those in the CtE registry.

An observational study, which compared treatment using MitraClip with surgery reported contradictory evidence to the EVEREST II RCT. The study by De Bonis *et al.* (2016) [70] was a retrospective review of MitraClip patients who had had an optimal procedural outcome (i.e. successful MitraClip procedure with MR reduction and without significant complications, n = 85), which was compared to a cohort (n = 58) who had undergone surgical repair. Both groups were similar at baseline. The authors reported that, although freedom from cardiac death was not statistically significant at 4 years follow up, the initial results of MitraClip did not remain stable, with evidence of deteriorating MR over time. Freedom from MR grade ≥3+ at 4 years was 75% ± 7.6% (SD) in the MitraClip group and 94% ± 3.3% in the surgical cohort (p = 0.04). Freedom from MR grade ≥2+ at 4 years was 37% ± 7.2% compared with 82% ± 5.2% for MitraClip and surgery respectively (p = 0.0001). The authors concluded that the results did not confirm previous observations from the Everest II RCT that reported sustained results for MitraClip at 4 years.

Surgery has consistently been reported as resulting in superior MR outcomes when compared with MitraClip in a number of observational studies [43, 60, 63-65]. Data from a systematic review by Takagi *et al.* (2017) [29] reported rates of freedom from ≥MR3+ was 75% for MitraClip compared with 96% for surgery after 3 years. A pooled analysis indicated significantly higher incidence of recurrent MR in patients receiving MitraClip compared with surgical repair, with a pooled HR/OR of 4.80 (95% CI, 2.58 to 8.93; p = 0.00001). This suggests that for people who can tolerate it, surgery is the better option to achieve a sustained reduction in MR. The EAC did not identify any studies that reported MR outcomes that compared MitraClip with conservative medical management.

Conclusion

The benefits of MitraClip were sustained for the follow up duration of the CtE registry. There is conflicting evidence from the literature about the longer-term reduction in MR associated with MitraClip compared with surgery, but most observational evidence suggests that surgery is a better long-term option.

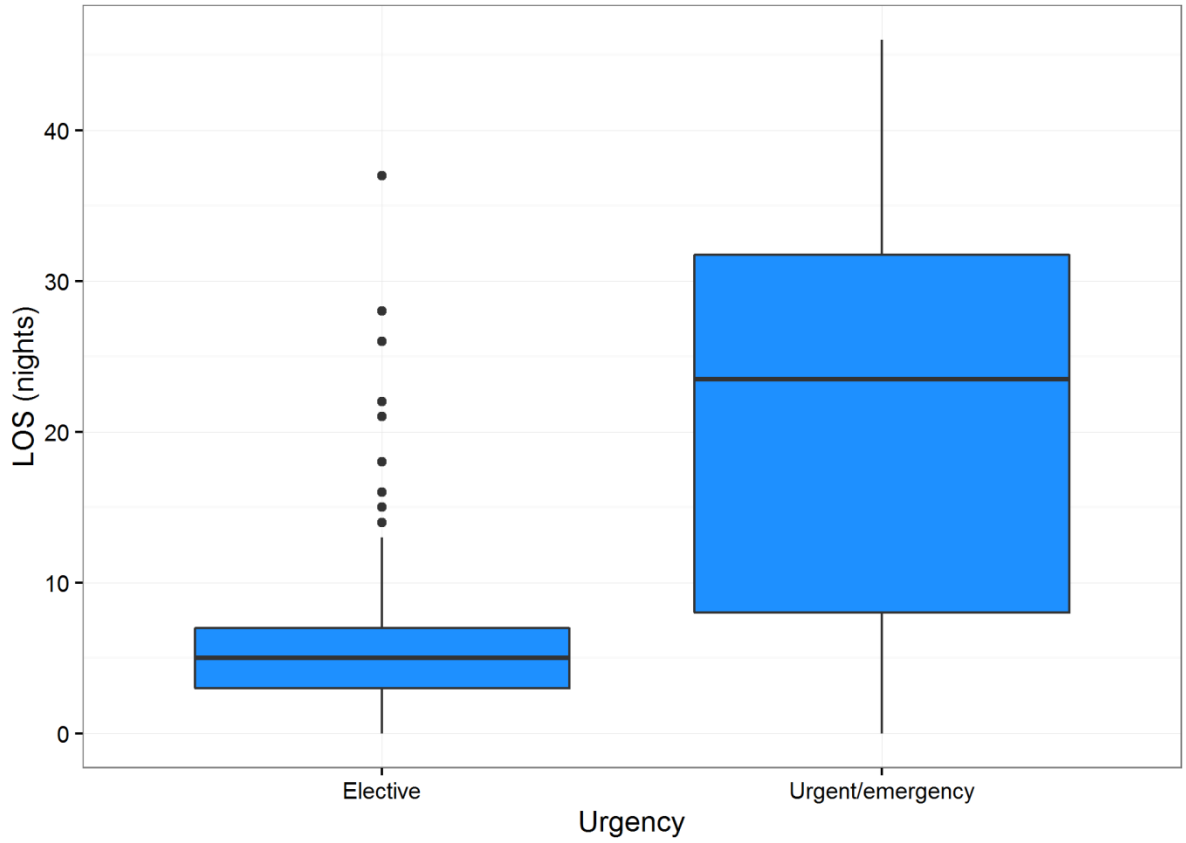
3.4.6 Question Six

> "What proportion of patients referred to a specialist MitraClip service as defined in the CtE documents were assessed by the MDT as suitable for the intervention? What proportion of the patients considered suitable for the procedures received it and what proportion of them benefitted (refer also to Question 5)?"

The CtE registry cannot directly answer this question. Centres did not use the registry to capture all cases presented to the MDT meeting; that is, patients not selected for the procedure were not subsequently enrolled into the registry; therefore this data cannot be used to reliably answer the question. The patient flow of patients following the MDT meeting is reported in Appendix 1. Of the 272 patients indicated for treatment with MitraClip, a total of 69 were excluded from the registry on grounds of non-elligibility. A further 4 patients were excluded because the procedure was not conducted within the timeframes or because procedure dates were contradictory to the discharge dates.

The registry reported that 15.6% of cases were urgent or emergency procedures, and thus would have bypassed *elective* MDT consultation. Patients who underwent the procedure urgently or as an emergency had a significantly different length of stay compared with elective patients, as illustrated in Figure 10, which will have an important impact on NHS resources. Differences in outcomes between these groups are reported in Question Eight.

Figure 10. Average length of stay by urgency.



The eligibility criteria for percutaneous leaflet repair using MitraClip is clearly stated by NHS England, including anatomic measurements [5]. However, it is unknown what proportion of potentially eligible patients fulfil these criteria. One cohort study consecutively recruited 160 patients with severe functional MR. Patients were assessed for eligibility for MitraClip based on anatomical suitability, with those who were judged unsuitable, or who withheld consent,

receiving optimal medical management [21]. Ninety (56%) of the patients received optimal medical management. This suggests about half of patients with severe functional MR unable to tolerate surgery may be suitable for the MitraClip procedure.

Conclusion

The registry cannot be used to answer this question. Extrapolated data from a prospective cohort study suggests around half of elective patients may be suitable candidates for MitraClip treatment. However, there remains considerable uncertainty regarding the prevalence of the indicated population.

3.4.7 Question Seven

"What are the short and medium term risk of complications from MitraClip use?

Answers to Questions 7 and 8 will be considered together by the NICE Interventional Procedures Advisory Committee when NICE updates the IP guidance on this procedure."

To answer this question, the EAC has defined "short term" as peri-procedural or in-hospital (or ≤ 30 days for some studies in the literature). "Medium term" refers to follow up out of hospital (up to 2 years). Complications were classified as being major, which would have a significant impact on the patient's wellbeing, or minor, which generally were transient and non-serious in nature.

The CtE registry reported that there was successful deployment of at least one clip in 94% of patients. The procedural success rate, defined as successful device deployment with no major complications, was 86%. This was somewhat lower (worse) than most values reported in the literature. However, a direct comparison with the literature is not possible due to the heterogeneous definitions of procedural success used in the studies. A comparison of procedural success rates is reported in Table 18.

Table 18. Procedural success in CtE registry compared with values reported in published studies.

Study	Procedural success rate (%)	Definition/comment
CtE registry	94	Successful deployment of at least one clip
	85.9 (95% CI 80.3 to 90.4)	Device implanted and no major complications
EVEREST II study [16]	100	Implied from 0% re-operation/repair rate following procedure
EVEREST II HR study [20]	96.0	Successful clip deployment
	79.5	Successful deployment with MR reduction ≤1 class
Giannini (2016) [21]	98	"Acute procedural success" (not further defined)
TRAMI registry (2012) [23]	97.0	Successful implant and MR ≤2+ achieved
ACCESS-EU study (2013) [25]	99.6	Successful implantation
Pilot European Sentinel study (2014) [26]	95.4	"Acute procedural success" (not further defined, but implied that procedure must reduce MR by ≤1 class)
Rahab (2017) [28]	95	Successful deployment of the device with absence of procedural mortality
	91	Placement of the device and MR ≥1 reduction to an absolute level of moderate MR
TVT registry [33]	91.8	Successful deployment with reduction to moderate or less MR, in the absence of cardiac surgery or in-hospital mortality
Abbreviations: MR – mitral valve regurgitation (grade)		

Sixteen major in-hospital complications were reported in the CtE registry, with ten of these being deaths. There was one recorded event of device embolisation requiring percutaneous retrieval, three additional surgeries, and two myocardial infarctions. There were 25 additional events occurring after discharge from hospital, including twenty additional deaths. Major and minor complications are listed in Appendix 4. The in-hospital major complication rate was 8.2% (95% CI 4.7 to 12.9%) and the major complication rate after discharge was 14.7% (95% CI 9.7 to 20.9%). The respective overall in-hospital rates (major and minor combined) were 15.2% (95% CI 10.5 to 20.9), compared with 25.9% (95%CI 19.5 to 33.1%) following discharge.

Major in-hospital complications are compared with values published in the literature in Table 19. Published values ranged from 3.1% to 27.8%. This wide range was probably due to differing definitions of major complications (including rules for multiple events and event hierarchy), and populations studied. For instance, the TRAMI registry [23] only reported Major Adverse Cardiac and Cerebrovascular events (MACCEs), and reported a particularly low in-hospital mortality rate (despite 9% of procedures being described as emergency).

Major complication events occurring after discharge are reported in Table 20. Again, comparison is limited by differing definitions but also by different follow up durations. The major complication rate of 14.7% in the CtE registry is relatively low compared to values published in these studies. The main contributory component was death, discussed in Question Three.

Table 19. Comparison of major in-hospital adverse events reported by the CtE registry and published literature.

Study	Proportion with major in-hospital complications/adverse event (%)	Definition / comment
CtE registry	8.2 (95% CI 4.7 to 12.9)	Includes death, neurological event, additional surgery, device embolisation, MI, endocarditis, pericardial effusion/tamponade (requiring intervention), major vascular injury (requiring intervention), MV complication, oesophageal rupture, major bleed, AKI (stage 2/3), cardiogenic shock
EVEREST II study [16]	15	30 days post-procedure Similar events included compared with CtE registry.
EVEREST II HR study [20]	26.9	30 days post-procedure Similar events included compared with CtE registry. 17.9% had requirement for ≥2 units of blood
Giannini (2016) [21]	19.9	Calculated by EAC* including incidences of sepsis, new onset AF, AKI, bleeding requiring transfusion, and partial clip detachment (5%). No in-hospital deaths recorded.
TRAMI registry (2012) [23]	3.1	In-hospital MACCE rate.
ACCESS-EU study (2013) [25]	17.1	Calculated by EAC (30 day event rate)*. Includes MACCE, renal failure, respiratory failure, need for resuscitation, cardiac tamponade, and bleeding complications.
Pilot European Sentinel study (2014) [26]	27.8	Calculated by EAC*. Includes death, tamponade, stroke, severe bleeding, need for transfusion, vascular complication, new onset AF.

Abbreviations: AF - atrial fibrillation; AKI – acute kidney injury; MACCE – major adverse cardiac and cerebrovascular events; MI – myocardial infarction; MV – mitral valve; NR – not reported.
* Crude count of sum of events (which may not be independent).

Table 20. Comparison of major adverse events after discharge reported by the CtE registry and published literature.

Study	Proportion with major post-discharge complications/adverse events (%)	Definition / comment
CtE registry	14.7 (95% CI 9.7 to 20.9)	Most events (11.8%) were deaths.
EVEREST II study [16]	45	Inverse of composite primary endpoint at 12 months. Includes death (6%), surgery for MV dysfunction (20%), and recurrence of grade ≥3+ MR (21%)*.
EVEREST II HR study [20]	42.3	12 months post-procedure. Similar events included compared with CtE registry.*
TRAMI registry (2012) [23]	20.3	MACCE at 12 months.
ACCESS-EU study (2013) [25]	36.2	Calculated by EAC (12 month event rate)**. Includes MACCE, renal failure, respiratory failure, need for resuscitation, cardiac tamponade, and bleeding complications.
Pilot European Sentinel study (2014) [26]	31.0	Survival from death or readmission.
Abbreviations: AF - atrial fibrillation; AKI – acute kidney injury; MACCE – major adverse cardiac and cerebrovascular events; MI – myocardial infarction; MV – mitral valve; NR – not reported. * Total events post-procedure (that is, includes in-hospital and post-discharge events). **Crude count of sum of events (which may not be independent).		

Conclusion

In the CTE registry, MitraClip was successfully deployed in 94% of the patients it was attempted in, with a procedural success rate of 86%. Around 8% of people admitted to hospital for the MitraClip procedure experienced a major complication, with 5% dying. Following discharge, there was a major complication rate of around 15%, with death being the most common contributor (12%). Superficially, these values appear to be only broadly consistent with those in the published literature. However, comparisons are limited because studies have used different terminology and methodology, and were conducted in different populations.

