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Transapical implantation of artificial chordae in patients with primary mitral regurgitation

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Methods

Agenas is a public body. Its mission is to promote innovation and development within the Italian national healthcare service and provide an Early Awareness and Alert (EAA) service by Horizon Scanning (HS) activities in the field of new and emerging health technologies.
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A full description of the methods used for the production of the present HS report can be found at www.agenas.it

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Limitations

This report is based on information available when the searches were made and does not contain data on subsequent developments or improvements of the evaluated technology. The observations made on effectiveness, safety or cost-effectiveness of the technology evaluated in the report are to be considered current, but may change as more evidence becomes available if an update of the document is commissioned.

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Declaration of Conflict of Interest

The authors declare that they will not receive either benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

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Name of the technology/procedure: **Transapical implantation of artificial chordae in patients with primary mitral regurgitation**

Target population

Patients with severe mitral regurgitation (i.e., grade 3+ or 4+) who are candidates for mitral valve repair or replacement due to elongated or ruptured native chords.

Description of the procedure and technology

Transapical implantation of artificial chordae is performed via mini-thoracotomy, while the heart is beating, unlike highly-invasive sternotomy-based repair procedures. Using 2D and 3D echo guidance, the system is introduced through apex of the left ventricle and navigated to the mitral valve. The prolapsing segment of the dysfunctional mitral valve leaflet is grasped using the expandable jaws of the device. Leaflet capture is verified using a fiber optic monitor in real time. The suture is then deployed placing the artificial chordae on the free edge of the prolapsing segment of the mitral valve leaflet [NeoChord website].

Clinical importance and burden of disease

Mitral regurgitation (MR) occurs when the mitral valve does not close properly, allowing blood to flow backwards from the ventricle to the atrium. MR can be acute or chronic. The latter is a long-term disorder associated with valvular or ventricular pathologies.

In patients with chronic MR, the regurgitation causes left ventricular volume overload that overtime induces ventricular remodelling. Progressively, the excessive chamber dilatation is not compensated by adequate hypertrophy, with decreased myocardial contractility and efficiency [Maisano F, 2014]. An enlarged atrium may develop a rapid and disorganised movement (a disorder called atrial fibrillation), which reduces the heart's ability to pump efficiently [AHA]. Progressive myocardial degeneration may finally lead to irreversible dysfunction and end-stage heart failure (HF) [Beeri R, 2007]. According to the aetiology, MR can be primary (also named degenerative) or secondary (also named functional) [EUnetHTA JA2 Pilot SB-15]. Primary MR covers all aetiologies in which intrinsic lesions affect one or several components of the mitral valve apparatus and is the most common in western countries counting 60–70% of MR in patients undergoing surgery [Iung B, 2003; Nkomo VT, 2006; Enriquez-Sarano M, 2009].

The prevalence of MR varies across regions and is inversely proportional to its severity. In a population-based cohort study, transthoracic echocardiography found MR in 19% of men and women [Singh JP, 1999]. Whereas in another population-based study (Strong Heart Study) transthoracic echocardiography found moderate or severe MR in 1.9% and 0.2%, respectively [Jones EC, 2001]. Estimates of severe MR in the Italian population range from 8,528 to 32,000 new patients per year [Bedogni F, 2017].

Medical, interventional and surgical therapies are available to treat people with MR. The treatment of choice depends on the aetiology and severity of the condition but, for most people with severe chronic MR, is represented by surgical repair or replacement of the mitral valve.

Mitral valve repair is performed with different techniques, according to the type and location of the mitral lesion(s): leaflet resection, implantation of artificial chordae, chordal transposition/transfer, edge-to-edge technique, and annuloplasty using a prosthetic ring or band. Chordal replacement is a surgical repair approach commonly used to treat MR [Laing G, 2011]. However, in some cases, surgical treatment may be delayed or

deferred due to the presence of other medical conditions that increase the risk of surgery [Vahanian A, 2012].

