CLINICAL PRIORITIES ADVISORY GROUP
20 May 2024

Agenda Item No	3.2
National Programme	Internal Medicine
Clinical Reference Group	Cardiac Services
URN	2254

Title
Transcatheter edge to edge repair/percutaneous mitral valve leaflet repair for moderately severe or severe secondary mitral regurgitation due to left ventricular dysfunction and/or dilatation (adults)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its relative prioritisation

Proposition
Service delegation status - Suitable for delegation. The proposition is transcatheter edge to edge repair/percutaneous mitral valve leaflet repair for moderately severe or severe secondary mitral regurgitation due to left ventricular dysfunction and/or dilatation within the criteria set out in the proposition document. The cause of mitral regurgitation is broadly divided into degenerative (or 'primary mitral regurgitation') where the valve itself is structurally abnormal, and functional (or 'secondary mitral regurgitation'), where the valve is structurally normal, but another condition affects the structure and/or function of the heart so that the valve cannot close properly. This proposition specifically relates to secondary mitral regurgitation (SMR) which is a functional problem due to Left Ventricular (LV) dysfunction or dilatation rather than a structural problem with the mitral valve. Moderate or severe SMR is present in approximately one-third of patients with heart failure and reduced left LV ejection fraction. NHS England already has a commissioning policy for percutaneous mitral valve leaflet repair for primary degenerative mitral regurgitation in adults (2019), and this

proposition would extend the commissioning position to include a wider cohort of patients.

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

The committee is asked to receive the following assurance:	
1.	The Deputy Director of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Deputy Director of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Director of Clinical Commissioning confirms that the service and operational impacts have been completed.

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

In the Population what is the clinical effectiveness and safety of the Intervention compared with Comparator?

Outcome	**Evidence statement**
Clinical effectiveness	
Critical outcomes	
Number of hospital admissions due to heart failure	This outcome is important to patients as it reflects how effective the treatment is compared to current standard of care and is a surrogate for control of symptoms and quality of life. In total, three systematic reviews and meta-analyses (SRMAs) and two randomised controlled trials (RCTs) provided evidence relating to hospital admissions due to heart failure in patients with secondary mitral regurgitation

Certainty of evidence: Very low to high	(SMR). All studies compared TEER combined with optimal medical therapy (OMT) with OMT alone. At 12 months: • One RCT (Obadia et al 2018) showed *no statistically significant difference* between those that received TEER (74/152, 48.7%) and those on OMT alone (72/152, 47.4%) in the risk of a hospital admission for heart failure at one year (HR 1.13, 95% CI 0.81 to 1.56). **(LOW)** Between 12 and 24 months: • One meta-analysis of two RCTs (Bertaina et al 2019) reported *no statistically significant difference* between treatment groups in the odds of hospital admission for heart failure (aOR 0.77, 95% CI 0.37 to 1.62, p=0.49). The model was adjusted for confounding factors; the confounders were not reported. Length of follow-up for the RCTs was not reported.[1] **(VERY LOW)** • A second meta-analysis of the same two RCTs (Lodhi et al 2019) reported *no statistically significant difference* between treatment groups in the risk of hospital admission for heart failure (HR 0.76, 95% CI 0.36 to 1.63, p=0.48). The median follow-up[2] for the RCTs was not reported. **(VERY LOW)** • One RCT (Iung al 2019) showed a *statistically significant* lower risk of hospital admission for heart failure between 12 and 24 months in those that received TEER (18.6/100 patient-years) compared to those on OMT alone (39.3/100 patient-years) (HR 0.47, 95% CI 0.22 to 0.98). **(LOW)** At 24 Months: • One RCT (Iung al 2019) reported *no statistically significant difference* between those that received TEER (55.9/100 patient-years) and those on OMT alone (62.3/100 patient-years) in the risk of a hospital admission for heart failure at two years (HR 0.97, 95% CI 0.72 to 1.30). **(VERY LOW)** • One RCT (Stone al 2018) reported a *statistically significant lower* risk of a hospital admission for heart failure at two years in those that received TEER (160/446.5 patient-years) compared to those on OMT alone (283/416.8 patient-years) (HR 0.53, 95% CI 0.40 to 0.70, p<0.001). Three patients needed to be treated with TEER compared with OMT alone to prevent one heart failure hospitalisation (NNT=3.1, 95% CI 1.9 to 7.9). **(HIGH)** **For patients that had TEER plus OMT, compared to patients that had OMT alone, one RCT provided high certainty evidence of a statically significantly lower risk of hospital admissions due to heart failure at 24 months follow-up and another RCT provided low certainty evidence of the same at 12 months and between 12 and 24 months follow-up. The latter RCT also provided very low certainty evidence of no statistically significant difference at 24 months follow-up. Two SRMAs that meta-analysed results from both RCTs provided very low certainty evidence of no statistically significant difference at between 12 and 24 months follow-up.**

[1] For all studies reported in Bertaina et al, 2 RCTs and 6 observational studies, the median follow-up was 438 days (IQR 360 to 625 days). Median follow-up for RCTs only was not reported for this outcome.

[2] For all studies reported in Lodhi et al, 2 RCTs and 5 observational studies, the median follow-up was 1.64 years. Median follow-up for RCTs only was not reported for this outcome.