3.4.8 Question Eight

"Are clinical outcomes with MitraClip associated with particular patient characteristics (clinical or demographic)?"

Due to the relatively low sample size of the CtE registry, and subsequently, the relatively low number of outcome observations, it was necessary to limit the number of covariates to two within the multivariate analysis modelling (Cox proportional hazards modelling and binary logistic regression modelling). A general rule of thumb in multivariate analyses is to allow a minimum number of 10 outcome observations per covariate included in the model. In all outcomes apart from one (n = 22), observations did not exceed 20, suggesting a maximum number of two covariates should be used in all cases. The two covariates were selected as being the most clinically relevant following consultation with the Clinical Leads (see Section 2.4.6).

The two covariates selected for multivariate analysis were aetiology of MR (functional or degenerate) and urgency of procedure (elective or urgent/emergency). Both these characteristics were deemed as fundamentally important and potentially could demarcate two different populations of patients. In turn, this could inform which patients benefit most from the MitraClip procedure and therefore who the procedure should be indicated for.

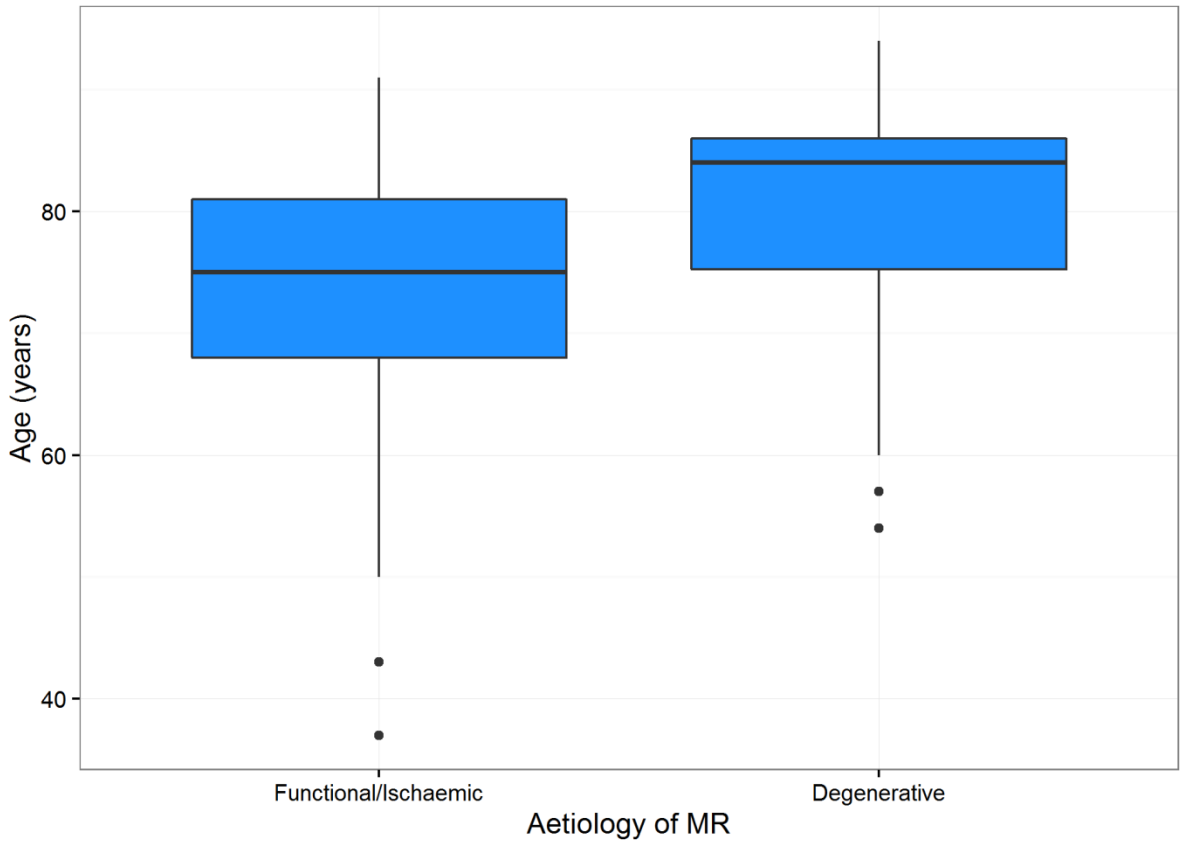
MR aetiology

The potential impact of MR aetiology on mortality rate, MR grade, NYHA class, and adverse events (major and minor complications) was assessed using multivariate analysis. For this analysis, patients were dichotomised as having functional (or ischaemic) MR, or degenerative MR. Patients with degenerative MR were significantly older (mean age 80.2 years) than those with functional MR (mean age 73.7 years, $p < 0.0001$); this is illustrated in Figure 11.

There was no significant difference in mortality observed between groups when time to event analysis was used (Cox proportional hazards model; $p = 0.404$). Additionally, there was no significant difference observed between patients with functional or degenerative MR when binary logistic regression was performed on the outcomes of MR grade (6 and 12 months), NYHA class (6 and 12 months), and adverse events (major or minor complications).

MitraClip is licensed for use for the management of both degenerative and functional MR in Europe. Post-marketing data suggests that around two thirds (65%) of MitraClip procedures have been performed on patients with functional MR, compared with 22% with solely degenerative MR and 13% with mixed aetiologies [66]. These proportions are reflected in the data reported by the CtE registry and by the composition of participants in the studies identified by the EAC (Table 10). In the US, where use of MitraClip in patients with functional MR is technically off label, most, but not all, patients treated with MitraClip have degenerative MR.

Figure 11. Distribution of age in patients with functional or degenerative MR.



Currently, the only directly comparative evidence for the benefit of MitraClip in these patient groups comes from the EVEREST II RCT. Subgroup analysis of the participants in this study reported that surgery was a better option than MitraClip in terms of the primary outcome in patients with degenerative MR. For patients with a diagnosis of functional MR, the evidence of benefit was equivocal [16].

The US TVT registry was the largest (single armed) observational study published to date, enrolling 2,952 patients [33]. Most (85.9%) of the patients had degenerative MR, with 8.6% having solely functional MR and 8.9% have mixed functional and degenerative aetiology (classed as functional for dichotomous analysis). The authors of this registry reported that the cumulative incidences of mortality (24.7%), re-hospitalisation for heart failure (20.5%), and the combined endpoint for both of these 2 outcomes (35.7%) were significantly lower for patients with degenerative MR, in comparison to those observed with functional MR (31.2%, 32.6%, and 49.0%, respectively). Thus the prognosis in patients with functional MR treated with MitraClip was worse than those with degenerative MR.

The European Pilot Sentinel Study reported that patients with functional MR were more likely to be re-hospitalised compared with patients with degenerative MR [26]. The ACCESS-EU study reported no significant differences in clinical outcomes between patients with functional and degenerative MR after 1 year follow up [25].

A recent systematic review and meta-analysis identified and pooled nine studies (one RCT and eight prospective observational studies) with the aim of identifying prognostic differences between functional and degenerative MR patients who had been treated with

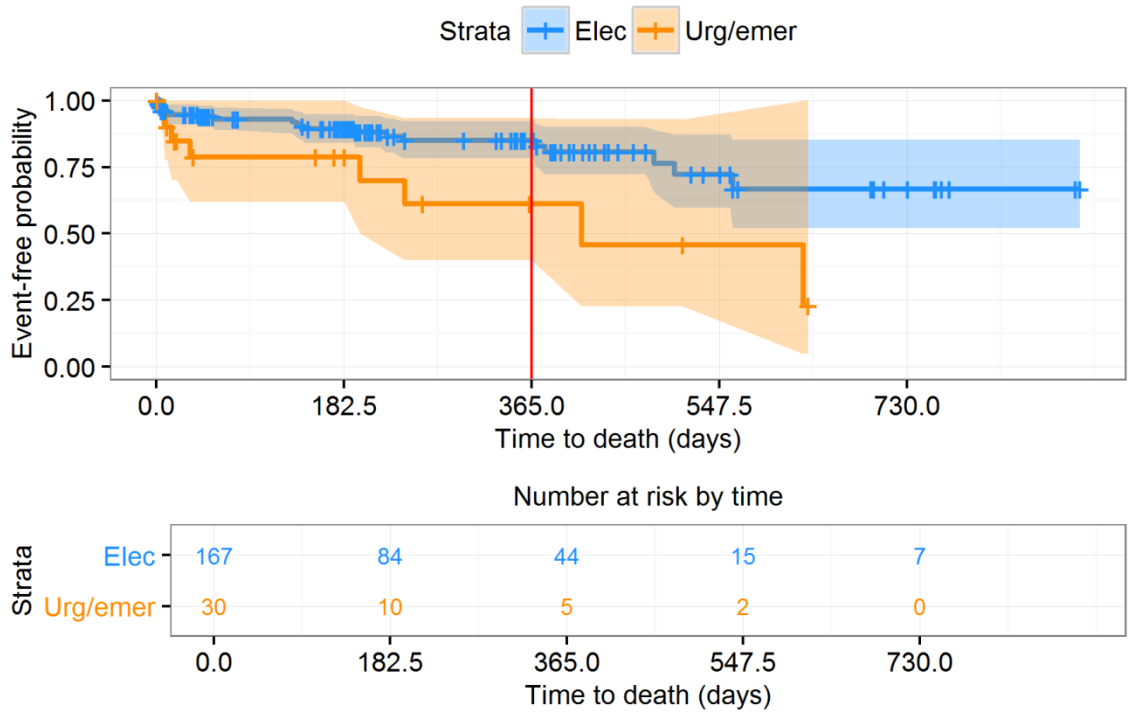
MitraClip [32]. The authors reported that functional MR was associated with a significantly lower rate of re-hospitalisation after 1 year (4%) compared with degenerative MR (10%), with a RR of 0.60 (95% CI: 0.38 to 0.97, p = 0.04).

Urgency of procedure

Most of the patients (84.4%) enrolled into the CtE registry were elective patients, fulfilling the criteria set by NHS England (see Section 2.3). However, 13.6% of patients were treated with MitraClip urgently, and 2.0% were treated as emergencies. The EAC considered that these were likely to represent a distinct cohort of patients compared with the elective group (in terms of overall health and reporting). Because of this, the EAC performed subgroup analysis in these cohorts on key outcomes.

Patients receiving MitraClip as an urgent or emergency case had a greater risk of death, using time to event analysis, than those admitted as elective cases. This is illustrated in the Kaplan-Meier analysis in Figure 12. For elective patients, there was an event rate of 22.1 (95% CI 13.9 to 33.5) per 100 PY, compared with 68.2 (95% CI 29.5 to 134.3) per 100 PY for urgent/emergency cases. This difference was significant (p = 0.0105). As might be expected, this increase is driven by an increased rate of in-hospital mortality; when only post-discharge mortality was considered, there was no significant effect.

Figure 12. Kaplan-Meier analysis comparing patients treated electively or urgently (or as an emergency).



There was no effect of the urgency of the procedure on MR and NYHA grades at 6 months and 12 months. Urgent and emergency procedures were associated with increased in-hospital adverse events compared with elective procedures (p = 0.0242), although this was not significant when Bonferroni correction for multiple outcome analysis was applied. There was no effect observed of procedural urgency on minor adverse events.

Concerning the literature, only the TRAMI registry reported that a proportion of the patients were enrolled as emergency cases (9%, as opposed to 91% recruited electively) [23]. However, no subgroup analysis was performed. The remaining studies either exclusively enrolled elective patients or did not specify what proportion were managed urgently or as emergencies (see Table 10).

Other factors

Univariate analysis and multivariate analysis was performed on device implanted (one or more clips successfully deployed) in *Supplementary Material - Table 4* and on in-hospital major and minor complications in *Supplementary Material - Table 5* and *Table 6*. After application of Bonferroni correction for multiple outcomes, no significant associations were identified.

Conclusion

Subgroup analysis of data reported from the CtE registry did not report any differences in outcomes in patients with functional or degenerative MR. Data from published studies, including the recently published large TVT registry [33], indicate that patients with functional MR have an increased mortality rate and are more likely to be re-admitted to hospital than patients with degenerative MR. Patients in the CtE registry who were admitted urgently or as emergencies had an increased risk of in-hospital mortality. This would be expected as these patients are at greater immediate risk by definition. However, the EAC, did not identify any published literature that performed comparable analysis.

3.4.9 Question Nine

"What are the full procedural costs of MitraClip to the NHS?"

Table 7 reports that the forecast cost for a MitraClip procedure ranges from about £28,800 to almost £34,100, with a central estimate of around £32,560. The device cost included in each scenario is £[redacted] per procedure and assumes manufacturers charge per procedure not per device. This is a key assumption given that 1.9 devices were opened per procedure. The device accounts for [redacted]% to [redacted]% of the total cost, depending on the scenario. The cost of the Abbott device pre-value added tax was provided by the manufacturer as 'commercial in confidence' (Personal communication, Dr Steven Fearn, Health Economics & Reimbursement Manager, Abbott; 4 October 2017). An additional 15% overhead was added to the post VAT costs to meet the overheads of the NHS Trusts associated with procurement, stores and onsite delivery.

Under the central cost scenario the pre-operative pathway accounted for 2%, the procedure 85% and subsequent management 13% of total costs respectively. A more detailed analysis of the cost components is provided at Appendix 9.

3.4.10 Question Ten

"What are the potential cost savings for the NHS arising from patients receiving MitraClip?"

This question cannot be answered by the CtE registry alone as currently there are no comparator data on English patients receiving optimal medical management. Hence no *de novo* analysis can be provided within this report. The response will thus be informed by the four economic studies identified in the literature review [67-70] (see Section 4.2). These studies were generally well conducted but did not have external validity and hence the findings cannot generalise directly to NHS England. However, they do provide evidence on the impact of the MitraClip procedure on hospitalisation rates and costs: these are the key economic variables. These findings, together with relevant clinical evidence, can help inform on the likelihood of MitraClip being cost-saving.