Products, manufacturers, distributors and approval

We identified on the Italian market only one system for the transapical implantation of artificial chordae in patients with primary mitral regurgitation, the NeoChord DS1000 manufactured by NeoChord, Inc. The device is classified according the Classificazione Nazionale dei Dispositivi Medici (CND) under the class *"H9099 - DISPOSITIVI DA SUTURA – ALTRI"* and registered within the Italian National medical device database (RDM) with the number 980246. NeoChord DS 1000 received the CE mark in 2013 as intended for repair of chordal elongation and rupture resulting in mitral valve prolapse in patients with grade 3+ or 4+ mitral valve regurgitation who are candidates for surgical mitral valve repair or replacement [NeoChord IFU]. NeoChord DS1000 is not approved by the US FDA.

The NeoChord DS1000 is a single-use Risk Class III hand-held device designed to deploy commercially available expanded polytetrafluoroethylene (ePTFE) suture, labelled for the use as artificial chordae tendineae as an alternative to the conventional surgical approach for this type of mitral valve repair. The NeoChord DS1000 consists of the hand-held delivery instrument, in which an off-the-shelf ePTFE suture will be loaded, a needle, and includes a tethered Leaflet Capture Verification (LCV) monitor, which enables confirmation of leaflet capture in the distal clamp of the device prior to deploying the suture and knot at the leaflet [Maisano F, 2013; Chiam PTL, 2011; EUnetHTA JA2 Pilot SB-15; NeoChord IFU].

NeoChord DS1000 is contraindicated in heavily calcified valves, valvular retraction with severely reduced mobility, active bacterial endocarditis, complex mechanism of MR (leaflet perforation, etc.), significant tethering of leaflets, inflammatory valve disease. The NeoChord DS1000 has not been studied in a functional MR patients population and has not been studied in patients with anterior leaflet prolapse [EUnetHTA JA2 Pilot SB-15].

Product name [Manufacturer]	Distributor	CE Mark	RDM	FDA
NeoChord™ Artificial Chordae Delivery System Model DS1000 [NeoChord, Inc.]	Medical Instruments S.p.A.	☑	☑	☐

Setting

NeoChord DS1000 implantation is a cardiothoracic procedure performed within an operating room under general anaesthesia. After the procedure, the patient can be awakened and extubated in the operating theatre. Transfer to the intensive care unit is recommended for at least a couple of hours after surgery for full monitoring of the patient's condition. No specific postoperative antithrombotic therapy is required, unless otherwise indicated. Single antiplatelet therapy is a valuable therapeutic option [Colli A, 2015].

☐ Home	☑ Hospital	☐ Outpatient
☐ Accident and Emergency	☐ Other:	

Roll out in Italy

The manufacturer stated that more than 700 procedures have been performed worldwide using NeoChord DS1000 and about 320 of them have been performed in Italy across 19 hospitals, 11 of which were public and 8 private. Searches on the "Flusso Consumi - NSIS", a database held by the Italian Ministry of Health to register all the acquisition procedures in public hospitals involving medical devices, showed that for the RDM/BM code 980246 (i.e., NeoChord DS1000), 51 units were acquired in 2014, 60 units in 2015, and 56 in 2016.

☐ Pre-marketing	☐ On the market for 1-6 months	☐ On the market for 7-12 months
☑ On the market for more than 12 months	☐ Not identified	

Comparators

Traditional and minimally-invasive surgical interventions for mitral valve repair involving artificial chordae implantation are the main comparators of the NeoChord DS1000.