Survival **Certainty of evidence:** Very low to high	This outcome is important to patients because it reflects how long people live after treatment, although it does not provide information about their health and wellbeing during that time. In total, three SRMAs and two RCTs provided evidence relating to survival in patients with SMR over a two-year follow-up period. The same studies provided evidence of cardiovascular mortality in patients with SMR from 12 to 24 months. All studies compared TEER combined with OMT with OMT alone. *All-Cause Mortality* At 30 days**:** • Two meta-analyses of two RCTs (Bertaina et al 2019 & Lodhi et al 2019) reported *no statistically significant difference* in odds of death at one month follow-up between those that received TEER and those on OMT alone (Bertaina: aOR 1.74, 95% CI 0.67 to 4.50, p=0.25) **(LOW)**; (Lodhi: OR 1.74, 95% CI 0.67 to 4.52, p=0.25). **(MODERATE)** • One of the SRMAs (Lodhi et al 2019) also reported *no statistically significant difference* in the risk of death at one month follow-up between those that received TEER and those on OMT alone (RR 1.72, 95% CI 0.66 to 4.36, p=0.26). **(VERY LOW)** At 12 months: • Two meta-analyses of two RCTs (Bertaina et al 2019 & Lodhi et al 2019) reported *no statistically significant difference* in odds of death at 12 months follow-up between those that received TEER and those on OMT alone (Bertaina: aOR 0.91, 95% CI 0.68 to 1.22, p=0.53) **(LOW)**; (Lodhi: OR 0.87, 95% CI 0.59 to 1.29, p=0.50). **(MODERATE)** • One of the SRMAs (Lodhi et al 2019) also reported *no statistically significant difference* in the risk of death at 12 months follow-up between those that received TEER and those on OMT alone (RR 0.90, 95% CI 0.66 to 1.23, p=0.51). **(LOW)** Between 12 and 24 months: • One meta-analysis of two RCTs (Bertaina et al 2019) reported *no statistically significant difference* between treatment groups in the risk of mortality (aOR 0.80, 95% CI 0.46 to 1.42, p=0.45). The model was adjusted for confounding factors; the confounders are not reported. Length of follow-up for the RCTs was not reported.[3] **(VERY LOW)** • One RCT (Iung al 2019) showed *no statistically significant difference* between those that received TEER (15.5/100 patient-years) and those on OMT alone (18.2/100 patient-years) in the risk of all-cause mortality between 12 and 24 months (HR 0.86, 95% CI 0.44 to 1.69). **(VERY LOW)** At 24 Months: • One meta-analysis of two RCTs (Zimarino et al 2020) showed *no statistically significant difference* between treatment groups in the risk of all-cause mortality at 24 months (HR 0.80, 95% CI 0.46 to 1.42, p=0.45). **(VERY LOW)** • One RCT (Iung al 2019) reported *no statistically significant difference* between those that received TEER (23.1/100 patient-years) and those on OMT alone (22.8/100 patient-years) in the risk of a mortality at two years (HR 1.02, 95% CI 0.70 to 1.50). **(VERY LOW)**

[3] For all studies reported in Bertaina et al, 2 RCTs and 6 observational studies, the median follow-up was 438 days (IQR 360 to 625 days). Median follow-up for RCTs only was not reported for this outcome.

	• One RCT (Stone et al 2018) reported a *statistically significantly lower* risk of mortality in those that received TEER + OMT (80/302, 29.1%[4]) compared to those on OMT alone (121/312, 46.1%) at 24 months (HR 0.62, 95% CI 0.46 to 0.82, p<0.001). **(MODERATE)** *Cardiovascular Mortality* Between 12 and 24 months: • One meta-analysis of two RCTs (Bertaina et al 2019) reported *no statistically significant difference* between treatment groups in the odds of cardiovascular mortality (aOR 0.78, 95% CI 0.43 to 1.42, p=0.41). The model was adjusted for confounding factors; the confounders were not reported. Length of follow-up was not reported for RCT studies.[5] **(VERY LOW)** • A second meta-analysis of the same two RCTs (Lodhi et al 2019) reported *no statistically significant difference* between treatment groups in the odds of cardiovascular mortality (OR 0.75, 95% CI 0.40 to 1.43, p=0.39). **(LOW)** The same meta-analysis reported *no statistically significant difference* between those that received TEER and OMT compared with those that had OMT only in the risk of cardiovascular mortality at the same time point (RR 0.81, 95% CI 0.50 to 1.31, p=0.38). Length of follow-up for the RCTs alone was not reported.[6] **(VERY LOW)** • One RCT (Iung al 2019) reported *no statistically significant difference* between those that received TEER (13.6/100 patient-years) and those on OMT alone (17.2/100 patient-years) in the risk of cardiovascular mortality between 12 and 24 months (HR 0.80, 95% CI 0.39 to 1.63). **(VERY LOW)** At 24 Months: • One SRMA including two RCTs (Zimarino et al 2020) reported *no statistically significant difference* in the risk of cardiovascular mortality between those that received TEER and OMT compared to those on OMT only at 24 months[7] (HR 0.78, 95% CI 0.43 to 1.42, p=0.41). **(VERY LOW)** • One RCT (Iung al 2019) reported *no statistically significant difference* between those that received TEER (20.5/100 patient-years) and those on OMT alone (21.1/100 patient-years) in the risk of cardiovascular mortality at two years (HR 0.99, 95% CI 0.66 to 1.48). **(VERY LOW)** • One RCT (Stone et al 2018) reported a *statistically significantly* lower risk of death related to heart failure in those that received TEER (28/302, 12.0%)[8] compared to those on OMT alone (61/312, 25.9%) at two years (HR 0.43, 95% CI 0.27 to 0.67, p <0.001). **(HIGH)** **One RCT provided moderate certainty evidence of a statistically significant lower overall mortality at 24 months in the TEER plus OMT group compared to the group on OMT alone and high certainty evidence of lower mortality related to heart failure in the same group; however, a different RCT and an SRMA of the two RCTs provided very low certainty evidence of no statistically significant difference between**