The main potential resource benefit from the MitraClip procedure is a reduction in hospitalisation episodes, reflecting the patients' improved clinical status, as evidenced by improved NYHA class (see response to Question Two). Medication use per patient may also decline but the registry did not capture change in use of medicines.

Admissions and days in hospital

One well-conducted study by Vemulapalli *et al*. (2017) [67] compared admission rates, inpatient days and inpatient costs in the year before and year after the MitraClip procedure. The study included 403 patients in the USA, recruited from the EVEREST II High-Risk Registry and REALISM Continued-Access Study [71]. In the year after the MitraClip procedure, all-cause admissions decreased from 1,854 to 1,435 per 1,000 PY (hazard rate 0.82), with a statistically significant reduction in heart failure admissions (749 versus 332 per 1,000 PY, hazard rate 0.46), but bleeding increased (199 versus 298 per 1,000 PY, hazard rate 1.72). The single most common cause for a hospital day remained heart failure. However, the number of days patients spent in hospital for all causes increased from 9,385 per 1,000 PY in the year before the procedure to 10,312 per 1,000 PY after it (hazard rate

1.36). A survivor analysis reported annual all-cause hospitalisation days reduced from 2,673 per 1,000 PY to 1,881 per 1,000 PY, rate 60%, after the procedure.

Two of the other studies only included hospitalisation for heart failure [68, 69], omitting changes in admissions for other causes. As Vemulapalli *et al*. (2017) [67] demonstrated, heart failure admissions alone are not a good measure of the impact of the procedure on total hospital resources.

The fourth study by Armeni *et al*. (2016) [70] was set in Italy. The authors extracted admission and length of stay data from hospital records for 232 patients treated with MitraClip and a control group of 151 patients treated with medical therapy only. The study reported a materially lower rate of annual hospitalisations for the MitraClip cohort (0.16 per patient versus 0.70 per patient in the medical therapy arm, ratio 0.23). However, these data are confounded because the cohorts were not matched at baseline. For example, the MitraClip cohort had fewer hospital admissions in the previous year than patients in the medical therapy group (1.5 versus 2.0).

The clinical evidence presented in response to question 4 from studies in high-risk patients reported a range of readmission rates from 64% at 12 months from the TRAMI registry [23, 24] to 23% from the Pilot European Sentinel Registry [62] and 21% from the TVT registry [33]. However, the last two studies did not report all-cause admissions but only admissions for specified vascular events. These will understate all-cause admission rates in patients after a MitraClip procedure.

Inpatient costs

The study by Vemulapalli *et al*. (2017) [67] reported mean inpatient costs for all patients of $19,006 in the year before MitraClip and $16,989 in the year after (cost ratio 0.89). A sub-group analysis showed the change in costs did not vary between those with improvement in MR (cost ratio = 0.65) or with no improvement (cost ratio = 0.64). A survivor analysis reported a statistically significant reduction in mean hospital costs in the year after MitraClip (from $18,131 to $11,679, cost ratio 0.64). It should be noted that none of these costs include the cost of the MitraClip procedure.

The only other economic study reporting inpatient costs was Armeni *et al*. (2016) [70]. This study assumed annual hospitalisation costs of 495€ [£396][1] for the MitraClip arm and 4,338€ [£3,470] for those managed on medical therapy (cost ratio 0.11).

Total costs per patient

Vemulapalli *et al*. (2017) [67] only reported inpatient costs, excluding cost of the MitraClip procedure.

Mealing *et al*. (2013) [68] only reported incremental costs of £26,989 per patient (2011 prices) for the MitraClip cohort compared to patients receiving medical therapy over five years. The MitraClip device accounted for £20,500 of this difference (76%) and short-term hospitalisation for a further £3,800 (14%). The cost of medicines was also higher in the MitraClip cohort (+£1,400) (5%) because these patients were modelled to have a longer mean survival than the medical management cohort.

[1] Exchange rate of £1 to 1.25€ adopted for exchange rate in 2012. Source: http://www.x-rates.com/average/?from=GBP&to=EUR&amount=1&year=2012

Cameron *et al*. (2014) [69] reported that over a lifetime, the mean cost per patient receiving a MitraClip was 62,510 Canadian dollars (C$) [£34,730)[2] compared to C$21,893 (£12,160) for medical therapy. All of the incremental cost of C$40,617 (£22,565) was accounted for by device related costs. These were C$43,439 (£24,130). Savings in hospitalisation costs for heart failure and surgery following the MitraClip procedure offset slightly higher disease management costs post procedure compared with medical therapy only.

Armeni *et al*. (2016) [70] only reported the incremental lifetime cost of 23,342€ (£18,670) per patient for the MitraClip cohort compared to those managed on medical therapy. Almost all of this cost is accounted for by the procedure (23,069€ [£18,455]).

Conclusions

The evidence from four economic studies is consistent with:

- A material reduction in admissions for heart failure in the years immediately after a MitraClip procedure;
- However, this reduction may be offset by increases in hospital admissions for other causes including bleeds [67], such that the use of hospital bed-days does not decline;
- A reduction in annual inpatient costs of around 10% in the first year following the procedure [67];
- The reduction in inpatient costs should be higher in the second year as the cost reduction for survivors was materially greater than for all patients (cost ratio 0.64).

No study found that the incremental cost of the MitraClip procedure (ranging from £28,800 to almost £34,100, with a central estimate of around £32,560) will be offset from savings from fewer hospitalisations or avoided surgery compared with managing patients on medical therapy.

Future work

A *de novo* economic study using English admissions rates, hospital days and mortality before and after the MitraClip procedure is required to inform whether these conclusions generalise to the NHS England setting. This work is planned using admission and length of stay information from Hospital Episode Statistics (HES) and mortality data from Office of National Statistics (ONS) for each patient entered into the CtE registry. These data would enable the EAC to calculate, for each patient, in the registry:

- Annual NHS resource use and costs before the procedure and at 12 to 24 months post-procedure.
- Mortality and other event rates over these time periods and to compare these with data in the registry.

Annual costs and mortality rates post-procedure would be extrapolated to life time using assumptions which align to the evidence on sustained clinical benefit as presented in response to Question 5.

The timing for the EAC to receive the linked datasets is uncertain.

[2] Exchange rate of £1 to 1.80 Canadian $ for exchange rate in 2014. Source: http://www.x-rates.com/average/?from=GBP&to=CAD&amount=1&year=2014

3.4.11 Question Eleven

"Is MitraClip cost-effective from the perspective of the NHS?"

As noted in response to Question Ten, currently there are no comparator data on English patients receiving optimal medical management to enable this question to be answered.

The response to Question Ten has set out evidence, albeit from non-UK settings, which indicates that MitraClip is likely to cost the NHS more per patient than the costs to manage similar patients with medical therapy. Three studies [67-69] indicate that, over the lifetime of a patient, the incremental cost of the MitraClip pathway, compared with managing patients on medical therapy, could be similar to the cost of the initial procedure. In the context of NHS England this could be around £32,560.

Each of the three studies conducted a cost utility analysis, calculating the additional quality adjusted life years gained with the MitraClip procedure compared to medical therapy. The incremental cost effectiveness ratios were calculated as:

- 7,900€ (£6,320) by Armeni *et al*. (2016) [70]
- C$23,433 (£13,020) by Cameron *et al*. (2014) [69]
- £14,800 by Mealing *et al*. (2013) [68].

All authors concluded that the intervention was cost-effective at the relevant willingness to pay threshold for a quality adjusted life year in their country. However, due to weaknesses in the conduct of the studies, particularly the use of admissions for heart failure only, these results are not reliable to inform decisions by NHS England.

Relevant evidence from the registry to inform a decision on cost-effectiveness includes the improved QoL reported by patients with a MitraClip device(s). The mean increase in QoL at two years, as measured by the EQ-5D instrument, was 0.21 (see Table 12).

There was no strong evidence to support improved survival rates following the procedure compared with optimal medical management (see response to Question Four).

The planned *de novo* economic analysis, using NHS and ONS data, will be able to include the value of the observed quality of life benefit.

Conclusion

The published evidence, using cost-utility analysis, suggests the MitraClip procedure is cost-effective. However, that evidence is not sufficiently robust to inform NHS England's procurement decision. The EAC plans to undertake *de novo* economic modelling, building on registry data, once linked datasets become available, to reduce the uncertainty on the cost-effectiveness of MitraClip.

3.4.12 Summary of answers to NHS England questions

Answers to the NHS England questions are summarised in Table 17.

Table 17. Summary of NHS England answers.

Final version of question, as amended NICE following discussion with EAC	Summary answer (from registry data supplemented by published literature)
1) Can UK clinical teams undertaking MitraClip reproduce the reduction in mitral regurgitation seen in the early clinical trials?	Evidence reported from the CtE registry shows that the MitraClip system results in immediate and dramatic improvements in MR grade with the proportion of patients with moderate-severe or severe MR (≥3+) reduced from 99.5% to 6.7%. This large effect is consistent with all the studies identified in the literature. However, after 1 year there is evidence that there is some deterioration in mitral valve function, with 24.4% of patients reporting moderate-severe or severe MR. Again, this is fully consistent with the published literature. Evidence from the EVEREST II RCT reported that reduction in MR grade was similar for both MitraClip and surgery patients; however, this is contradicted by several observational studies which have reported surgery is superior, especially in the longer term.
2) Is reduction in mitral regurgitation mediated by MitraClip associated with improvements in quality of life?	The CtE registry reported significant improvements in QoL, as measured by utility and VAS, at all follow up time points compared with baseline. There were statistically significant improvements in all domains of EQ-5D at 6 months. The use of MitraClip was also associated with an immediate and sustained improvement in NYHA class. These results were consistent with those published in the literature.
3) Does MitraClip improve survival rates?	The CtE registry reported an in-hospital mortality rate of 5.0% (95% CI 2.4% to 9.0%) and a 1 year mortality rate of 11.6% (95% CI 7.5% to 16.8%). These data appear consistent with results from observational studies performed in patients with similar characteristics. However, there is no robust comparative data to inform whether survival rates are improved compared to optimal medical management.
4) Does MitraClip reduce the frequency of subsequent hospital admissions?	There is no reliable evidence from the registry concerning the relative rate of readmission in patients following the MitraClip procedure. Evidence from observational studies indicated that the rate of readmission for MitraClip patients is high in the first year, ranging from approximately 20 to 60%. It is hoped that this question will be fully answered through linkage with Hospital Episodes Statistics (HES) data.
5) Are the early benefits in reduction in mitral regurgitation maintained in the medium-term? Is there a need for repeat treatment over time (either by a repeat percutaneous procedure or surgery)?	The benefits of MitraClip were sustained for the follow up duration of the CtE registry. There is conflicting evidence on the benefits of MitraClip reducing MR compared with surgery in the longer term.

Final version of question, as amended NICE following discussion with EAC	Summary answer (from registry data supplemented by published literature)
6) What proportion of patients referred to a specialist MitraClip service as defined in the CtE documents were assessed by the MDT as suitable for the intervention? What proportion of the patients considered suitable for the procedures received it and what proportion of them benefitted?	The CtE registry cannot be used to answer this question. The EAC did not identify any robust UK based data which would inform this question.
7) What are the short and medium term risk of complications from MitraClip use?	MitraClip was successfully deployed in 94% of the patients it was attempted in, with a procedural success rate of 86%. Around 8% of people admitted to hospital for the MitraClip procedure experienced a major complication, with 5% dying. Following discharge, there was a major complication rate of around 15%, with death being the most common contributor (12%). These values appear to be broadly consistent with those reported in the literature, although comparisons of complications are limited due to issues with generalisability.
8) Are clinical outcomes with MitraClip associated with particular patient characteristics (clinical or demographic)?	Limited data volume meant that subgroup analysis was limited to procedural urgency and disease aetiology. Patients in the CtE registry who were admitted urgently or as emergencies had an increased risk of in-hospital mortality. There were no significant differences in outcomes in patients with functional or degenerative MR. Data from published studies indicate that patients with functional MR have an increased mortality rate and are more likely to be re-admitted to hospital than patients with degenerative MR.
9) What are the full procedural costs of using MitraClip to the NHS?	The central estimate of the cost of a MitraClip procedure is about £32,560, range £28,800 to £34,100.
10) What are the potential cost savings for the NHS arising from patients receiving MitraClip?	Limited evidence from non-NHS settings indicate MitraClip will not be cost saving compared with current practice. This is true for all time-periods.
11) Is MitraClip cost-effective from the perspective of the NHS?	This question will require *de novo* economic analysis using robust NHS England generated data.

Section 4: Discussion

4.1 SUMMARY OF FINDINGS FROM PRIMARY DATA COLLECTION (CTE DATABASE)

A total of 199 patients were enrolled into the CtE registry. The mean age of patients was 76.2 years (10.5 years SD); most (68.8%) were men; and most (60%) had a diagnosis of functional or ischaemic MR. Patients with degenerative MR were significantly older than those with functional or ischaemic MR. The majority of patients were recruited electively (84.4%) with 13.6% admitted urgently and 2.0% undergoing the procedure as an emergency. All but one patient enrolled had moderate or severe MR (grade 3+ or 4+), and the large majority of patients had significant dyspnoea symptoms as measure by NYHA class (92.4% being class 3 or 4). The mean EuroSCORE II was 6.4 (5.7 SD).

One hundred and eighty seven patients were recorded as having a MitraClip device implanted. Both admission and discharge dates were reported for 182 procedures (91.5%), showing a median length of stay of 5 days (IQR 3.3 to 8.0 days, range 0 to 46 days). Procedural success, defined as device implanted with no major in-hospital complications was 85.9% (95% CI 80.3 to 90.4%). In-hospital major complications were reported in 16 patients (8.2%, multiple events permitted), the majority of which were deaths (10 patients). Four patients required an additional intervention. In-hospital minor complications were reported in 15 patients (7.6%). MitraClip was associated with an immediate improvement in MR class, with 93% of patients being ≤MR 2+ on discharge. There were corresponding improvements in NYHA class.