Effectiveness and safety

Given that the technology was assessed during EUnetHTA Joint Action 2, within the Work Package 5-B 5th Pilot on *"Transcatheter implantable devices for mitral valve repair in adults with chronic mitral valve regurgitation"* [EUnetHTA JA2 Pilot SB-15] authored by Agenas in 2015, the authoring team agreed to update searches previously performed. Time frame for the searches was defined as 16th May 2015 to 13th September 2017. An update was performed on 13th November 2017.
Searches were performed on PubMed, EMBASE and the Cochrane Library looking for studies, in English or Italian, reporting on the effectiveness and safety of NeoChord DS1000. Searches were limited to humans.
A list of 90 records was initially identified by database searches and manufacturer enquiry. After screening by title and abstract, no secondary or comparative studies on the use of NeoChord DS1000 were identified. Records were then screened to identify non-comparative primary studies. A total of 85 records were excluded as published before the time frame or were already included in 2015 review or presented a single case report or being narrative review of different approaches. Five records were considered eligible for inclusion and retrieved in full-text. Only 1 full-text study [Colli A, 2016a] was finally included since the remaining 4 records were conference abstracts (no full-text) [Colli A, 2016b; Colli A, 2016c; Colli A, 2016d; Colli A, 2017] (Figure 1). Given the paucity of available evidence, the authoring team decided to present the included study within the text and in Table 1 and to present the 4 conference abstracts within the text only.

The study by Colli et al. [Colli A, 2016a] is an observational non-comparative prospective study performed within a single centre in Italy. Between November 2013 and December 2014, all patients referred with severe MR were screened with 2D/3D TEE to assess eligibility for transapical off-pump mitral valve intervention with NeoChord DS1000. Among the 111 MR referred patients, 96 (86%) presented primary MR and among these, 49 (51%) were treated with NeoChord DS1000 and represented the cohort observed in the study. Follow-up visits were performed at discharge and at 3 months. All 49 patients had severe MR (3+ or 4+) and most of them were symptomatic under medical treatment. Posterior mitral leaflet (PML) disease was present in 44 (89.8%) patients, while 4 (8.2%) presented an anterior mitral leaflet (AML) disease, and 1 (2%) a combined disease.

- ***Clinical effectiveness***

  Acute procedural success, defined as implantation of at least 3 neochords with residual MR ≤ 2+, was

achieved in all 49 (100%) patients. Up to 6 neochords were implanted during a single procedure with most of the patients (40.8%) receiving 4 neochords.

At discharge (n=49), the residual MR ≤ 2+ (primary efficacy outcome) was 96% (47). A total of 22 patients (45%) presented no residual MR, 14 (28.6%) mild MR (grade 1+) and 11 (22.4%) moderate MR (grade 2+). Two patients (4.1%) presented a 3+ residual MR at discharge.

At 3 months (n=48), MR was absent in 16 patients (33.4%), mild MR (grade 1+) in 15 patients (31.2%), moderate MR (grade 2+) in 12 patients (25%). Two patients (4.1%) presented a recurrence of MR > 2+ after 30 days due to AML chordal rupture and were finally treated with conventional mitral valve replacement.

Significant improvement in NYHA functional class was observed at discharge and at 3 months (n=48) with 41 (85.4%) patients in NYHA Class I, 2 (4.1%) in NYHA II and 5 (10.4%) in NYHA III.

The rate of re-intervention for NeoChord procedure failure at 3 months follow-up was 8.2% (4/49).

The authors of the study presented also a sub-groups analysis based on anatomical characteristics determined during the preoperative assessment, and identified 3 anatomical types: 10 (20.4%) patients were classified as Type A (flail/prolapse limited to P2 segment), 26 (53.1%) were Type B (multi-segment disease involving P1–P2 or P2–P3 or P1–P2–P3), and 13 (26.5%) were Type C (anterior leaflet disease, bileaflet disease, pericommissural disease or presence of calcifications of the annulus or leaflet). Type A was associated to the highest technical success rate of the NeoChord procedure (100%), followed by Type B (96%), and Type C (83%).

- ***Safety***

  Intra- and perioperative complications were 1 (2%) ventricular fibrillation, 1 (2%) cardio-pulmonary bypass, and 4 (8.2%) cases of bleeding requiring more than 2 blood units.

  Major adverse events (AE) were represented by 1 (2%) death due to sudden cardiac arrest for right ventricular dysfunction, 1 (2%) acute myocardial infarction due to the occlusion of a diagonal branch with the apical purse string and 1 (2%) septicaemia.