[4] Percentages are calculated using Kaplan-Meier methodology (estimates of event rate).
[5] For all studies reported in Bertaina et al, 2 RCTs and 6 observational studies, the median follow-up was 438 days (IQR 360 to 625 days). Median follow-up for RCTs only was not reported for this outcome.
[6] For all studies reported in Lodhi et al, 2 RCTs and 5 observational studies, the median follow-up was 1.64 years. Mean follow-up for RCTs only was not reported for this outcome.
[7] Mean follow-up 24 months (+/-15) months for all studies including observational studies. Mean follow-up for RCTs only was not reported for this outcome.
[8] Percentages are calculated using Kaplan-Meier methodology (estimates of event rate).

	treatment groups in overall mortality or cardiovascular mortality at 2 years follow up. One of the RCTs and two different SRMAs of the two RCTs between them provided very low to moderate certainty evidence that compared to OMT alone, TEER does not decrease overall mortality at up to 23 months follow-up or cardiovascular mortality at between 12 and 24 months.
NYHA grade **Certainty of evidence:** Low to moderate	This outcome is important to patients because reduction of grade will also mean reduction of symptoms. This directly improves the patient's quality of life. In total, two RCTs provided evidence relating to NYHA grade[9] at five time points across 24 months of follow up. Both studies compared TEER combined with OMT with OMT alone. At 30 days: • One RCT (Stone et al 2018) showed a *statistically significantly better* NYHA grade at 30 days in those that received TEER + OMT (n=283; NYHA I: 15.5%, II: 60.8%, III: 19.4%, IV: 3.5%) compared to those on OMT alone (n=281; NYHA I: 5.0%, II: 42.7%, III: 41.6%, IV: 9.6%) (p<0.001). **(MODERATE)** At 6 months: • One RCT (Stone et al 2018) showed a *statistically significantly better* NYHA grade at 6 months in those that received TEER + OMT (n=263; NYHA I: 19.4%, II: 52.9%, III: 21.3%, IV: 2.7%) compared to those on OMT alone (n=261; NYHA I: 5.4%, II: 44.8%, III: 38.3%, IV: 2.7%) (p<0.001). **(MODERATE)** At 12 months: • One RCT (Stone et al 2018) showed a *statistically significantly better* NYHA grade at 12 months in those that received TEER + OMT (n=237; NYHA I: 16.9%, II: 55.3%, III: 17.7%, IV: 2.5%) compared to those on OMT alone (n=232; NYHA I: 7.8%, II: 41.8%, III: 28.0%, IV: 4.7%) (p<0.001). **(MODERATE)** • One RCT (Obadia et al 2018) reported that there was no significant difference between NYHA groups at 12 months (TEER n=114; OMT, n=112) (p value not reported). **(LOW)** At 18 months: • One RCT (Stone et al 2018) showed a *statistically significantly better* NYHA grade at 18 months in those that received TEER + OMT (n=183; NYHA I: 12.6%, II: 53.6%, III: 20.2%, IV: 1.1%) compared to those on OMT alone (n=183; NYHA I: 8.2%, II: 38.3%, III: 20.2%, IV: 4.4%) (p<0.001). **(MODERATE)** At 24 Months: • One RCT (Stone et al 2018) showed a *statistically significantly better* NYHA grade at 24 months in those that received TEER + OMT (n=157; NYHA I: 12.1%, II: 42.7%, III: 21.7%, IV: 5.7%) compared to

[9] The New York Heart Association (NYHA) functional classification is a widely used tool for risk stratification on the basis of severity of symptoms and limitation of physical activity. It places patients in one of four categories: Class I — no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, breathlessness, or palpitations; Class II — slight limitation of physical activity. Comfortable at rest but ordinary physical activity results in undue breathlessness, fatigue, or palpitations; Class III — marked limitation of physical activity. Comfortable at rest but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations; Class IV — unable to carry out any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken discomfort is increased.

	those on OMT alone (n=153; NYHA I: 5.2%, II: 28.1%, III: 23.5%, IV: 3.3%) (p<0.001). **(MODERATE)** • One RCT (Iung et al 2019) reported that there was no significant difference between NYHA groups at 24 months (TEER n=90; OMT, n=87) (p value not reported). **(LOW)** **One RCT provided moderate certainty evidence that in those receiving TEER and OMT compared with those on OMT alone, NYHA grade is improved for up to 2 years follow up; a second RCT provided low certainty evidence of no significant difference in NYHA grades between the treatment groups at 12 and 24 months follow up.**
Important outcomes	
Health related quality of life (HRQL) **Certainty of evidence:** Low to moderate	This outcome is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived well-being and their ability to participate in activities of daily living. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. In total, two RCTs provided evidence relating to health-related quality-of-life (HRQL) at one year. Both studies compared TEER combined with OMT with OMT alone. At 12 months: • One RCT (Stone et al 2018) showed a *statistically significantly greater improvement* in patients' KCCQ scores[10] from baseline to 12 months in those that received TEER and OMT (n=237; mean score at 12 months: 66.4, sd: 28.6) compared to those on OMT alone, whose average score worsened (n=228; mean score at 12 months: 49.6, sd: 32.0)(adjusted mean change TEER: 12.5, sd 1.8; OMT: -3.6, sd 1.9; p<0.001). **(MODERATE)** • One RCT (Obadia et al 2018) reported similar results in EQ5D scores[11] for those that received TEER and OMT compared with those that had OMT alone at 12 months (60.8, sd 20.3 compared to 58.6, sd 18.2). The groups were not statistically compared. **(LOW)** **One RCT provided moderate certainty evidence that those receiving TEER and OMT had a statistically significantly improved HRQL at 12 months follow-up compared with those on OMT alone; a second RCT provided low certainty evidence of no difference in HRQL between the treatment groups at 12 months follow up (the two groups were not statistically compared).**
Pre discharge grading of mitral regurgitation **Certainty of evidence:**	This outcome is important to patients because reduction of severity will reflect how effective the treatment is, although it does not provide information about their symptom control and quality of life. In total, two RCTs provided evidence relating to pre-discharge grading of mitral regurgitation[12]. One RCT presented data only from the treatment group