Post-discharge follow-up was reported in 170 patients (90.9%). Significant improvements in MR and NYHA grades compared with baseline persisted for up to 2 years, and there was significant improvement in QoL during this period. Major complications occurring post-MitraClip procedure discharge were recorded in 25 patients (including 20 deaths) and minor complications in 22 patients. In total 30 deaths were reported pre- and post-discharge, accounting for 15.1% of the cohort. Patients undergoing urgent or emergency procedures were associated with significantly increased occurrence of in-hospital death, with no other significant associations detected.

The central estimate of procedural cost for MitraClip was £32,560 (range £28,800 to £34,100). The pre-operative pathway accounted for 2%, the procedure 85% and subsequent management 13% of total costs respectively. Device cost itself accounted for 67% to 79% of total costs.

4.2 RESULTS IN THE CONTEXT OF OTHER STUDIES

The EAC performed a literature search which informed a literature review document that reported on the current evidence base for MitraClip [8]. All the studies included for analysis were published subsequent to the IP664 overview document of IPG309 [6]. One RCT was identified. The EVEREST II RCT [16] failed to report equivalence of the MitraClip device with open surgery in its primary composite outcome. Data from this trial was not considered generalisable to the CtE registry because the patients were healthy enough to be surgical candidates, whereas the only option available to the CtE cohort patients was conventional medical management.

Three observational studies were identified which included comparator groups receiving medical management [20-22]. However, the comparator arms used in these studies were

historical or actively selected for, thus results were considered to be at high risk of bias and confounding. The EAC also identified three large prospective single-armed registries [23, 25, 26] and one large retrospective study [28]. Additionally, the TVT registry [33], which was published subsequent to the literature review [8], was included for analysis due to its large size (n = 2952) and reporting of relevant outcomes. All the observational studies included high-risk populations that largely reflected those of the CtE registry.

The CtE registry provided good data on the procedural efficacy and in-hospital safety of MitraClip. Although statistical comparisons could not be performed due to data heterogeneity, peri-procedural outcomes were generally consistent with those reported in the literature from observational studies. These studies indicated MitraClip is associated with an immediate and significant improvement in MR grade, which appears to positively reduce symptoms, as evidenced by improved NYHA class and QoL. However, MitraClip was also associated with a substantial in-hospital risk of death, reported as 5.0% in the CtE registry and consistent with observational studies. This rate included patients admitted urgently or as an emergency, which was poorly reported in the literature.

In the medium term, the CtE registry concurred with observational studies that the reduction in MR and improvements in NYHA associated with MitraClip were sustained. However, the mortality rate at 1 year was high, ranging from 10.3% in the Giannini study [21] to 25.3% in the TVT registry [33]. In addition to readmission, there is observational evidence that a high proportion of patients receiving MitraClip are subsequently readmitted for cardiac indications. The CtE registry could not provide data on the longer-term safety and efficacy of MitraClip. However, limited observational evidence suggests that the device may not be as effective in reducing MR as surgery after 4 years [60].

The EAC identified four economic studies with medium internal validity that informed the economics of the MitraClip procedure [67-70]. These reported that costs per patient are higher in patients who receive a MitraClip device compared to those who do not, and that savings in future years from reduced hospital admissions from heart failure are not sufficient to offset the initial cost of the procedure. However, there were key uncertainties relating to overall clinical effectiveness of MitraClip compared with other treatment strategies, and the impact of this on resource use, particularly in the longer-term.

A further three economic studies were identified but these were judged to have low internal and external validity and hence not used in further analyses (Asgar, 2017, Guerin, 2016, Palmieri, 2015) [72-74].

In summary, the EAC has analysed data collected from the CtE registry and qualitatively compared it with published data. Procedural and peri-procedural data from patients was comparable with the registry, as was medium-term efficacy and safety data. Importantly, MitraClip appears to be associated with significant improvements in QoL. However, this population of patients have a high mortality rate and requirement for further hospital treatment. There remains considerable uncertainty concerning the longer-term efficacy of MitraClip and how it compares with conservative medical management. This uncertainty also means it is unclear what the true costs of this intervention are in this high-morbidity population.

4.3 LIMITATIONS AND FUTURE PROPOSALS (FOR NHS ENGLAND REPORT)

4.3.1 Limitations

The CtE registry was a single armed study and thus comparisons had to be made implicitly with results published in the literature [75]. This had two limitations. Firstly, no statistical or quantitative comparisons could be made with the comparator of interest, which was conservative medical management (*not* surgery). Secondly, some of the published literature was not directly comparable to the registry. Specifically, evaluation of CtE results with trial data was limited by differences in outcome terminology and measurement, and possible issues with generalisability of the population (this was particularly with respect to the single RCT identified, the EVEREST II trial [16]). Thus inferences of equivalence (or not) of CtE and trial data are subject to considerable uncertainty.

Other specific and non-specific limitations with the registry include the following:

- Two of the key outcomes were MR grade and NYHA class, neither of which are "hard" outcomes. Measurement of MR grade has frequently involved subjective judgement on behalf of the assessor [76], and over optimism in interpretation could have led to detection bias. Similarly, NYHA class can lead to performance bias on behalf of the patient [46].
- Although initially designed for 5 years follow up, CtE registry follow up was limited to a maximum of 2 years. This meant that longer-term efficacy outcomes or data on longer-term complications were not available.
- In addition to the 2-year cut off point, most patients were not eligible for assessment at this time point because of the timeframe of the study and associated deadlines. For instance, only 45 patients were eligible for follow up at 2 years (28.3% of the total cohort), because most patients had the procedure within the previous 2 years, and were therefore not qualified for the 2-year follow up. Of these 45 patients, only 11 had follow up data reported (24.4%).
- Kaplan-Meier analysis assumed "no event" status of patients unless an event was recorded. Thus the analysis relies on complete reporting of all event data. Patients who are lost to follow up are censored from the analysis, but it is unclear if these are representative of the overall cohort. Finally, patients may have multiple events (excluding death), but the Kaplan-Meier protocol only analyses time to first event.

4.3.2 Strengths

The CtE registry had several strengths. Firstly, the registry enrolled indicated patients consecutively and represented a pragmatic real-world cohort of patients receiving treatment with MitraClip as performed in the NHS. Thus the external applicability of the registry to future practice is high, although improvements in the procedure protocol and the learning curve effect may ultimately lead to improved outcomes.

Secondly, following an initial disappointing response from centres in providing follow-up data, this improved considerably such that there was 111.2 PY follow up available for analysis. Follow up was particularly robust up to 1 year, with 79.4% of eligible patients reporting follow up data at this time point. The completion of individual data fields varied, but overall, data completeness was regarded as good. The number reporting results for each data field are presented in the *Supplementary Material Table 3* of this report.

Thirdly, the CtE registry reported important clinical outcomes, which also allowed for limited subgroup analysis. In addition, the registry captured quality of life data and, through the use of *pro formas* directed at a centre level, estimated the cost of the procedure.

4.3.3 Future proposals

The registry analysis would be more robust with data linkage to the ONS (Office of National Statistics) mortality dataset, to validate calculated mortality rates in the CtE cohort and provide greater coverage. This could be potentially continued beyond the final follow up date of the study (2 years). Potentially, data linkage to HES (Hospital Episodes Statistics) could also provide further validation and coverage of readmission data, which would be useful in informing cost information and resource use. At the time of submission of this final CtE report to NHS England, NICOR are awaiting a decision on a Data Access Request Service (DARS) application to NHS Digital for data linkage.

The EAC notes that the evidence base on MitraClip is growing at a rapid rate. In particular, the EAC is aware of three on-going RCTs using medical management as a comparator [34-36], and one RCT comparing MitraClip with surgery [37]. It would therefore be prudent to horizon scan the literature base for publication of these, and other, studies.

Section 5: Conclusion

The MitraClip CtE registry enrolled 199 patients with a mean age of 76.2 years (10.5 years SD). Nearly all patients had clinically significant symptomatic MR, with the majority (60%) being of functional or ischaemic aetiology. A minority of patients (16%) were treated urgently or as an emergency. Patients were considered to be at high risk from conventional cardiac open surgery, with a mean EuroSCORE II of 6.4 (5.7 SD). The patient characteristics were broadly similar to those identified in observational studies in the published literature, but were different from those recruited to the only published RCT to date, the EVEREST II study [16], with the patients in the RCT being well enough to have open surgery.

One hundred and eighty seven patients (94%) had a MitraClip device successfully implanted, with a procedural success rate (device implanted and no major complications) of 85.9% (95% CI 80.3 to 90.4%). There was a major in-hospital adverse rate of 8.2% (95% CI 4.7 to 12.9%) which included 10 deaths (about 5%). This was broadly comparable to data reported in the literature, although direct comparisons could not be made due to differences in the terminology used. The MitraClip device was associated with a median length of hospital stay of 5 days (IQR 3.3 to 8.0, range 0 to 46 days).

In patients who had a MitraClip successfully implanted, there was an immediate and significant reduction in MR grade at discharge, from 100% MR grade ≥3+ to 7% MR grade ≥3+. This benefit diminished slightly over time, with 24% of patient reporting MR grade ≥3+ after 1 year. Reduction in MR was associated with a corresponding improvement in dyspnoea symptoms as measured by NYHA class. Furthermore there was a significant improvement reported in QoL as measured by EQ-5D, both in terms of overall health utility and all individual domains. These results are consistent with those reported in the literature.

The registry reported an overall death rate of 15.1% (95% CI 10.4 to 20.8%). The death rate at 1 year was 11.6% (95% CI 7.5% to 16.8%). The annualised death rate using time to event analysis, derived from a total of 111.2 recorded person years (PY), was 27.0 (95% CI 18.2 to 38.5%) per 100 PY; this higher mortality rate was likely artefactual due to issues with censoring. The mortality rate in the CtE MitraClip cohort generally compared favourably with similar patients reported in the literature, with annual rates of between 10% and 25% reported. Three observational studies reported that MitraClip improved survival compared to matched comparators receiving optimal medical management [20-22], but these were subject to confounding. Thus it is currently unknown whether MitraClip is associated with improved survival.

MitraClip is an expensive procedure, with an estimated cost ranging from about £28,800 to almost £34,100, with a central estimate of around £32,560. In addition to the cost of the procedure, data from the literature indicates that a large proportion of patients will require hospital readmission following discharge. It is unclear if this rate of readmission is different to patients receiving conservative medical management.

In conclusion, the CtE registry has demonstrated that MitraClip, when successfully implanted, is causally associated with clinically important reductions in MR which improve QoL. MitraClip has been the subject of extensive observational research since the publication of IPG309 in August 2009 [1], and the results of the registry broadly concur with the results reported in this evidence base. However, there is currently no comparative evidence that shows MitraClip reduces rates of mortality or hospital readmission compared

with medically treated patients with similar characteristics. It is hoped that the publication of three on-going RCTs will provide this information [34, 35, 37].

Section 6: Acknowledgements

External Assessment Centre (EAC) Administrator in Newcastle, Emma Belilios, acted as secretary and produced minutes of meetings and teleconferences throughout the duration of the cardiac CtE project.

EAC literature searches were conducted by Mick Arber, Senior Information Specialist at York Health Economics Consortium.

Roseanne Jones, Research Scientist within the Newcastle EAC team, supported literature sifting as a second reviewer to Iain Willits and Helen Cole.

Julie Burn, Clinical Scientist in Clinical Computing at Newcastle, acted as an adviser to Kim Keltie and Sam Urwin, in support of their data analysis work for cardiac CtE.

Section 7: References

1. National Institute for Health and Care Excellence. Percutaneous mitral valve leaflet repair for mitral regurgitation (IP309) 2009.
2. Willits I, Jones R, Bousfield D, Arber M, Cole H, Sims AJ. OUTPUT ONE: Recommendations on three NHS England Commissioning through Evaluation (CtE) registry draft datasets for MitraClip, LAAO and PFO Closure cardiovascular procedures. In: EAC NY, editor. Unpublished; 2014.
3. Cole H, Willits I, Craig J, Sims AJ. OUTPUT TWO: Data quality monitoring process. Unpublished; 2015.
4. Willits I, Craig J, Cole H, Urwin S, Sims AJ. OUTPUT THREE: Draft registry data analysis protocol - MitraClip. In: EAC NY, editor. Unpublished; 2015.
5. NHS England. Specialised Services Circular: Percutaneous mitral valve leaflet repair (using MitraClip) CtE Provider Selection Confirmed (SSC 1454). 2014.
6. National Institute for Health and Care Excellence. Interventional procedure overview of percutaneous mitral valve leaflet repair for mitral regurgitation (IP664). 2008.
7. R Core Team. . R Foundation for Statistical Computing V, Austria, . URL http://www.R-project.org/. R: A language and environment for statistical computing. Vienna; 2016.
8. Willits I, Craig J, Arber M, Cole H. RX085 Commissioning through Evaluation (CTE) registry of 3 cardiovascular procedures. MitraClip literature review document. Unpublished; 2016.
9. Agency for Healthcare Research and Quality (AHRQ). Registries for evaluating patient outcome: a user's guide: Volume 1. 3rd ed. Rockville, MD; 2012.
10. Agency for Healthcare Research and Quality (AHRQ). Registries for evaluating patient outcome: a user's guide: Volume 2. 3rd ed. Rockville, MD; 2012.
11. Willits I, Craig J, Cole H, Urwin S, Sims AJ. OUTPUT THREE: Draft registry data analysis protocol - LAAO. In: EAC NY, editor. Unpublished; 2015.
12. Department of Health. NHS reference costs 2015 to 2016. 2016.
13. Curtis L, Burns A. Unit Costs of Health and Social Care 2016. 2016.
14. Van Reenen M, Janssen B. EQ-5D-5L User Guide: Basic information on how to use the EQ-5D-5L instrument. 2015.
15. Moher D, Liberati A, Tetzlaff J, Altman G, Prisma PRISMA. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009;6(7).
16. Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, et al. Percutaneous repair or surgery for mitral regurgitation.[Erratum appears in N Engl J Med. 2011 Jul 14;365(2):189 Note: Glower, Donald G [corrected to Glower, Donald D]]. New England Journal of Medicine. 2011 Apr 14;364(15):1395-406.
17. Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, et al. Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II. Journal of the American College of Cardiology. 2015 Dec 29;66(25):2844-54.
18. Feldman T, Foster E, Qureshi M, Whisenant B, Williams J, Glower D, et al. The everest ii randomized controlled trial (RCT): Three year outcomes. Journal of the American College of Cardiology; 2012. p. B229-b30.
19. Feldman T, Kar S, Rinaldi M, Fail P, Hermiller J, Smalling R, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. Journal of the American College of Cardiology. 2009 Aug 18;54(8):686-94.
20. Whitlow PL, Feldman T, Pedersen WR, Lim DS, Kipperman R, Smalling R, et al. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study. Journal of the American College of Cardiology. 2012 Jan 10;59(2):130-9.
21. Giannini C, Fiorelli F, De Carlo M, Guarracino F, Faggioni M, Giordano P, et al. Comparison of Percutaneous Mitral Valve Repair Versus Conservative Treatment in Severe Functional Mitral Regurgitation. American Journal of Cardiology. 2016 Jan 15;117(2):271-7.