  The most common minor AE included acute renal failure, which occurred in 4 patients (8.2%) with 1 (2%) required continuous veno-venous hemofiltration treatment and new onset of persistent atrial fibrillation, which occurred in 20 (40.8%) patients.

The authors concluded that, although safety profile and clinical success among the treated patients were good, the limitations of the study which were related to the single-centre experience, the limited number of patients and limited follow-up time, and stated that no definitive conclusions can be drawn regarding the long-term durability of this new procedure.

Conference abstracts

Among the 4 identified conference abstracts, 1 abstract [Colli A, 2016c] presented results from a European observational registry and 1 abstract [Colli A, 2017] presented a 2-years follow-up of the cohort treated within the Italian centre mentioned in Colli et al. 2016 [Colli A, 2016a]. Since the remaining 2 abstracts [Colli A, 2016b; Colli A, 2016d] presented earlier follow-up of the same Italian cohort, they will not be discussed further.

The abstract by Colli et al. 2016 [Colli A, 2016c] presented results for 158 patients with severe MR due to flail/prolapse of PML treated across several centres in Europe between February 2013 and May 2016. Patients were divided in 2 groups according anatomical characteristics of the mitral valve: 56 (35%) had isolated central segment (ICS) disease while 102 (65%) had multisegment (MS) disease.

At 30 days, MR ≤ moderate was present in 148 (95%) in the overall population, 55 (98.3%) in ICS group and 92 (92%) in MS group.

One-year follow-up was completed for 87 (55%) patients. Overall 1-year survival was 99.4±0.6%. Freedom from MR > moderate was 90.6±2.6% for overall population, 97.3±2.7% for ICS group and 85.9±3.8% for MS group (p = 0.027). At one year, freedom from re-intervention was 95.8±1.9% for overall population, 100% for ICS group and 93.8±2.7% for MS group (p = 0.122). Primary endpoint (defined as composite of procedural success, freedom from mortality/stroke/re-intervention/recurrence of MR>moderate/rehospitalisation and decrease of at least 1 NYHA class) was 88.8±2.9% for the overall population, 96.6±3.4% for ICS group and

85.1±3.8% for MS group (p = 0.032).

The abstract by Colli et al. 2017 [Colli A, 2017] presented results for 152 patients with severe MR due to flail/prolapse of mitral leaflet treated within an Italian centre between November 2013 and May 2017.
Patients were divided in 4 groups according anatomical characteristics of the mitral valve: 65 (42.8%) patients in Type A (isolated P2 prolapse); 61 (40.1%) in Type B (posterior multisegment involvement); 14 (9.2%) in Type C (anterior leaflet); 12 (7.9%) in Type D (bileaflet para-commissural disease, leaflet/annular calcifications).
At 30 days' follow-up, MR ≤ moderate was present in 136 (96.5%) in the overall population, 63 (100%) in Type A, 51 (94.4%) in Type B, 12 (85.7%) in Type C, and 10 (100%) in Type D.
Two-year follow-up was completed for 64 (42%) patients. Overall 2-years survival was 98.6±1%.
Patient success (defined as freedom from recurrence of MR>moderate/mortality/stroke/re-intervention and re-hospitalisation and 30-days) was 84.1±3.4% for the overall population, 96±2.8% for type A, 82.7±5% for type B, 66.1±14.3% for type C, and 57.1±17.2% for type D (p = 0.006).

Forthcoming evidence
To identify further evidence, searches were performed on the clinicaltrial.gov database (18th September 2017) using *"chordae replacement"* and *"NeoChord"* as keywords and identified 3 clinical studies within the time frame of the present evidence update (Table 2).
One study (NCT01784055), already described within the EUnetHTA Pilot [EUnetHTA JA2 Pilot SB-15], had status update from *"recruiting"* to *"completed"* in July 2016. It is a patient registry aimed to assess procedural success at 1 day. No results were reported in the database.
One study (NCT02803957) was labelled as *"recruiting"* and planned to be completed within July 2020. It is an RCT of 585 subjects assigned to two groups: subjects with DMR undergoing artificial chordae implantation using NeoChord DS1000 *versus* subjects with primary MR undergoing standard surgical mitral valve repair (i.e., annuloplasty ring and some form of leaflet repair or artificial chordae). The study aims to assess major AE at 1 day and grade of MR, mitral valve replacement or mitral valve re-intervention at 1 year.
One study (NCT02829749) was labelled as *"not yet recruiting"* and planned to be completed within December 2019. It is a RCT of 194 subjects assigned to two groups: NeoChord implantation *versus* traditional mitral valve repair performed under cardiac arrest. The study aims to assess several outcomes at 1 year, including incidence of death, re-intervention, grade of MR, and change in functional status.