[10] The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item self-administered questionnaire developed to independently measure the patient's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life (QoL) within a 2-week recall period. KCCQ responses are provided along a rating scale continuum (0 to 100) and frequently summarized in 25-point ranges: 0 to 24: very poor to poor; 25 to 49: poor to fair; 50 to 74: fair to good; and 75 to 100: good to excellent.
[11] The EQ5D is a measure of quality of life based on 5 dimensions: activities, anxiety, mobility, pain and self-care. A higher score indicates a better quality of life with a visual acuity scale ranging from 0 (worst imaginable health) to 100 (best imaginable health).
[12] MR is graded using echocardiogram on a scale of 0 to 4+: 0 (none or trace), 1+ (mild), 2+ (mild-to-moderate), 3+ (moderate-to-severe), 4+ (severe).

Very low to moderate	(TEER), the second RCT compared the TEER group with 30 day follow-up MR grading in those receiving OMT alone. • One RCT (Obadia et al 2018) reported that 95.1% of TEER patients had a reduction of at least one MR grade at the time of discharge (117/123); 91.9% had an MR grade of 2+ or lower following TEER (113/123) and 75.6% had an MR grade from 0+ to 1+ at the time of discharge following the TEER procedure (93/123). The groups were not statistically compared to OMT or baseline measures. **(VERY LOW)** • One RCT (Stone et al 2018) reported lower MR grading in patients treated with TEER at discharge (n=260, Grade 1+ or lower: 82.3%, 2+: 12.7%, 3+: 3.5%, 4+: 1.5%) compared with patients on OMT alone at 30 days (n=257, Grade 1+ or lower: 8.2%, 2+: 26.1%, 3+: 37.4%, 4+: 28.4%). The groups were not statistically compared. **(MODERATE)** **Two RCTs provided very low to moderate certainty evidence suggesting that the TEER procedure reduces mitral regurgitation grade in those with SMR; the data were not statistically compared.**
Duration/durability of mitral regurgitation reduction **Certainty of evidence:** Low to moderate	This outcome is important to patients because it gives an indicator of how long any changes in grade or symptom burden of SMR may last. One RCT provided evidence relating to durability of mitral regurgitation reduction at five time points and using two variables across 24 months of follow up. The study compared TEER combined with OMT therapy with OMT alone. *Mitral Regurgitation Severity* At 30 days: • One RCT (Stone et al 2018) showed a *statistically significantly lower* MR severity at 30 days in those that received TEER + OMT (n=273; Grade 0: 0.7%, 1+: 72.2%, 2+: 19.8%, 3+: 5.9%, 4+: 1.5%) compared to those on OMT alone (n=257; Grade 0: 0.8%, 1+: 7.4%, 2+: 26.1%, 3+: 37.4%, 4+: 28.4%) (p<0.001). **(MODERATE)** At 6 months: • One RCT (Stone et al 2018) showed a *statistically significantly lower* MR severity at 6 months in those that received TEER + OMT (n=240; Grade 0: 0.4%, 1+: 66.3%, 2+: 27.1%, 3+: 4.6%, 4+: 1.7%) compared to those on OMT alone (n=218; Grade 0: 0.5%, 1+: 8.7%, 2+: 28.9%, 3+: 42.2%, 4+: 19.7%) (p<0.001). **(MODERATE)** At 12 months: • One RCT (Stone et al 2018) showed a *statistically significantly lower* MR severity at 12 months in those that received TEER + OMT (n=210; Grade 0: 0.5%, 1+: 68.6%, 2+: 25.7%, 3+: 4.3%, 4+: 1.0%) compared to those on OMT alone (n=175; Grade 0: 1.1%, 1+: 10.3%, 2+: 35.4%, 3+: 34.3%, 4+: 18.9%) (p<0.001). **(MODERATE)** At 18 months: • One RCT (Stone et al 2018) showed a *statistically significantly lower* MR severity at 18 months in those that received TEER + OMT (n=141; Grade 0: 0.7%, 1+: 74.5%, 2+: 19.9%, 3+: 4.3%, 4+: 0.7%) compared to those on OMT alone (n=114; Grade 0: 0.9%, 1+: 11.4%, 2+: 28.1%, 3+: 41.2%, 4+: 18.4%) (p<0.001). **(MODERATE)** At 24 Months: • One RCT (Stone et al 2018) showed a *statistically significantly lower* MR severity at 24 months in those that received TEER + OMT