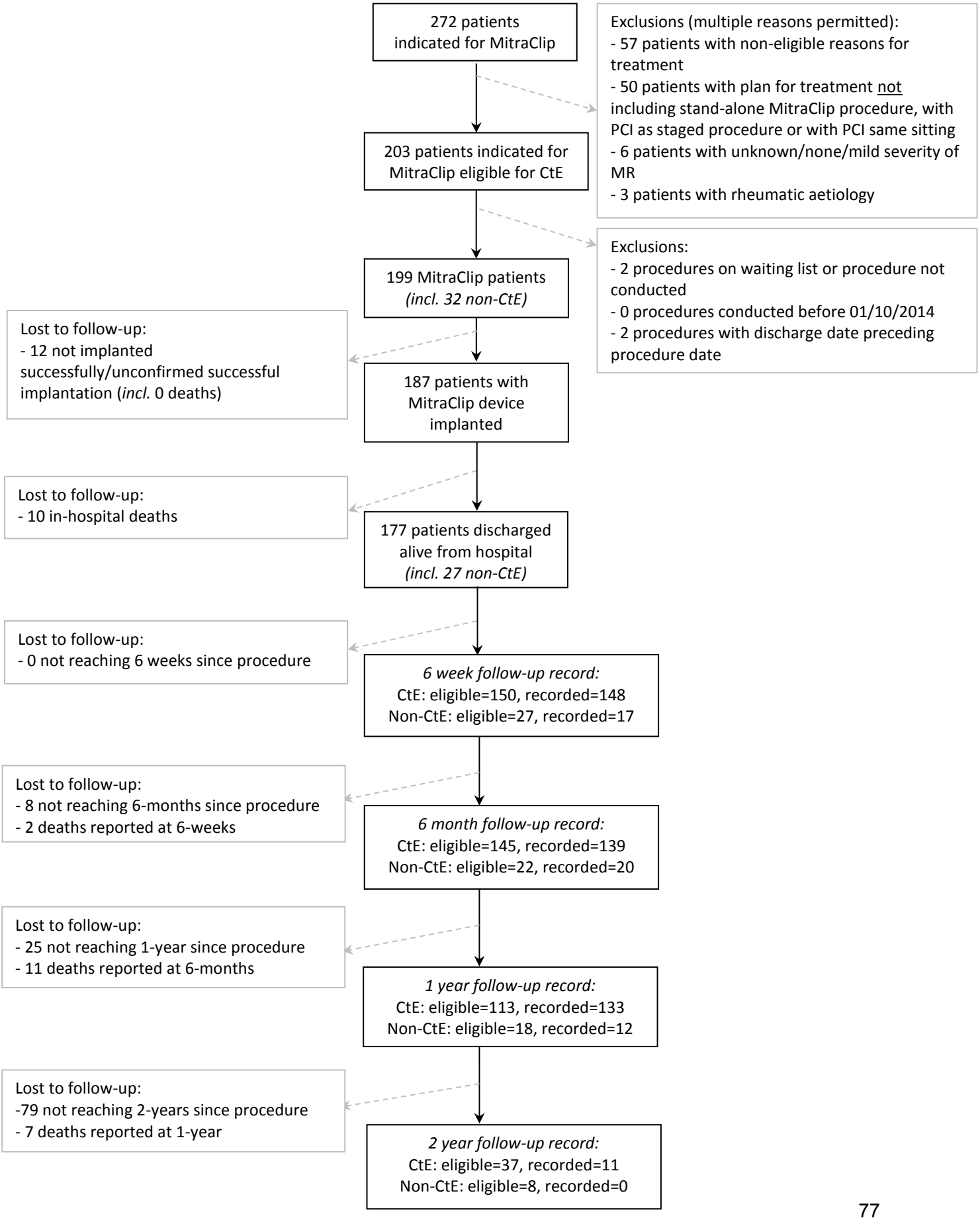
22. Velazquez EJ, Samad Z, Al-Khalidi HR, Sangli C, Grayburn PA, Massaro JM, et al. The MitraClip and survival in patients with mitral regurgitation at high risk for surgery: A propensity-matched comparison. American Heart Journal. 2015 Nov;170(5):1050-9.e3.
23. Baldus S, Schillinger W, Franzen O, Bekeredjian R, Sievert H, Schofer J, et al. MitraClip therapy in daily clinical practice: initial results from the German transcatheter mitral valve interventions (TRAMI) registry. European Journal of Heart Failure. 2012 Sep;14(9):1050-5.
24. Puls M, Lubos E, Boekstegers P, von Bardeleben RS, Ouarrak T, Butter C, et al. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral valve interventions registry. European Heart Journal. 2016 Feb 21;37(8):703-12.
25. Maisano F, Franzen O, Baldus S, Schafer U, Hausleiter J, Butter C, et al. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. Journal of the American College of Cardiology. 2013 Sep 17;62(12):1052-61.
26. Nickenig G, Estevez-Loureiro R, Franzen O, Tamburino C, Vanderheyden M, Luscher TF, et al. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011-2012 Pilot European Sentinel Registry. Journal of the American College of Cardiology. 2014 Sep 2;64(9):875-84.
27. Pighi M, Estevez-Loureiro R, Maisano F, Ussia GP, Dall'Ara G, Franzen O, et al. Immediate and 12-Month Outcomes of Ischemic Versus Nonischemic Functional Mitral Regurgitation in Patients Treated With MitraClip (from the 2011 to 2012 Pilot Sentinel Registry of Percutaneous Edge-To-Edge Mitral Valve Repair of the European Society of Cardiology). American Journal of Cardiology. 2017 Feb 15;119(4):630-7.
28. Rahhab Z, Kortlandt FA, Velu JF, Schurer RAJ, Delgado V, Tonino P, et al. Current MitraClip experience, safety and feasibility in the Netherlands. Netherlands Heart Journal. 2017 Jun;25(6):394-400.
29. Takagi H, Ando T, Umemoto T, Group A. A review of comparative studies of MitraClip versus surgical repair for mitral regurgitation. International Journal of Cardiology. 2017 Feb 01;228:289-94.
30. Philip F, Athappan G, Tuzcu EM, Svensson LG, Kapadia SR. MitraClip for severe symptomatic mitral regurgitation in patients at high surgical risk: A comprehensive systematic review. Catheterization & Cardiovascular Interventions. 2014 Oct 1;84(4):581-90.
31. Vakil K, Roukoz H, Sarraf M, Krishnan B, Reisman M, Levy WC, et al. Safety and efficacy of the MitraClip system for severe mitral regurgitation: a systematic review. Catheterization & Cardiovascular Interventions. 2014 Jul 1;84(1):129-36.
32. Chiarito M, Pagnesi M, Martino EA, Pighi M, Scotti A, Biondi-Zoccai G, et al. Outcome after percutaneous edge-to-edge mitral repair for functional and degenerative mitral regurgitation: a systematic review and meta-analysis. Heart. 2017 Jun 29;29:29.
33. Sorajja P, Vemulapalli S, Feldman T, Mack M, Holmes DR, Jr., Stebbins A, et al. Outcomes With Transcatheter Mitral Valve Repair in the United States: An STS/ACC TVT Registry Report. J Am Coll Cardiol. 2017 Nov 7;70(19):2315-27.
34. Mack M, Stone G, Abraham WT, Lindenfield J. Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (The COAPT Trial). 2017 [cited 2017 3rd October]; Available from: https://clinicaltrials.gov/ct2/show/NCT01626079
35. Anker S, Schillinger W. A Clinical Evaluation of the Safety and Effectiveness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation (Reshape-HF2). 2017 [cited 2017 3rd October]; Available from: https://clinicaltrials.gov/ct2/show/NCT02444338
36. Obadia JF, Mewton N. Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR). 2017 [cited 2017 3rd October]; Available from: https://clinicaltrials.gov/ct2/show/NCT01920698
37. Volker R, Baldus S. A Multicenter, Randomized, Controlled Study to Assess Mitral vAlve reconsTrucTion for advancEd Insufficiency of Functional or iscHemic ORigiN (MATTERHORN). 2017 [cited 2017 11th October]; Available from: https://clinicaltrials.gov/ct2/show/NCT02371512

38. Prins C, de Villiers Jonker I, Botes L, Smit FE. Cardiac surgery risk-stratification models. Cardiovasc J Afr. 2012 Apr;23(3):160-4.
39. European System for Cardiac Operative Risk Evaluation. EuroSCORE calculator. 2011 [cited 2018 22nd February]; Available from: http://www.euroscore.org/
40. The Society of Thoracic Surgeons. Risk calculators. [cited 2018 22nd February]; Available from: https://www.sts.org/resources/risk-calculators
41. Apostolakis EE, Baikoussis NG. Methods of estimation of mitral valve regurgitation for the cardiac surgeon. J Cardiothorac Surg. 2009 Jul 15;4:34.
42. Alozie A, Paranskaya L, Westphal B, Kaminski A, Sherif M, Sindt M, et al. Clinical outcomes of conventional surgery versus MitraClip therapy for moderate to severe symptomatic mitral valve regurgitation in the elderly population: an institutional experience. BMC Cardiovascular Disorders. 2017 Mar 20;17(1):85.
43. Taramasso M, Denti P, Buzzatti N, De Bonis M, La Canna G, Colombo A, et al. Mitraclip therapy and surgical mitral repair in patients with moderate to severe left ventricular failure causing functional mitral regurgitation: a single-centre experience. European Journal of Cardio-Thoracic Surgery. 2012 Dec;42(6):920-6.
44. De Bonis M, Lapenna E, Buzzatti N, La Canna G, Denti P, Pappalardo F, et al. Optimal results immediately after MitraClip therapy or surgical edge-to-edge repair for functional mitral regurgitation: are they really stable at 4 years? European Journal of Cardio-Thoracic Surgery. 2016 Sep;50(3):488-94.
45. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013 Sep;22(7):1717-27.
46. Raphael C, Briscoe C, Davies J, Ian Whinnett Z, Manisty C, Sutton R, et al. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. Heart. 2007 Apr;93(4):476-82.
47. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. Br Med Bull. 2010;96:5-21.
48. Taramasso M, Maisano F, Denti P, Latib A, La Canna G, Colombo A, et al. Percutaneous edge-to-edge repair in high-risk and elderly patients with degenerative mitral regurgitation: midterm outcomes in a single-center experience. Journal of Thoracic & Cardiovascular Surgery. 2014 Dec;148(6):2743-50.
49. Estevez-Loureiro R, Settergren M, Pighi M, Winter R, D'Allara G, Jacobsen P, et al. Effect of advanced chronic kidney disease in clinical and echocardiographic outcomes of patients treated with MitraClip system. International Journal of Cardiology. 2015 Nov 1;198:75-80.
50. Downs EA, Lim DS, Saji M, Ailawadi G. Current state of transcatheter mitral valve repair with the MitraClip. Annals of Cardiothoracic Surgery. 2015 Jul;4(4):335-40.
51. Yeo KK, Yap J, Yamen E, Muda N, Tay E, Walters DL, et al. Percutaneous mitral valve repair with the MitraClip: early results from the MitraClip Asia-Pacific Registry (MARS). EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2014 Sep 22;10(5):620-5.
52. Lesevic H, Sonne C, Braun D, Orban M, Pache J, Kastrati A, et al. Acute and Midterm Outcome After MitraClip Therapy in Patients With Severe Mitral Regurgitation and Left Ventricular Dysfunction. American Journal of Cardiology. 2015 Sep 1;116(5):749-56.
53. Glower D, Ailawadi G, Argenziano M, Mack M, Trento A, Wang A, et al. EVEREST II randomized clinical trial: predictors of mitral valve replacement in de novo surgery or after the MitraClip procedure. Journal of Thoracic & Cardiovascular Surgery. 2012 Apr;143(4 Suppl):S60-3.
54. Cheng R, Tat E, Siegel RJ, Arsanjani R, Hussaini A, Makar M, et al. Mitral annular calcification is not associated with decreased procedural success, durability of repair, or left ventricular remodelling in percutaneous edge-to-edge repair of mitral regurgitation. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2016 Oct 20;12(9):1176-84.