Potential benefits to patients

The NeoChord procedure aims to reduce MR severity and improve NYHA class for the treated patients. These improvements would have a relevant impact on other outcomes related to the quality of life.

☑ Mortality reduction or increased survival	☑ Reduction of the morbidity	☑ Improved quality of life (patient/users)
☐ Improved patient monitoring	☐ Other:	☐ Not identified

Cost of the technology/procedure

We searched bibliographic databases (Pubmed, Embase and Cochrane Library) to find economic evaluations and cost analyses on the NeoChord DS1000 or the related procedure. The searched yielded 63 studies but none was an economic or cost analysis on NeoChord DS1000. According to the manufacturer, the list price of

NeoChord DS1000 is 18,000 Euros. As stated by manufacturer, training is provided free of charge to the investigators and funded by NeoChord Inc. and the local distributor.

☐ Increased costs compared to alternative treatments	☐ Increased costs due to increased demand	☐ Increased costs due to the required investments
☑ New costs	☐ Other:	☐ Not identified

Potential structural and organisational impact

Structural impact

In addition to the standard equipment used for lateral thoracotomy, as anaesthesia and procedural patient monitoring, the NeoChord DS1000 procedure requires the use of trans-esophageal echocardiography (TEE). Even if the procedure does not require it, stand-by cardiopulmonary bypass should be ensured in case of need, so the related equipment should be available [Colli A, 2015].

☑ Increase in requirement of instruments	☐ Always be used	☑ Can be used only under specific circumstances
☐ Decrease in requirement of instruments	☐ Other:	☐ Not identified

Organisational impact

Transapical implantation of artificial chordate with NeoChord DS1000 does not require structural changes to the dynamics of the operating room or cardiac surgery team [Colli A, 2015]. In fact, according the manufacturer, NeoChord DS1000 procedure requires a cardiac surgeon/interventional cardiologist, an echocardiographer for TEE guidance of the procedure, and nurses. The NeoChord DS1000 should be used in accordance with the necessary safety precautions appropriate to a thoracic device implantation procedure. To allow cardiopulmonary bypass in case of need, a perfusionist should be available. Use of the NeoChord DS1000 should be limited to physicians that have received training on the use of the device and requires a minimum of one trained physician/operator and one trained member of the operating room staff.

☐ Increase in the number of procedures	☐ Re-organisation required	☑ Training required for users
☐ Reduction in the number of procedures	☐ Other:	☐ Not identified

Conclusions

The NeoChord DS1000 device, indicated for use in patients with severe (grade 3+ or 4+) MR who are candidates for surgical mitral valve repair or replacement, is currently in use in Europe and in some Italian