	(n=114; Grade 0: 0.9%, 1+: 76.3%, 2+: 21.9%, 3+: 0%, 4+: 0.9%) compared to those on OMT alone (n=76; Grade 0: 2.6%, 1+: 13.2%, 2+: 27.6%, 3+: 40.8%, 4+: 15.8%) (p<0.001). **(MODERATE)** *Unplanned mitral valve intervention* At 24 Months: • One RCT (Stone et al 2018) showed *no statistically significant difference* between those that received TEER + OMT (n=10/114) and those on OMT alone (n=15/76) in the risk of unplanned mitral-valve interventions[13] at 2 years. (HR 0.61, 95% CI 0.27 to 1.36, p=0.23). **(LOW)** **One RCT provided moderate certainty evidence of a statistically significantly lower mitral regurgitation severity in those with SMR following the TEER procedure compared to the group on OMT alone, and this was sustained for up to 24 months; the same study also provided low certainty evidence of no statistically significant difference in the number of unplanned mitral valve interventions.**
Functional outcomes **Certainty of evidence:** Low to moderate	This outcome is important to patients because it directly impacts independence and quality of life. In total, two RCTs provided evidence relating to functional outcomes, both using the 6-minute walk test[14] at one year. Both studies compared TEER combined with OMT therapy with OMT alone. At 12 months: • One RCT (Obadia et al 2018) showed little difference between those that received TEER and OMT (n=120; mean distance (metres) at 12 months: 339, sd: 151) and those on OMT alone (n=103; mean distance (metres) at 12 months: 363, sd: 157) in the change in the patients' 6 min walk test distance from baseline to 12 months (TEER: 25, IQR -40 to 71; OMT: 19, IQR -27 to 75). The groups were not statistically compared. **(LOW)** • A different RCT (Stone et al 2018) showed a *statistically significantly smaller deterioration* in patients' 6 min walk test distance from baseline to 12 months in those that received TEER and OMT (n=230; mean distance (m) at 12 months: 256.7, sd: 157.7) compared to those on OMT alone (n=237; mean distance (m) at 12 months: 188.8, sd: 166.7) (adjusted mean change TEER: -2.2, sd 9.1; OMT: -60, sd 9.0; p <0.001). **(MODERATE)** At 24 months: • One RCT (Iung et al 2019) reported similar results in 6 min walk tests for those that received TEER and OMT (n=120; mean distance (metres) at 24 months: 335, IQR 280 to 462) compared with those that had OMT only (n=103; mean distance (metres) at 24 months: 398, IQR 280 to 462[15]) and also in the change in the patients' 6 min walk test distance from baseline to 24 months (change from baseline to 24 months, TEER: 15, IQR -18 to 67; OMT: 22, IQR -6 to 94). The groups were not statistically compared. **(LOW)** **One RCT provided moderate certainty evidence of a statistically significantly smaller deterioration in functional outcomes as measured by the six minute walk test at 12 months for those who had TEER plus OMT compared with OMT alone. A second RCT provided low certainty**

[13] Additional / new MitraClip implantation and/or mitral-valve surgery.
[14] The six-minute walk distance test is usually performed on a treadmill and is the distance in metres that the patient can walk in 6 minutes. Benefit is indicated by a higher result.
[15] Likely to be incorrectly reported as the IQR is the same as reported for the TEER group.

	evidence of little difference between the two groups in six minute walk test distance at 12 and 24 months; the groups were not compared statistically.
Safety	
Procedural complications **Certainty of evidence:** Vey low to moderate	Safety is important to patients as it reflects the risks involved in undergoing TEER and allows a risk to benefit assessment to be undertaken. In total, two RCTs provided evidence relating to safety. Some outcomes were reported only for the treatment group (TEER); all other data compared TEER combined with OMT therapy with OMT alone. *Procedural complications* • One RCT (Obadia et al 2018) reported procedural complications for the device group (TEER); a total of 21/144 patients (14.6%) had surgical complications: device implantation failure (4.2%), haemorrhage resulting in transfusion or vascular complication resulting in surgical intervention (3.5%), atrial septum lesion or defect (2.8%), cardiogenic shock resulting in intravenous inotropic support (2.8%), cardiac embolism (1.4%), tamponade (1.2%). None of the patients required urgent conversion to heart surgery. **(MODERATE)** *Device related complications*[16] At 12 months: • One RCT (Stone et al 2018) reported that the rate of freedom from device related complications at 12 months of 96.9% (95% CI lower boundary 94.8%) was statistically significantly higher at 12 months than the safety goal of 80.0% adopted by the study (p <0.001). **(MODERATE)** *Adverse event rates* At 30 days: • One RCT (Stone et al 2018) reported little difference in adverse events at 30 days in patients in the TEER plus OMT group (n=302) compared to those treated with OMT alone (n=312) (Stroke: TEER 2, OMT 0; MI: TEER 3, OMT: 0) The groups were not statistically compared. **(MODERATE)** At 12 months: • One RCT (Obadia et al 2018) reported a set of pre-specified adverse events in those that received TEER plus OMT (n=152; total adverse events: 82.2%, heart transplantation or mechanical cardiac assistance: 3.9%, ischaemic or haemorrhagic stroke: 4.6%, MI: 0%, renal-replacement therapy: 3.3%, severe haemorrhage: 7.2%, infections: 18.4%) compared with those that received OMT alone (n=152; total adverse events: 79.6%, heart transplantation or mechanical cardiac assistance: 5.9%, ischaemic or haemorrhagic stroke: 0.7%, MI: 1.3%, renal-replacement therapy: 0.7%, severe haemorrhage: 3.9%, infections: 17.8%) at 12 months. The groups were not statistically compared. **(LOW)** At more than1 year: • One RCT (Iung et al 2019) reported the rate of a set of pre-specified adverse events at between 12 and 24 months follow up in those that received TEER plus OMT (n=152; rates per 100 patient-years; total

[16] A device related complication was defined as any occurrence of single-leaflet device attachment, embolization of the device, endocarditis that led to surgery, mitral stenosis (as confirmed by the echocardiographic core laboratory) that led to mitral-valve surgery, implantation of a left ventricular assist device, heart transplantation, or any other device-related event that led to nonelective cardiovascular surgery.