55. Braun D, Lesevic H, Orban M, Michalk F, Barthel P, Hoppe K, et al. Percutaneous edge-to-edge repair of the mitral valve in patients with degenerative versus functional mitral regurgitation. Catheterization & Cardiovascular Interventions. 2014 Jul 1;84(1):137-46.
56. Calvert MJ, Freemantle N, Cleland JG. The impact of chronic heart failure on health-related quality of life data acquired in the baseline phase of the CARE-HF study. Eur J Heart Fail. 2005 Mar 2;7(2):243-51.
57. Feldman T, Young A. Percutaneous approaches to valve repair for mitral regurgitation. Journal of the American College of Cardiology. 2014 May 27;63(20):2057-68.
58. Office for National Statistics. Statistical bulletin: Deaths registered in England and Wales: 2016. 2017 [cited 2017 6th December]; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregistrationsummarytables/2016#decrease-in-deaths-at-ages-75-and-over
59. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Kober L, Squire IB, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J. 2013 May;34(19):1404-13.
60. De Bonis M, Taramasso M, Lapenna E, Denti P, La Canna G, Buzzatti N, et al. MitraClip therapy and surgical edge-to-edge repair in patients with severe left ventricular dysfunction and secondary mitral regurgitation: mid-term results of a single-centre experience+. European Journal of Cardio-Thoracic Surgery. 2016 Jan;49(1):255-62.
61. Abbot Vascular. MitraClip Transcatheter Mitral Valve Repair. 2017 [cited 2017 7th December]; Available from: https://www.vascular.abbott/us/products/structural-heart/mitraclip-mitral-valve-repair.html
62. Nickenig G, Schueler R, Dager A, Martinez Clark P, Abizaid A, Siminiak T, et al. Treatment of Chronic Functional Mitral Valve Regurgitation With a Percutaneous Annuloplasty System. J Am Coll Cardiol. 2016 Jun 28;67(25):2927-36.
63. Swaans MJ, Bakker ALM, Alipour A, Post MC, Kelder JC, de Kroon TL, et al. Survival of transcatheter mitral valve repair compared with surgical and conservative treatment in high-surgical-risk patients. Jacc: Cardiovascular Interventions. 2014 Aug;7(8):875-81.
64. Conradi L, Treede H, Rudolph V, Graumuller P, Lubos E, Baldus S, et al. Surgical or percutaneous mitral valve repair for secondary mitral regurgitation: comparison of patient characteristics and clinical outcomes. European Journal of Cardio-Thoracic Surgery. 2013 Sep;44(3):490-6; discussion 6.
65. Buzzatti N, Maisano F, Latib A, Taramasso M, Denti P, La Canna G, et al. Comparison of outcomes of percutaneous MitraClip versus surgical repair or replacement for degenerative mitral regurgitation in octogenarians. American Journal of Cardiology. 2015 Feb 15;115(4):487-92.
66. Deuschl F, Schofer N, Lubos E, Blankenberg S, Schafer U. Critical evaluation of the MitraClip system in the management of mitral regurgitation. Vasc Health Risk Manag. 2016;12:1-8.
67. Vemulapalli S, Lippmann SJ, Krucoff M, Hernandez AF, Curtis LH, Foster E, et al. Cardiovascular events and hospital resource utilization pre- and post-transcatheter mitral valve repair in high-surgical risk patients. American Heart Journal. 2017 Jul;189:146-57.
68. Mealing S, Feldman T, Eaton J, Singh M, Scott DA. EVEREST II high risk study based UK cost-effectiveness analysis of MitraClip in patients with severe mitral regurgitation ineligible for conventional repair/replacement surgery. Journal of Medical Economics. 2013 Nov;16(11):1317-26.
69. Cameron HL, Bernard LM, Garmo VS, Hernandez JB, Asgar AW. A Canadian cost-effectiveness analysis of transcatheter mitral valve repair with the MitraClip system in high surgical risk patients with significant mitral regurgitation. Journal of Medical Economics. 2014 Aug;17(8):599-615.
70. Armeni P, Boscolo PR, Tarricone R, Capodanno D, Maggioni AP, Grasso C, et al. Real-world cost effectiveness of MitraClip combined with Medical Therapy Versus Medical therapy alone in patients with moderate or severe mitral regurgitation. International Journal of Cardiology. 2016 Apr 15;209:153-60.
71. Glower DD, Kar S, Trento A, Lim DS, Bajwa T, Quesada R, et al. Percutaneous mitral valve repair for mitral regurgitation in high-risk patients: results of the EVEREST II study. Journal of the American College of Cardiology. 2014 Jul 15;64(2):172-81.

72. Palmieri V, Baldi C, Di Blasi PE, Citro R, Di Lorenzo E, Bellino E, et al. Impact of DRG billing system on health budget consumption in percutaneous treatment of mitral valve regurgitation in heart failure. Journal of Medical Economics. 2015 Feb;18(2):89-95.
73. Guerin P, Bourguignon S, Jamet N, Marque S. MitraClip therapy in mitral regurgitation: a Markov model for the cost-effectiveness of a new therapeutic option. Journal of Medical Economics. 2016 Jul;19(7):696-701.
74. Asgar AW, Khairy P, Guertin M-C, Cournoyer D, Ducharme A, Bonan R, et al. Clinical outcomes and economic impact of transcatheter mitral leaflet repair in heart failure patients. Journal of Medical Economics. 2017 Jan;20(1):82-90.
75. AHRQ. Role of Single Group Studies in Agency for Healthcare Research and Quality Comparative Effectiveness Reviews. 2013.
76. McAlister NH, McAlister NK, Buttoo K. Understanding cardiac "echo" reports. Practical guide for referring physicians. Can Fam Physician. 2006 Jul;52:869-74.
77. National Clinical Guideline Centre. Preoperative tests Routine preoperative tests for elective surgery. Appendix M: Economic considerations for Delphi. 2016 [cited 2018 3rd January]; Available from: https://www.nice.org.uk/guidance/ng45/evidence/appendix-m-economic-considerations-for-delphi-pdf-87258149464
78. Information service Division. Theatre Services. October 2016. 2016 [cited 2018 3rd January]; Available from: http://www.isdscotland.org/Health-Topics/Finance/Costs/Detailed-Tables/Theatres.asp
79. BNF. British National Formularly Online. 2017 June 2017 [cited 2017 18th December]; Available from: https://www.bnf.org/products/bnf-online/

Appendix 1 – Data flow diagram



Appendix 2 – Patient characteristics

Patient characteristics for all eligible MitraClip patients and those with recorded information from follow-up appointments.

Patient characteristic†	All eligible MitraClip patients (n=199)	All patients with device implanted and follow-up recorded (n=170)	P-value
Female	62 (31.2%)	51 (30.0%)	0.83
Age, years median (Q1,Q3) [range]	78 (69,85) [37-94]	79 (69,85) [37-94]	1.00
Body surface area median (Q1,Q3) [range]	1.9 (1.7,2.0) [1.4-2.4]	1.9 (1.7-2.0) [1.4-2.4]	0.95
Ethnic origin:			1.00
Caucasian	179 (91.3%)	152 (91.0%)	
Black	3 (1.5%)	3 (1.8%)	
Asian	11 (5.6%)	9 (5.4%)	
Other	3 (1.5%)	3 (1.8%)	
eGFR median (Q1,Q3) [range]	57.0 (42.0, 72.2) [6.1-117.1]	57.0 (41.8,71.8) [6.1-117.1]	0.83
Dialysis	5 (2.5%)	3 (1.8%)	0.73
Smoking status:			1.00
Never smoked	93 (53.4%)	81 (54.0%)	
Ex-smoker	77 (44.3%)	66 (44.0%)	
Current smoker	4 (2.3%)	3 (2.0%)	
Diabetes	36 (18.1%)	32 (18.8%)	0.89
Hypertension	104 (53.3%)	87 (52.4%)	0.92
Previous neurological disease	26 (13.1%)	24 (14.1%)	0.88
Peripheral vascular disease (PVD)	28 (14.4%)	26 (15.6%)	0.77
Previous myocardial infarction (MI)			0.96
No	117 (59.7%)	98 (58.3%)	
Yes (within 90 days)	8 (4.1%)	4 (4.27%)	
Yes (> 90 days)	71 (36.2%)	63 (37.5%)	
Critical pre-op status	5 (2.6%)	3 (1.8%)	0.73
CCS angina status			0.99
No angina	147 (75.0%)	125 (73.5%)	
No limitation of physical activity	22 (11.2%)	19 (11.2%)	
Slight limitation of ordinary activity	17 (8.7%)	16 (9.4%)	
Marked limitation of ordinary physical activity	9 (4.6%)	9 (5.3%)	
Symptoms at rest or minimal activity	1 (0.5%)	1 (0.6%)	
NYHA dyspnoea status			0.90
No limitation of physical activity	3 (1.5%)	3 (1.8%)	
Slight limitation of ordinary physical activity	12 (6.1%)	10 (5.9%)	
Marked limitation of ordinary physical activity	124 (62.6%)	112 (65.9%)	
Symptoms at rest or minimal activity	59 (29.8%)	45 (26.5%)	
Killip class			0.93
No clinical signs of heart failure	128 (67.7%)	114 (69.9%)	
Rales in lungs/S3/elevated JVP but not class 3	46 (24.3%)	39 (23.9%)	
Acute pulmonary oedema	14 (7.4%)	10 (6.1%)	
Cardiogenic shock	1 (0.5%)	0 (0.0%)	
CSHA frailty score			0.86
Very fit/Well/Well with treated comorbidities	48 (28.1%)	46 (30.1%)	
Apparently vulnerable/Mildly frail	54 (31.6%)	50 (32.7%)	
Moderately/Severely frail	69 (40.4%)	57 (37.3%)	
Katz index of independence			0.98
0	4 (2.4%)	3 (2.1%)	
2	3 (1.8%)	1 (0.71%)	
3	3 (1.8%)	3 (2.1%)	
4	12 (7.2%)	10 (6.8%)	
5	6 (3.6%)	5 (3.4%)	
6	139 (83.2%)	124 (84.9%)	
6 minute walk test, m median (Q1,Q3) [range]	190 (108,294) [0-450]	195 (115,291) [0-450]	0.85

Patient characteristic†	All eligible MitraClip patients (n=199)	All patients with device implanted and follow-up recorded (n=170)	P-value
Previous PCI	45 (23.1%)	39 (23.2%)	1.00
Previous cardiac surgery	78 (39.6%)	66 (39.1%)	1.00
Severe liver disease	1 (0.5%)	1 (0.6%)	1.00
History of pulmonary disease	51 (26.0%)	43 (25.6%)	1.00
Previous electric device therapy	51 (25.8%)	48 (28.2%)	0.64
Heart rhythm pre-op			0.97
Sinus rhythm	80 (40.6%)	66 (39.1%)	
Atrial fibrillation/flutter	93 (47.2%)	80 (47.3%)	
Paced	17 (8.6%)	16 (9.5%)	
Other	7 (3.6%)	7 (4.1%)	
Severity of mitral regurgitation (MR)			0.93
Grade 2 (mild-moderate)	1 (0.5%)	1 (0.6%)	
Grade 3 (moderate-severe)	20 (10.1%)	18 (10.6%)	
Grade 4 (severe)	178 (89.4%)	151 (88.8%)	
MR aetiology			0.91
Functional/ischaemic	117 (60.0%)	101 (60.8%)	
Degenerative	78 (40.0%)	65 (39.2%)	
MR jet area			0.99
Grade 1	1 (0.6%)	1 (0.7%)	
Grade 2	3 (1.8%)	3 (2.1%)	
Grade 3	31 (18.6%)	26 (18.2%)	
Grade 4	121 (72.5%)	102 (71.3%)	
Unknown or not applicable	11 (6.6%)	11 (7.7%)	
Heart rate at time of echo, beats per minute median (Q1,Q3) [range]	71 (65,83) [44-114]	70 (65,81) [44-114]	0.83
LVIDd, mm median (Q1,Q2) [range]	57 (51,63) [35-81]	57 (51,63) [35-81]	0.87
LVIDs, mm median (Q1,Q2) [range]	43 (32,50) [18-76]	45 (33,51) [18-76]	0.74
Peak TR velocity, m/s median (Q1,Q2) [range]	3.2 (2.8,3.6) [0.0-4.6]	3.2 (2.8,3.6) [0.0-4.6]	0.84
PA systolic pressure, mmHg median (Q1,Q2) [range]	46 (37,62) [20-100]	48 (38,62) [20-100]	0.74
TAPSE, cm median (Q1,Q2) [range]	1.6 (1.3,1.9) [0.5-3.0]	1.6 (1.3,1.9) [0.5-3.0]	0.77
LVEF			0.94
Good (≥55%)	66 (39.5%)	53 (36.1%)	
Mild impairment (45-54%)	31 (18.6%)	28 (19.0%)	
Moderate impairment (30-44%)	39 (23.4%)	37 (25.2%)	
Severe impairment (<30%)	31 (18.6%)	29 (19.7%)	
Estimate of TR severity			0.99
No TR	14 (8.6%)	13 (9.2%)	
Mild	75 (46.0%)	67 (47.2%)	
Moderate	50 (30.7%)	41 (28.9%)	
Severe	24 (14.7%)	21 (14.8%)	
Aortic regurgitation (regardless of prev. surgery)			0.97
None	88 (53.7%)	77 (54.2%)	
Mild	72 (43.9%)	61 (43.0%)	
Moderate	4 (2.4%)	4 (2.8%)	
Aortic stenosis (regardless of prev. surgery)			1.00
None	147 (91.3%)	127 (90.7%)	
Mild	11 (6.8%)	10 (7.1%)	
Moderate	3 (1.9%)	3 (2.1%)	
Coronary vessel disease			0.96
No vessel with >50% diameter stenosis	68 (65.4%)	59 (62.1%)	
1 vessel with >50% diameter stenosis	12 (11.5%)	12 (12.6%)	
2 vessels with >50% diameter stenosis	9 (8.7%)	9 (9.5%)	
3 vessels with >50% diameter stenosis	15 (14.4%)	15 (15.8%)	
Left main stem (LMS) disease			1.00
No LMS disease or LMS disease ≤50% diameter stenosis	92 (92.0%)	81 (91.0%)	
LMS>50% diameter stenosis	8 (8.0%)	8 (9.0%)	
BNP (pre-op), pg/ml median (Q1,Q3) [range]	376 (162,846) [13-2000]	353 (156-831) [13-2000]	0.78

Patient characteristic†	All eligible MitraClip patients (n=199)	All patients with device implanted and follow-up recorded (n=170)	P-value
Logistic EuroSCORE median (Q1,Q2) [range]	15.6 (9.6,27.1) [1.9-74.7]	15.0 (9.6,26.3) [1.9-74.7]	0.69
Logistic EuroSCOREII median (Q1,Q2) [range]	4.8 (3.0,7.6) [0.7-42.5]	4.7 (2.9,7.6) [0.7-42.5]	0.92
Betablocker (pre-op)	136 (73.9%)	120 (75.5%)	0.80
ACE-I/ARB (pre-op)	133 (72.3%)	114 (71.7%)	0.90
Aldosterone antagonist (pre-op)	49 (26.6%)	47 (29.6%)	0.55
Loop diuretic (pre-op)	146 (79.3%)	126 (79.2%)	1.00
Metolazone/thiazide diuretic	26 (14.1%)	23 (14.5%)	1.00
Digoxin	40 (21.7%)	34 (21.4%)	1.00
Ivabradine	8 (4.3%)	8 (5.0%)	0.80

Note:
† Not all data fields were complete for every patient at baseline and follow up. The percentages presented in this table are calculated using the number of patients with each characteristic reported as the denominator.