centres. Available evidence, already assessed in 2015 within the EUnetHTA Joint Action 2, remains extremely limited and does not allow us to reach final conclusions on effectiveness and safety of the technology. As of today, no comparative studies are available to support the use of this technology. Only an additional study was identified which was non-comparative in design, small in sample size (49 patients), and very short in follow-up (3 months). The authors of such study claimed positive results in terms of procedural success (cautionary defined as residual MR ≤2+), reduction of MR severity, improvement in NYHA class, and observed procedural complications and adverse events. However, generalizability appears to be very low. Since available studies were non-comparative in design, no conclusions can be drawn on the relative effectiveness and safety of the procedure in relation to the available alternatives. Long-term durability of the implanted artificial chordae, which plays a critical role for the success of the procedure, has not been assessed yet. Results presented at international conferences referred to follow-up extended up to 2 years but only for a small group of patients (64 patients treated within a single centre). The most active group in using this technology is currently studying the relation between anatomical characteristics of the mitral valve disease and procedural and clinical success. Further analyses will probably help in defining patients for whom the procedure has the highest benefit. Concomitant interventions (e.g., annuloplasty) could be considered as well.
Results from ongoing studies (NCT02803957 and NCT02829749), which should be completed between 2019 and 2020, given their randomised design may allow a better understanding of the role of the technology. However, such results should be assessed carefully considering the short follow-up (1 year) and the risk of reporting bias for the incidence of adverse events. Effects of a learning curve should also be studies. Once comparative evidence is available, prospective data from all treated patients should be collected in a registry.

Future prospects

A competitor device could enter the market in the very near future. The US-based Harpoon Medical, Inc. is developing a device, identified as Harpoon Medical TSD-5, able to perform mitral valve repair by implantation of artificial chordae during a minimally invasive procedure. The company signed an agreement with Edwards Lifesciences, Inc. for the funding of the initial clinical study which should lead to the approval in Europe (TRACER, NCT02768870). On December 2017 Edwards acquired the company [Edwards website]. The approval of Harpoon Medical's device is expected in the very near future while results from the study on 30 patients are supposed to be available by April 2019 [Harpoon Medical website].

Table 1: Summary of the included studies on NeoChord DS1000.

Ref. (country) [study design]	Objective	Patients' characteristics	Follow-up	Effectiveness outcomes (as reported in the study)	Safety outcomes (as reported in the study)	Conflict of interest
Colli A, 2016a (Italy) [Case series]	To evaluate clinical outcomes of the TOP-MINI procedure in the early postoperative period.	49 patients with severe MR (3+ or 4+) • 44 patients (89.8%) with PML disease; • 4 (8.2%) with AML disease; • 1 (2%) with a combined disease. Median age: 72 (IQR 58–78)	3 months	**Acute procedure success rate*:** All 49 patients (100%). **Residual MR ≤ 2+** ***At discharge (n=49):*** 0+ = 22 (44.9%) 1+ = 14 (28.6%) 2+ = 11 (22.4%) 3+ = 2 (4.1%) ***At 3 months (n=48):*** 0+ = 16 (33.4%) 1+ = 15 (31.2%) 2+ = 12 (25%) 3+ = 5 (10.4%) **NYHA class improvement** ***At discharge (n=49):*** I = 47 (95.9%) II = 1 (2%) III = 1 (2%) ***At 3 months (n=48):*** I = 41 (85.4%) II = 2 (4.1%) III = 5 (10.4%) **Reoperation for Neochord failure (at 3 mo.) = 4/48 (8.2%)** 1 (2%) = New NeoChord implant. 3 (6.1%) = MV replacement	**In-hospital mortality:** 1 patient (2%). **Perioperative complications:** Ventricular fibrillation = 1 (2%) CPB/ECMO = 1 (2%) Bleeding** = 4 (8.2%) **Major and minor AEs:** Death = 1 (2%) AMI = 1 (2%) Septicaemia = 1 (2%) Severe PE = 3 (6.1%) Deep wound dehiscence = 1 (2%) ARF = 4 (8.2%) ARF needing CVVH = 1 (2%) New onset PAF = 20 (40.8%) New onset permanent AF = 3 (6.1%)	The authors report no relationships that could be construed as a conflict of interest. Some received travel grants from NeoChord Inc.

* Defined as successful placement of at least 3 neochords with reduction of residual MR to less than 2+.
** Requiring ≥2 blood units.

Key: TOP-MINI = Transapical Off-Pump Mitral valve Intervention with Neochord Implantation; MR = mitral regurgitation; PML = posterior leaflet; AML = anterior leaflet; IQR = interquartile range; NYHA = New York Heart Association; CPB = Cardio-pulmonary bypass; ECMO = Extracorporeal membrane oxygenation; AMI = acute myocardial infarction; PE = pericardial effusion; CVVH = continuous veno-venous hemofiltration; PAF = persistent atrial fibrillation; AF = atrial fibrillation; MV = mitral valve.