	adverse events: 6.8, heart transplantation or mechanical cardiac assistance: 1.7, ischaemic or haemorrhagic stroke: 0, MI: 0, renal-replacement therapy: 1.7, severe haemorrhage: 3.4, infections: 6.8) compared with those that received OMT alone (n=152; rates per 100 patient-years; total adverse events: 12.5, heart transplantation or mechanical cardiac assistance: 0, ischaemic or haemorrhagic stroke: 3.6, MI: 1.8, renal-replacement therapy: 1.8, severe haemorrhage: 0, infections: 5.4). The groups were not statistically compared. **(LOW)** • One RCT (lung et al 2019) reported a set of pre-specified adverse events at 24 months follow-up in those that received TEER plus OMT (n=152; rates per 100 patient-years; total adverse events: 84.9, heart transplantation or mechanical cardiac assistance: 4.6, ischaemic or haemorrhagic stroke: 4.6, MI: 0, renal-replacement therapy: 3.9, severe haemorrhage: 8.6, infections: 21.1) compared with those that received OMT alone (n=152; total adverse events: 82.1, heart transplantation or mechanical cardiac assistance: 5.8, ischaemic or haemorrhagic stroke: 1.9, MI: 1.9, renal-replacement therapy: 1.3, severe haemorrhage: 3.8, infections: 19.2). The groups were not statistically compared. **(LOW)** • One RCT (Stone et al 2018) reported *no statistically significant difference* in adverse events at 24 months in patients in the TEER plus OMT group (n=302) compared to those treated with OMT alone (n=312) for stroke and MI (Stroke: HR 0.96, 95% CI 0.42 to 2.22, p=0.93; MI: HR 0.82, 95% CI 0.38 to 1.78, p=0.62). **(VERY LOW)** **These studies provided very low to moderate certainty evidence of little difference in adverse event rates between those receiving TEER and those on OMT alone (statistical tests were only carried out for rates of MI and stroke). One RCT provided moderate certainty evidence that the rate of freedom from device related complications at 12 months was in the region of 96.9%, which was higher than the safety goal of 80.0% adopted by the study. A second RCT reported procedural surgical complications in 14.6% of patients (moderate certainty evidence).**

Abbreviations
aOR: adjusted odds ratio; CI: confidence interval; COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation Trial; HR: hazard ratio; HRQL: health related quality-of-life; IQR: interquartile range; KCCQ: The Kansas City Cardiomyopathy Questionnaire; m: metres; MI: myocardial infarction; MR: mitral regurgitation; NNT: number needed to treat; NYHA: New York Heart Association; OMT: optimal medical therapy; OR: odds ratio; RCT: randomised controlled trial; RR: relative risk; sd: standard deviation; SMR: secondary mitral regurgitation; SRMA: systematic review and meta-analysis; TEER: transcatheter edge to edge repair; TIA: transient ischaemic attack

In people with moderately severe to severe secondary mitral regurgitation what is the cost effectiveness of TEER combined with current standard care compared with current standard care alone?

Outcome	Evidence statement
Cost effectiveness	In total, two studies were found reporting on the cost effectiveness of TEER with OMT compared OMT alone in people with moderately severe to severe secondary mitral regurgitation from a UK NHS perspective. Both studies were mostly based on 2-year clinical and resource inputs from the COAPT trial (n=614).

	5-year time horizon: • One cost effectiveness study (Shore et al 2020) reported an incremental cost effectiveness ratio (ICER) of £63,608 per quality-adjusted life-year (QALY) gained. 10-year time horizon: • One cost effectiveness study (Shore et al 2020) reported an ICER of £37,440 per QALY gained. Lifetime time horizon: • One cost effectiveness study (Shore et al 2020) reported an ICER of £30,057 per QALY gained. • One cost effectiveness study (Cohen et al 2022) reported an ICER of £23,270 per QALY gained and 18% probably that the ICER was <£20,000 per QALY gained and 89% probability that it was <£30,000 per QALY gained. • Cohen et al (2022) also reported an ICER of £17,140 per life year gained and 76% probability that the ICER was <£20,000 per life year gained and 96% probability that it was <£30,000 per life year gained. **These studies provided evidence that the incremental cost effectiveness ratio of TEER with OMT compared with OMT alone in people with moderately severe to severe secondary mitral regurgitation from a UK NHS perspective ranged from £23,270 to £30,057 per QALY gained over a lifetime, £37,440 per QALY gained over 10 years and £63,608 per QALY gained over 5 years. In terms of life years gained, one study reported an ICER of £17,140 per life year gained over a lifetime time horizon.**
Abbreviations COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation Trial; ICER: incremental cost effectiveness ratio; NHS: National Health Service; OMT: optimised medical therapy; QALY: quality-adjusted life-year; TEER: transcatheter edge to edge repair; UK: United Kingdom	

From the evidence selected, are there any subgroups of patients that may benefit from TEER more than the wider population of interest?

Outcome	Evidence statement
Subgroups	Subgroup results by baseline NYHA grade[17] were reported from one RCT for all the critical, important and safety outcomes. Subgroup analysis was pre-planned in the RCT, and results were reported as TEER plus OMT vs OMT alone for the different patient subgroups. **Critical Outcomes** **Number of hospital admissions due to heart failure** • One RCT (Giustino et al 2020) reported a lower rate of hospitalisations related to heart failure at 24 months for patients that received TEER and OMT compared to patients on OMT alone across all NYHA baseline grades; NYHA Class II (TEER: 40 hospitalisations, 33.0%[18]; OMT: 51 hospitalisations, 51.3%; HR 0.57, 95% CI 0.38 to 0.86), NYHA III (TEER: 49, 35.9%; OMT: 84, 55.6%; HR 0.53, 95% CI 0.37 to 0.76), NYHA IV (TEER: 6, 40.9%; OMT: 22, 78.3%; HR

[17] The New York Heart Association (NYHA) functional classification is a widely used tool for risk stratification on the basis of the burden of heart failure symptoms related to the activities of daily life.
[18] Percentages are estimated using the Kaplan-Meier time-to-event methodology.