Appendix 3 – Procedural characteristics

Procedural details for all eligible MitraClip patients and those with recorded information from follow-up appointments.

Procedural characteristic†	All eligible MitraClip patients (n=199)	All patients with device implanted and follow-up recorded (n=170)	P-value
Treating hospital			0.59
Bristol Royal Infirmary	46 (23.1%)	42 (24.7%)	
Royal Brompton Hospital	94 (47.2%)	83 (48.8%)	
University Hospital of North Staffordshire (non-CtE)	15 (7.5%)	7 (4.1%)	
Wythenshawe Hospital	44 (22.1%)	38 (22.4%)	
Procedural urgency			0.50
Elective	168 (84.4%)	148 (87.1%)	
Urgent	27 (13.6%)	21 (12.4%)	
Emergency	4 (2.0%)	1 (0.6%)	
Anaesthesia			1.00
General anaesthesia	193 (98.0%)	164 (97.6%)	
Local anaesthesia ± sedation	4 (2.0%)	4 (2.4%)	
Intra-operative imaging‡			1.00
3D TOE	194 (97.5%)	166 (97.6%)	
2D TOE	3 (1.5%)	2 (1.2%)	
None	2 (1.0%)	2 (1.2%)	
Delivery approach			1.00
Femoral transvenous trans-septal (percutaneous)	191 (97.9%)	163 (98.2%)	
Femoral transvenous trans-septal (surgical cut-down)	2 (1.0%)	2 (1.2%)	
Femoral arterial (retrograde)	1 (0.5%)	1 (0.6%)	
Unknown or not applicable	1 (0.5%)	0 (0.0%)	
Large venous sheath, Fr median (Q1:Q3) [range]	18 (18,24) [1-26]	18 (18,22) [1-24]	0.66
IABP/Impella/CPB	0 (0.0%)	0 (0.0%)	NA
Cerebral protection	0 (0.0%)	0 (0.0%)	NA
Arterial sheath			0.89
Not used	117 (72.2%)	102 (72.9%)	
Used – femoral	37 (22.8%)	33 (23.6%)	
Used – radial/brachial	8 (4.9%)	5 (3.6%)	
No. of clips opened			0.86
1	54 (28.0%)	44 (25.9%)	
2	111 (57.5%)	103 (60.6%)	
3	24 (12.4%)	21 (12.4%)	
4	4 (2.1%)	2 (1.2%)	
No. of clips successfully deployed			0.96
1	58 (31.0%)	52 (30.6%)	
2	103 (55.1%)	96 (56.5%)	
3	26 (13.9%)	22 (12.9%)	
Venous closure technique			0.94
Manual/Compression	17 (8.8%)	13 (7.8%)	
Percutaneous/Device	166 (86.0%)	145 (86.8%)	
Surgical	1 (0.5%)	0 (0.0%)	
Other	9 (4.7%)	9 (5.4%)	
Arterial management			1.00
Manual/Compression	63 (87.5%)	56 (86.2%)	
Device	5 (6.9%)	5 (7.7%)	
Other	4 (5.6%)	4 (6.2%)	
Fluoroscopy time, mins median (Q1:Q3) [range]	32 (22,43) [8-79]	32 (22,43) [10-79]	0.87
X-ray dose, mGray.cm^2 median (Q1:Q3) [range]	3879 (3000,6948) [3000-20,000]	3757 (3000,6543) [3000-18,260]	0.66

Procedural characteristic†	All eligible MitraClip patients (n=199)	All patients with device implanted and follow-up recorded (n=170)	P-value
Contrast dose, ml median (Q1:Q3) [range]	0 (0,0) [0-105]	0 (0,0) [0-20]	0.67
Procedural duration, mins median (Q1:Q3) [range]	180 (137,221) [54-300]	184 (140,222) [62-300]	0.82
Time from procedure to extubation, mins median (Q1,Q3) [range]	210 (160,276) [72-10140]	210 (160,280) [78-935]	0.73
ITU days	38 (31.4%)	31 (28.2%)	0.67
Length of stay, days Median (Q1:Q3) [range]	5 (3.25,8) [0,46]	-	NA
Note: † Not all data fields were complete for every patient at baseline and follow up. The percentages presented in this table are calculated using the number of patients with each characteristic reported as the denominator. ‡ multiple choices permitted			

Appendix 4 – Outcomes

Outcomes for all eligible MitraClip patients.

	In-hospital (n=199)		After discharge (6w, 6m, 1y, 2y combined) (n=170)	
	Total no. of procedures (multiple events permitted)	**% [95% CI]**	**Total no. of procedures (multiple events permitted)**	**% [95% CI]**
Major complications:	**16**	**8.2 [4.7:12.9]**	**25**	**14.7 [9.7:20.9]**
Death	10	5.1 [2.5:9.2]	20	11.8 [7.3:17.6]
Neurological event	1	0.5 [0.0:2.8]	2	1.2 [0.1:4.2]
Additional surgery	3	1.5 [0.3:4.5]	4	2.4 [0.6:5.9]
Device embolisation (percutaneous retrieval)	1	0.5 [0.0:2.9]	0	0.0 [0.0:2.1]
MI	2	1.0 [0.1:3.7]	0	0.0 [0.0:2.1]
Endocarditis	0	0.0 [0.0:1.9]	0	0.0 [0.0:2.1]
Pericardial effusion/tamponade (requiring intervention)	0	0.0 [0.0:1.9]	NA	NA
Major vascular injury (requiring intervention)	0	0.0 [0.0:1.9]	NA	NA
MV complication	0	0.0 [0.0:1.9]	NA	NA
Oesophageal rupture	1	0.5 [0.0:3.0]	NA	NA
Major bleed	3	1.6 [0.3:4.6]	NA	NA
AKI (stage 2/3)	4	2.1 [0.6:5.3]	NA	NA
Cardiogenic shock	2	1.1 [0.1:3.9]	NA	NA
Minor complications:	**15**	**7.6 [4.3:12.2]**	**22**	**12.9 [8.30:18.9]**
Device failure	0	0.0 [0.0:1.9]	NA	NA
Partial detachment	1	0.5 [0.0:2.9]	1	0.6 [0.0:3.2]
Pericardial effusion/tamponade (treated conservatively)	3	1.6 [0.3:4.5]	NA	NA
Thrombus	0	0.0 [0.0:1.9]	NA	NA
New moderate/severe mitral stenosis	3	1.8 [0.4:5.2]	21	12.4 [7.8:18.3]
Minor bleed	7	3.7 [1.5:7.5]	NA	NA
AKI (stage 1)	1	0.5 [0.0:3.0]	NA	NA
Minor vascular complication	0	0.0 [0.0:1.9]	NA	NA
Any complication	**30**	**15.2 [10.5:20.9]**	**44**	**25.9 [19.5:33.1]**
Device implanted	**187**	**94.0 [89.7:96.8]**	NA	NA
Procedural success (device implanted in absence of major complications)	**171**	**85.9 [80.3:90.4]**	NA	NA
New requirement for permanent pacing	**3**	**1.6 [0.3:4.7]**	NA	NA

Note:
NA Not applicable

Appendix 5 – Outcomes for elective/emergency cases

	Elective (n=168)		Urgent/Emergency (n=31)	
	Total no. of patients	**% [95% CI]**	**Total no. of patients**	**% [95% CI]**
In-hospital major complications	10	6.1 [2.9:10.9]	6	19.4 [7.5:37.5]
In-hospital minor complications	14	8.4 [4.7:13.7]	1	3.2 [0.1:16.7]
Device implanted	158	94.0 [89.3:97.1]	29	93.5 [78.6:99.2]
New requirement for permanent pacing	3	1.9 [0.4:5.6]	0	0.0 [0.0:11.9]
Major complications (after discharge)	21	14.2 [9.0:20.9]	4	18.2 [5.2:40.3]
Minor complications (after discharge)	21	14.2 [9.0:20.9]	1	4.5 [0.1:22.8]

Appendix 6 – Outcomes (time to event analysis)

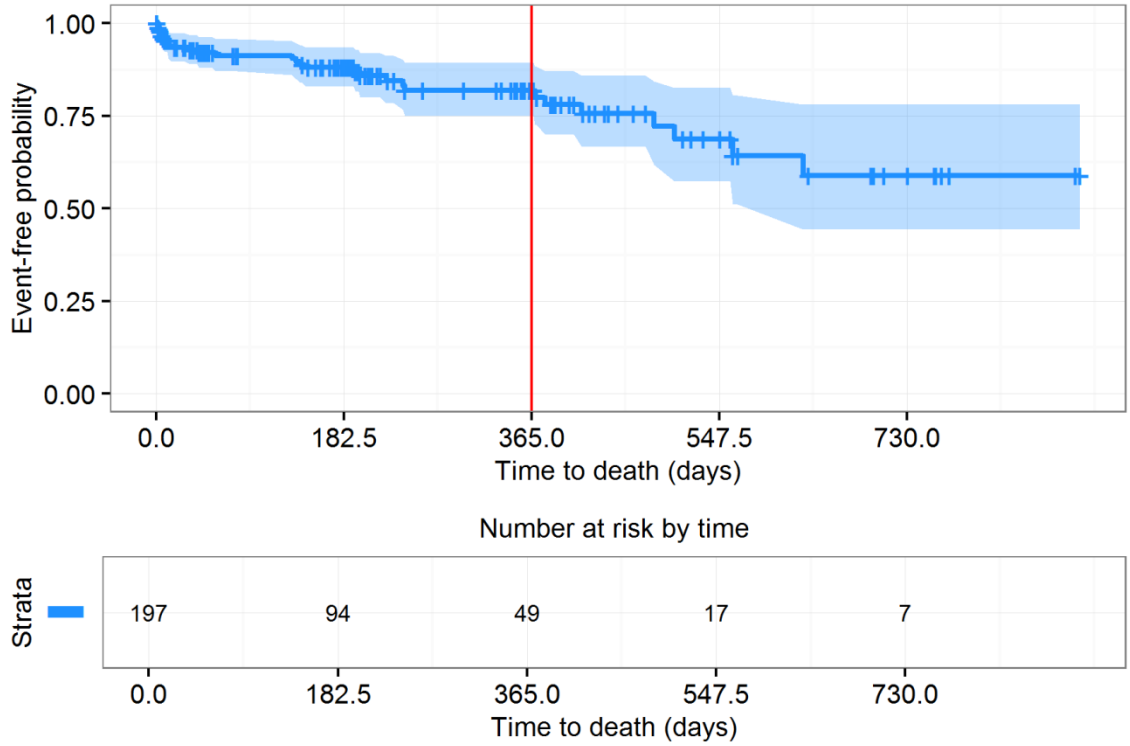
Patient outcomes (in-hospital and after discharge as reported at any follow-up combined) for all eligible MitraClip patients.

	No. of patients with event	**Total follow-up (person years)**	**Event rate (per 100 person years follow-up) [95%CI]**	**No. of patients at risk at 1-year**	**1-year event-free probability (95%CI)**
Death	30 (15.1%)	111.2	27.0 [18.2:38.5]	49	0.818 (0.750 to 0.894)
MV intervention	3 (1.8%)	96.8	3.1 [0.6:9.1]	42	0.967 (0.927 to 1.000)
Infective endocarditis	0 (0.0%)	-	-	-	-

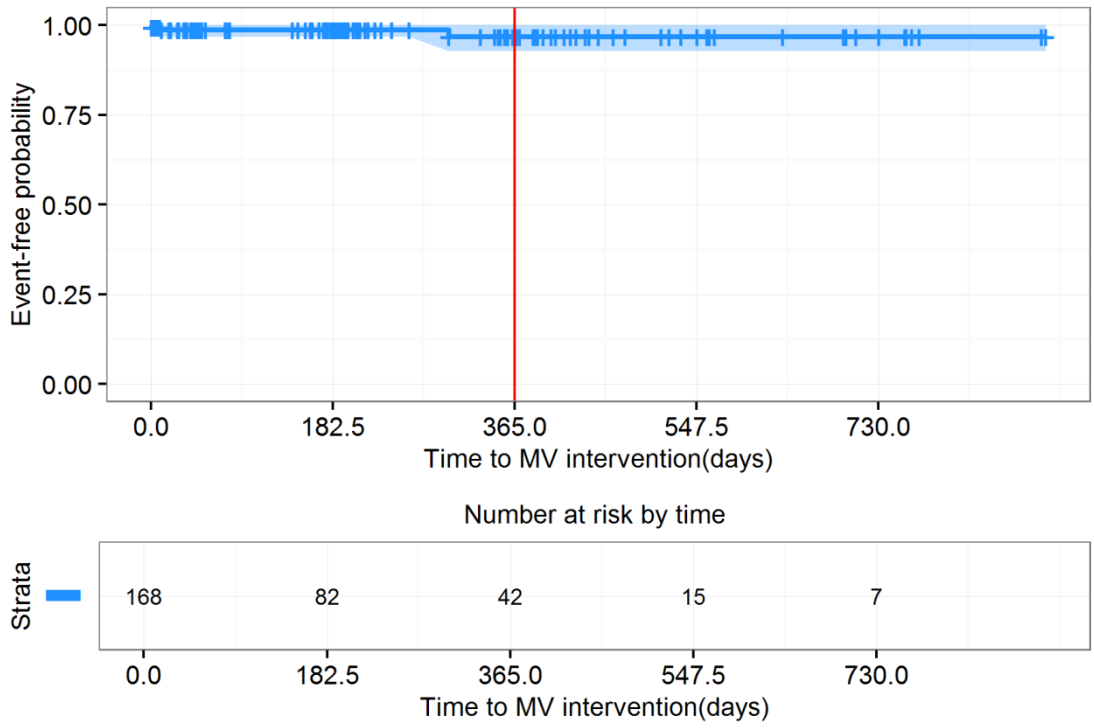
Appendix 7 – Kaplan-Meier curves

Kaplan-Meier curve for death (a) and MV intervention (b): Time to event (solid lines), corresponding 95% confidence limits (shaded area), and proportions of patients event-free at 1 year (red line).

a. Mortality.