Table 2: Summary of the registered studies on NeoChord DS1000 identified on clinicaltrials.gov.

NCT number	Study type and design	Purpose	Comparisons	Number enrolled	Start and completion	Endpoints	Sponsor(s)
COMPLETED							
NCT01784055 TACT Registry	Observational* Cohort Prospective	*"To monitor the long-term performance of the CE Marked NeoChord Artificial Chordae Delivery System."*	NA	126	Jan-2013 Jul-2016	• Procedure Success (at 1 day)	NeoChord, Inc.
RECRUITING							
NCT02803957 ReChord	Interventional Randomized Parallel Assignment Open Label	*"To assess the safety and effectiveness of the study device in subjects with degenerative mitral valve disease receiving a mitral valve repair without cardiopulmonary bypass (treatment group) when compared to subjects receiving mitral valve repair using standard surgical techniques with cardiopulmonary bypass (control group)."*	***Experimental:*** Subjects with degenerative mitral valve insufficiency treated with artificial chordae implanted using the NeoChord DS1000 ***Active Comparator:*** Subjects with degenerative mitral valve insufficiency treated with standard surgical mitral valve repair (i.e., annuloplasty ring and some form of leaflet repair or artificial chordae)	585	Nov-2016 Jul-2019	• Proportion of subjects free of Major Adverse Events (MAEs) in the treatment group when compared to subjects in the control group (at 30 days). • Proportion of subjects free of Grade II, III or IV mitral regurgitation, mitral valve replacement or mitral valve reintervention in the treatment group when compared to subjects in the control group (at 1 year).	NeoChord, Inc.
NOT YET RECRUITING							
NCT02829749 MITRACHORD	Interventional Randomized Parallel Assignment Open Label	*"To assess the effectiveness and safety of the NeoChord DS1000 repair technique as compared with conventional open-heart on-pump mitral valve surgery in patients with severe primary mitral regurgitation"*	***Experimental:*** Subjects randomized to the experimental group will undergo the NeoChord implantation ***Control:*** Traditional mitral valve repair performed under cardiac arrest	194	Dec-2016 Dec-2019	***Primary*** • Combined incidence of Death from any cause, redo surgery for valve dysfunction, and moderate-severe (3+) or severe (4+) mitral regurgitation (at 1 year). ***Secondary*** • Proportion of patients with any major adverse events (at 30 days) • Overall survival (at 12 months) • Mitral valve reoperation free survival (at	Hospices Civils de Lyon

						12 months) • Mitral regurgitation > 2+ (at 12 months) • Freedom from rehospitalization for heart failure (at 12 months) • Change in functional evaluation (NYHA) (at 12 months) • Change in functional evaluation (6 minute walk test) (at 12 months) • Change in quality of life score (at 12 months) by using the EQ-5D questionnaire instrument • Number of device success (at 30 days)	

* patient registry.

Key: NA = not applicable;

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Evidence searches

Clinical effectiveness and safety

Searches of the databases were carried out on 13th September 2017 using the following strategy:

PubMed (16th May 2015 – 13th September 2017)

"Mitral Valve Insufficiency" MESH term OR [Title/Abstract] "Mitral Valve Incompetence" OR "Failed Mitral valve" OR "Mitral Regurgitation" OR "Mitral Valve Insufficiency" OR "Mitral Valve Regurgitation" OR "Mitral Valve Incompetence" OR "Mitral Insufficiency" OR "mitral valve repair" OR "Mitral Incompetence" OR "transapical chordal repair" OR "mitral valve repair" OR "transapical mitral valve repair" OR "transapical chordal replacement" OR "percutaneous chordal repair" OR "transcatheter chordal repair"	AND	(NeoChord*" AND chordal) OR neochord	AND	"Safety" MESH term OR "Comparative Effectiveness Research" MESH term OR "quality of life" MESH term OR "Return to work" MESH term OR "Patient Satisfaction" MESH term OR "Hospitalization MESH term OR "Patient discharge" MESH term OR Survival Rate MESH term OR Treatment Outcome MESH term OR "Follow-Up Studies" MESH term OR "Quality of life" MESH term [Title/Abstract] "Length of stay OR "Duration of inotropic support" OR "Exercise capacity" OR Safety OR Mortality OR Effectiveness OR "return-to-work" OR
"mitral valve" and transcatheter	AND		AND	"Back-to-Work" OR Complication* OR pain OR "Adverse events" OR "side effects" OR morbility OR survival