	0.34, 95% CI 0.14 to 0.86). The RCT reported *no statistically significant interaction* for the NYHA subgroups at 24 months; patients in the TEER plus OMT group had fewer hospitalisations than the OMT group and this was not influenced by baseline NYHA grade (p=0.55 for interaction). **Survival** • One RCT (Giustino et al 2020) reported a lower rate of death from any cause at 24 months for patients that received TEER and OMT versus patients on OMT alone across all NYHA baseline classifications; NYHA II (TEER: 31 deaths, 24.4%[19]; OMT: 42 deaths, 40.8%; HR 0.55, 95% CI 0.35 to 0.88), NYHA III (TEER: 44, 29.4%; OMT: 64, 41.2%; HR 0.71, 95% CI 0.48 to 1.04), NYHA IV (TEER: 8, 44.4%; OMT: 19, 61.2%; HR 0.64, 95% CI 0.28 to 1.46). The RCT reported *no statistically significant interaction* for the NYHA subgroups at 24 months; patients in the TEER plus OMT group had fewer deaths than the OMT group and this was not influenced by baseline NYHA grade (p=0.74 for interaction). • One RCT (Giustino et al 2020) reported a lower rate of death from heart failure at 24 months for patients that received TEER and OMT versus patients on OMT alone across all NYHA baseline classes; NYHA II (TEER: 9 deaths, 8.0%[20]; OMT: 18 deaths, 19.8%; HR 0.37, 95% CI 0.17 to 0.83), NYHA III / IV (TEER: 21, 14.4%; OMT: 45, 26.9%; HR 0.50, 95% CI 0.30 to 0.84). The baseline NYHA subgroups were not statistically compared. **NYHA Grade** • One RCT (Giustino et al 2020) reported *a statistically significantly better* NYHA grade at 24 months in those that received TEER combined with OMT compared with patients on OMT alone. This difference remained when stratifying by NYHA grade at baseline; For those in NYHA Class II at baseline (TEER n=88, OMT=74), numbers in each NYHA Class at 24 months were: NYHA I: TEER: 19, 21.6%; OMT: 8, 10.8%; NYHA II: TEER: 42, 47.7%; OMT: 28, 37.8%; NYHA III: TEER: 16, 18.2%; OMT: 19, 25.7%; NYHA IV: TEER: 11, 12.5%; OMT: 19, 25.7% (p=0.04); For those in NYHA Class III or IV at baseline (TEER n=118, OMT=130), numbers in each NYHA Class at 24 months were: NYHA I: TEER: 12, 10.2%; OMT: 4, 3.1%; NYHA II: TEER: 49, 41.5%; OMT: 41, 31.5%; NYHA III: TEER: 28, 23.7%; OMT: 34, 26.2%; NYHA IV: TEER: 29, 24.6%; OMT: 51, 39.2% (p=0.01). The baseline NYHA subgroups were not statistically compared. **Important Outcomes** **Health related quality of life (HRQL)** • One RCT (Giustino et al 2020) reported a *statistically significantly greater* improvement in patients' KCCQ scores[21] from baseline to 12 months in those that received TEER and OMT compared to those on OMT alone (whose average score worsened) for those who were in NYHA Class II at baseline (paired change TEER: 0.8, sd 31.5; OMT: -20.0, sd 33.2; p<0.0001), and in those in NYHA Class III or IV at

[19] Percentages are estimated using the Kaplan-Meier time-to-event methodology.
[20] Percentages are estimated using the Kaplan-Meier time-to-event methodology.
[21] The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item self-administered questionnaire developed to independently measure the patient's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life (QoL) within a 2-week recall period. KCCQ responses are provided along a rating scale continuum (0 to 100) and frequently summarized in 25-point ranges: 0 to 24: very poor to poor; 25 to 49: poor to fair; 50 to 74: fair to good; and 75 to 100: good to excellent.

	baseline (paired change TEER: 12.8, sd 36.5; OMT: -7.4, sd 34.2; p<0.0001). The baseline NYHA subgroups were not statistically compared. **Pre-discharge grading of mitral regurgitation** • One RCT (Giustino et al 2020) reported pre-discharge MR grading for the 260 COAPT trial patients that received the TEER intervention, stratified by NYHA grade at baseline. (All patients had an MR grade of 3+ or higher at baseline.) Of those categorised as NHYA Class II at baseline, 95.7% had an MR grade of 2+ or lower at hospital discharge (111/116); of those in NYHA Class III at baseline, the corresponding figures were 95.4% (122/128), and for those in NYHA Class IV at baseline they were 87.5% (14/16). Data for the OMT group were not reported. The baseline NYHA subgroups were not statistically compared. **Duration/durability of mitral regurgitation reduction** *Mitral Regurgitation Severity* • One RCT (Giustino et al 2020) reported *a statistically significantly lower* MR severity at 24 months in those that received TEER + OMT compared to those on OMT alone. This difference remained when stratifying by NYHA grade at baseline: For those in NYHA Class II at baseline: MR grade at 24 months was for the TEER group (n=76), Grade 0+: 1.3%, 1+: 80.3%, 2+: 17.1%, 3+: 0%, 4+: 1.3%; and for the OMT group (n=50) MR grade at 24 months was Grade 0+: 2.0%, 1+: 12.0%, 2+: 28.0%, 3+: 30.0%, 4+: 28.0%; p<0.0001; For those in NYHA Class III or IV at baseline: in the TEER group (n=86), MR grade at 24 months was Grade 0+: 1.2%, 1+: 74.4%, 2+: 24.4%, 3+: 0%, 4+: 0%; and in the OMT group (n=73), MR grade at 24 months was Grade 0+: 1.4%, 1+: 20.5%, 2+: 27.4%, 3+: 37.0%, 4+: 13.7%; p<0.0001. *Unplanned mitral-valve intervention* • One RCT (Giustino et al 2020) showed *a statistically significantly lower* risk of unplanned mitral-valve interventions[22] at 2 years in those that received TEER + OMT compared to those on OMT alone in those patients that were NYHA Class II at baseline (HR 0.12, 95% CI 0.01 to 0.97). The RCT reported *no statistically significant difference* between those that received TEER + OMT and those on OMT alone in the risk of unplanned mitral-valve interventions at 2 years in those patients that were NYHA Class III or IV at baseline (HR 0.89, 95% CI 0.37 to 2.15). The difference between the two baseline NYHA subgroups was *not statistically significant* (p=0.09 for interaction). **Functional Outcomes** *6 min walk test* • One RCT (Giustino et al 2020) showed *no statistically significant difference* between those that received TEER and OMT and those on OMT alone in the change in the patients' 6-minute walk test distance[23] from baseline to 12 months in those with an NYHA Class II at baseline (paired change from baseline: TEER (metres): -88.3, sd 161.3; OMT: -97.4, sd 175.4; p=0.64). For those with an NYHA Class III or IV at baseline, the RCT reported a *statistically significantly smaller* deterioration in 6-minute walk test distance at 12 months in