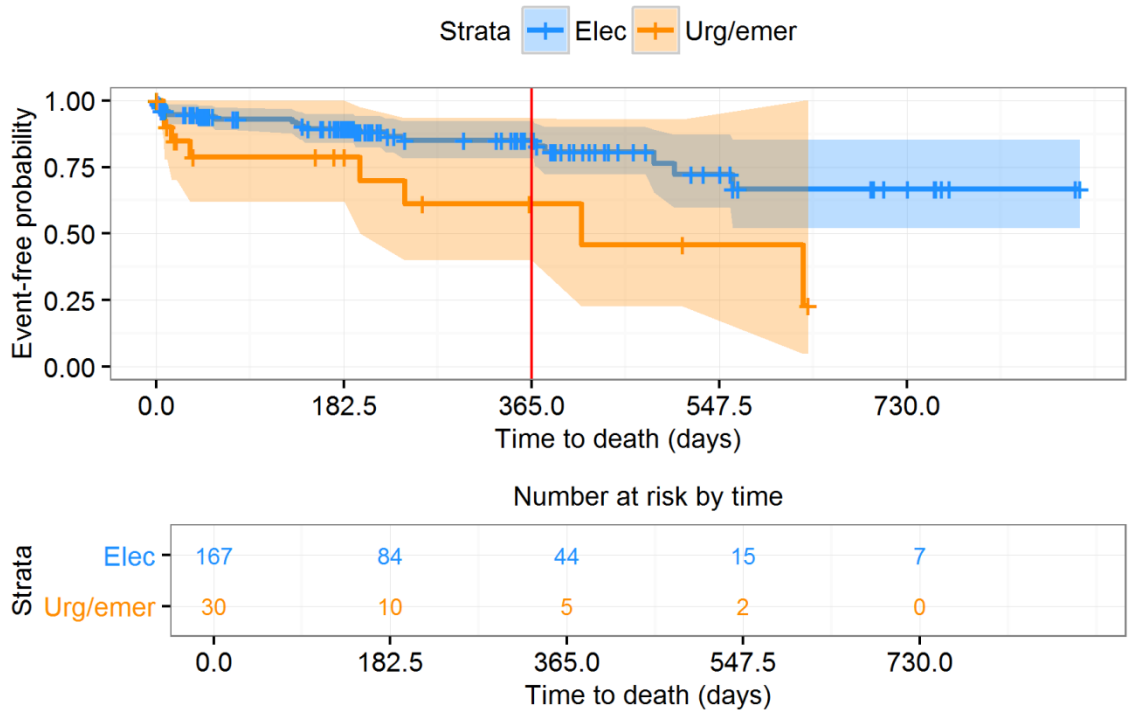


b. MV intervention.

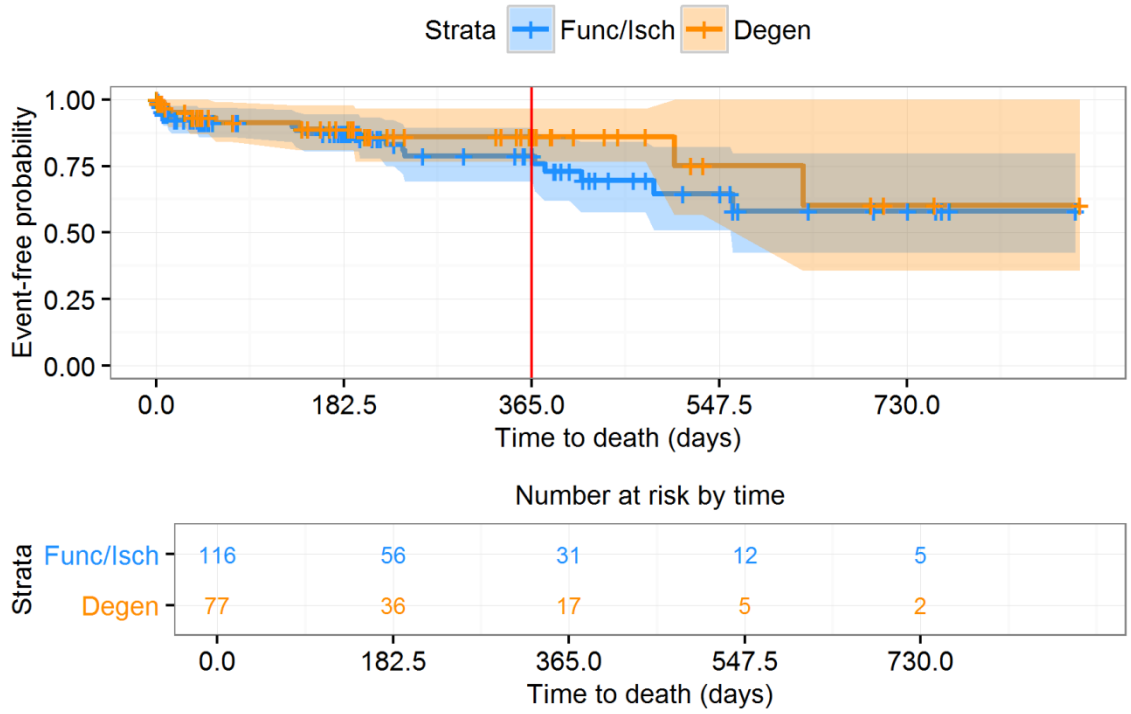


Kaplan-Meier curve for death in the elective versus urgent/emergency cohorts (c), plus the functional/ischaemic MR versus degenerative MR cohorts (d): Time to event (solid lines), corresponding 95% confidence limits (shaded area), and proportions of patients event-free at 1 year (red line).

c. Urgency of intervention.



d. Aetiology of MR.



Appendix 8 – Mitral regurgitation over time

Mitral regurgitation grade over time [* denotes significant difference when compared to pre-procedure grade]

	Pre-op (n=187)	**Post-op (n=178)**	**Discharge (n=174)**	**6 weeks (n=144)**	**6 months (n=107)**	**1 year (n=62)**	**2 years (n=10)**
None	0 (0.0%)	21 (11.8%)	38 (21.8%)	2 (1.4%)	2 (1.9%)	1 (1.6%)	0 (0.0%)
Mild	0 (0.0%)	102 (57.3%)	60 (34.5%)	47 (32.6%)	35 (32.7%)	24 (38.7%)	7 (70.0%)
Mild/Moderate	1 (0.5%)	43 (24.2%)	59 (33.9%)	61 (42.4%)	50 (46.7%)	22 (35.5%)	2 (20.0%)
Moderate/Severe	19 (10.2%)	10 (5.6%)	13 (7.5%)	25 (17.4%)	16 (15.0%)	12 (19.4%)	1 (10.0%)
Severe	167 (89.3%)	2 (1.1%)	4 (2.3%)	9 (6.2%)	4 (3.7%)	3 (4.8%)	0 (0.0%)
Fisher's exact P-value [n pairs]	reference	P<0.0001* [n=178]	P=0.0005* [n=174]	P<0.0001* [n=144]	P<0.0001* [n=107]	P<0.0001* [n=62]	P<0.0001* [n=10]

Appendix 9 – Cost of a MitraClip procedure

Table A.9.1 identifies all the inputs and sources used to calculate the central cost. Table A.9.2 provides information on the sensitivity analyses conducted to provide high and low cost ranges.

Table A.9.1 Cost of pathway for a MitraClip procedure

Parameter	Usage	Unit cost	% patients	Total cost	Source
MitraClip pre-operative assessment costs					
Consultant cardiologist	50 mins	£104.00 per hr	100%	£86.67	1 MDT of 2 cardiologists and 1 nurse for 15 mins per patient + pre-assessment clinic taking 20 mins cardiologist and 60 mins nurse time advised by clinical experts. Costs from PSSRU [13].
Nurse band 6	75 mins	£44.00 per hr	100%	£55.00	
Echocardiogram with contrast	1	£87.83	100%	£87.83	Imaging use from clinical experts; costs from NHS Reference costs [77]
ECG	1	£40.35	100%	£40.35	
TOE (day case)	1	£506.30	100%	£506.30	
Blood gases	1	£6.42 - £9.84	100%	£8.13	Tests from clinical experts; costs from 'Preoperative tests' by National Clinical Guideline Centre [77]
FBC	1	£3.00	100%	£3.00	Tests from clinical experts; costs from NHS Reference costs [12]
U&E	1	£3.00	100%	£3.00	
Sub-total pre-operative assessment costs			**£790**		All costs include overheads.
Peri-operative costs:					
Cardiologist	1.726 for 3.34 hours	£104.00 per hr	100%	£600.74	Operators from registry, cost PSSRU [13].
Registrar	0.274 for 3.01 hours	£40.00 per hr	100%	£33.03	
Anaesthetist	1 for for 3.01 hours	£105.00 per hr	100%	£316.40	Staffing structure from clinical experts; cost PSSRU [13]
Cath lab assistant band 3	1 for 3.01 hours s	£25.00 per hr	100%	£75.33	
Echocardiographer	0.75 for 3.01 hours	£46.00 per hr	100%	£103.96	
Nurse Band 6	1 for 3.34 hours	£44.00 per hr	100%	£147.25	
Nurse band 5	1 for 3.01 hours	£35.00 per hr	100%	£105.47	
Cardiac physiologist	0.75 for 3.01 hours	£46.00 per hr	100%	£103.96	
Radiographer	0.75 for 3.01 hours	£46.00 per hr	100%	£103.96	
Procedural time in theatre	180.80 mins.	£[redacted] per hr	100%	£[redacted]	Time from registry; cost from Information Services Division (ISD) cost of theatres excluding staff and consumables costs [78]
TOE or ICE	1	£1,437	100%	£1,437	Use from database; costed as EY502 complex echocardiogram for an elective inpatient from NHS Reference costs [12]

Parameter	Usage	Unit cost	% patients	Total cost	Source
X-ray	1	£27.00	45%	£12.15	Portsmouth NHS Trust
Anaesthetic drugs - desflurane & remifentanil	1	£82.18	100%	£82.18	Drugs agreed with clinical experts; price from a submitted template.
Heparin 2 hrs per surgery and 8/12 hrs after.	1	£5.80	100%	£5.80	
Cefuroxime X 2 1.5 g, 8 hours apart	1	£10.10	100%	£10.10	Drugs from clinical experts; costs from BNF [79]
Consumables	1	£[redacted]	100%	£[redacted]	Two well-completed templates totalled £877 and £909 ; used £900.
Device cost includes VAT and 15% overheads per procedure	1	£[redacted]	100%	£[redacted]	Cost of devices from manfacturer.
Sub-total peri-operative costs				**£27,707**	All costs include overheads.
Post-operative management					
Inpatient stay	7.76 days	£356 per day	100%	£2,765	Stay mean value from dataset; costed using mean cost for codes EY23A to C for Standard Other Percutaneous Transluminal Repair of Acquired Defect of Heart. Reference costs [12].
Transthoracic Echocardiogram	1	£1,437	0.77	£1,106	Use from database; costed as EY502 complex echocardiogram for an inpatient from NHS Reference costs [12].
Outpatient follow-up	1	£191	100%	£191	Use from clinical experts; cost Cardiac Surgery consultant-led outpatients. Reference costs [12]
Sub-total post-operative management				**£4,062**	
GRAND TOTAL				**£32,560**	All costs include overheads.

Table A.9.2 Low and high cost scenarios for pathway for a MitraClip procedure

Scenarios	Changes from central case	New cost
Pre-operative assessment central cost £790		
Low cost	Use first quartile cost for TOE (£185 vs central value £506) and 20% decrease in all other costs.	£412
High cost	Use third quartile cost for TOE (£657 vs central value £506) and 20% increase in all other costs.	£998
Peri-operative costs central cost £27,707		
Low cost	Use quartile 1 for procedure time, 20% decrease in all other costs except device.	£26,681
High cost	Use quartile 3 for procedure time, 20% increase in all other costs except device.	£28,714
Post-operative management central cost £4,062		
Low cost	Use length of stay time of 3 days and tariff cost for complex echocardiogram for congenital heart disease elective patient.	£1,697
High cost	Use 2 days length of stay and 20% increase in all other costs.	£4,407
Total cost central case and % accounted for by device:		**£32,560 ([redacted]%)**
Total case low cost and % accounted for by device		**£28,790 ([redacted]%)**
Total cost high cost and % accounted for by device		**£34,119 ([redacted]%)**

Thus the forecast cost for a MitraClip procedure ranges from about £28,800 to £34,100 with the device cost per procedure (£[redacted]) accounting for between [redacted]% to [redacted]% of the total cost.