[22] Additional / new MitraClip implantation and/or mitral-valve surgery.
[23] The six-minute walk distance test is usually performed on a treadmill and is the distance in metres that the patient can walk in 6 minutes. Subjects who experienced a heart failure-related death prior to follow-up (or were unable to walk due to cardiac reasons) were assigned a score of 0 for the 6-min walk test.

	those that received TEER + OMT compared to those that received OMT alone (paired change from baseline: TEER (m): -33.3, sd 147.0; OMT: -86.4, sd 160.5; p=0.005). The baseline NYHA subgroups were not statistically compared. **Safety** *Adverse event rates* • One RCT (Giustino et al 2020) reported adverse events in the two patient groups, stratified by NYHA Classification (NYHA Class II: TEER n=130, OMT n=110; NYHA Class III/IV: TEER=172, OMT=201). The RCT reported *no statistically significant difference* in adverse events of stroke and MI at 24 months in patients in the TEER plus OMT group compared to those treated with OMT alone, stratified by baseline NYHA class. • Stroke: NYHA Class II: TEER 4.2%[24], OMT 6.3%, HR 0.77 (95% CI 0.22 to 2.66); NYHA Class III/IV: TEER 4.3%, OMT 6.6%, HR 0.66 (95% CI 0.24 to 1.81). The baseline NYHA subgroups were not statistically compared. • MI: NYHA Class II: TEER 5.2%, OMT 7.3%, HR 0.75 (95% CI 0.24 to 2.34); NYHA Class III / IV: TEER 4.6%, OMT 7.7%, HR 0.70 (95% CI 0.27 to 1.80); p=0.90 for interaction **One RCT compared outcomes in patients treated with TEER and OMT compared with OMT alone stratified by baseline NYHA grade and reported no difference in the effectiveness of TEER in terms of hospitalisations for heart failure, survival or unplanned mitral valve interventions or in the risk of MI in different baseline NYHA subgroups (no statistically significant interaction). For other effectiveness and safety outcomes, results by baseline NYHA grade were presented without statistical comparison.**
Abbreviations: CI: confidence interval; COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation Trial; HR: hazard ratio; HRQL: health related quality-of-life; KCCQ: The Kansas City Cardiomyopathy Questionnaire; K-M: Kaplan-Meier; m: metres; MI: myocardial infarction; MR: mitral regurgitation; NYHA: New York Heart Association; OMT: optimal medical therapy; RCT: randomised controlled trial; SMR: secondary mitral regurgitation; TEER: transcatheter edge to edge repair	

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **mobility:** patients with mitral regurgitation and left ventricular dysfunction commonly experience shortness of breath and reduced exercise tolerance which significantly negatively impacts mobility. This impacts activities of daily living, functional ability, quality of life and mental health. Left ventricular dysfunction is associated with increasing age, and the multiple admissions with decompensated heart failure that these patients experience can lead to significant deconditioning. • **ability to provide self-care:** patients with severe mitral regurgitation and left ventricular dysfunction experience reduced mobility and function. The progressive nature of the condition can mean patients can rapidly lose their

[24] Percentages are estimated using the Kaplan-Meier time-to-event methodology.

independence, become dependent on others for care and on the state for financial support.

- **undertaking usual activities:** The reduced mobility experienced by these patients, especially those with severe disease will severely impact on their ability to carry out their usual activities, activities of daily living, employment, and their ability to care for dependants (socially and financially). This is particularly relevant as patients with left ventricular dysfunction are often elderly and therefore are already at higher risk of frailty syndromes and their complications. Multiple and often prolonged hospital admissions have a negative impact on usual activities.
- **experience of pain/discomfort:** patients with mitral regurgitation and left ventricular dysfunction often experience shortness of breath upon minimal exertion. This is a highly uncomfortable symptom for these patients to live with.
- **experience of anxiety/depression:** Mental health problems, including or compounded by loneliness and isolation can be a consequence of a lack of mobility. This is especially relevant given left ventricular dysfunction is associated with age and patients risk becoming housebound if symptoms such as shortness of breath become severe.

Further details of impact upon patients:
The condition severely impacts all areas of everyday life given the symptom burden and the recurrent hospitalisations.

Further details of impact upon carers:
Those living with and caring for people with mitral regurgitation and left ventricular dysfunction are at increased risk of becoming the main care provider, helping with activities of daily living, as well as hospital appointments and emergency attendances for decompensated heart failure.

Considerations from review by Rare Disease Advisory Group
Not Applicable.

Pharmaceutical considerations
Not applicable.

Considerations from review by National Programme of Care
The proposal received the full support of the Internal Medicine PoC on 19th September 2023, and reviewed (with continued support) prior to submission in April 2024.