EMBASE (16th May 2015 – 13th September 2017)

'mitral valve repair'/exp EMTREE term OR "mitral valve disease"/exp EMTREE term OR 'mitral valve regurgitation'/exp EMTREE term OR "Mitral Valve Incompetence" OR "Failed Mitral valve" OR "Mitral Regurgitation" OR "Mitral Valve Insufficiency" OR "Mitral Valve Regurgitation" OR "Mitral Valve Incompetence" OR "Mitral Insufficiency" OR " Miitral valve repair" OR "Mitral Incompetence" OR "transapical chordal repair" OR "transapical chordal replacement" OR "percutaneous chordal repair" OR "transcatheter chordal repair"	AND	(NeoChord*" AND DS1000 AND chordal) OR neochord	AND	EMTREE TERM: 'quality of life'/exp OR EMTREE TERM:"clinical effectiveness" OR EMTREE TERM: "comparative effectiveness" OR EMTREE TERM: 'device safety'/exp OR EMTREE TERM: 'program effectiveness'/exp OR EMTREE TERM: 'program evaluation'/exp OR EMTREE TERM: 'risk assessment'/exp OR EMTREE TERM: Mortality/exp OR EMTREE TERM: "return-to-work"/exp OR EMTREE TERM: "Back-to-Work"/exp OR EMTREE TERM: 'program acceptability'/exp OR
"mitral valve" and transcatheter	AND		AND	EMTREE TERM: Safety/exp OR EMTREE TERM: 'heart failure'/exp EMTREE TERM: Ventricular Function, Left" OR EMTREE TERM:" Ventricular Dysfunction" OR "Length of stay" OR " "Exercise capacity" OR Complications OR pain OR 'device failure analysis'/exp OR Effectiveness OR "Comparative Effectiveness Research" Survival Rate OR Treatment Outcome OR "Postoperative Complications" "Adverse events" OR "side effects" OR "quality of life" OR QoL OR "Right Ventricular failure"OR survival OR morbility OR effectiveness

Cochrane Library (16th May 2015 – 13th September 2017)

"Mitral Valve Insufficiency" MESH term OR [Title/Abstract] "Mitral Valve Incompetence" : ti,ab,kw OR "Failed Mitral valve" : ti,ab,kw OR OR "Mitral Regurgitation" : ti,ab,kw OR OR "Mitral Valve Insufficiency" : ti,ab,kw OR "Mitral Valve Regurgitation" : ti,ab,kw OR "Mitral Valve Incompetence" : ti,ab,kw OR "Mitral Insufficiency" : ti,ab,kw OR " mitral valve repair" : ti,ab,kw OR "Mitral Incompetence" : ti,ab,kw OR "transapical chordal repair" : ti,ab,kw OR "transapical chordal replacement" : ti,ab,kw OR "percutaneous chordal repair" : ti,ab,kw OR "transcatheter chordal repair" : ti,ab,kw	AND	neochord	AND	MESH descriptor: Safety OR MESH descriptor: Comparative Effectiveness Research OR MESH descriptor: "quality of life" OR MESH descriptor: "Return to work" OR MESH descriptor: "Patient Satisfaction" OR MESH descriptor: "Hospitalization OR MESH descriptor:"Patient discharge" OR MESH descriptor: Survival Rate OR MESH descriptor: Treatment Outcome OR MESH descriptor: "Postoperative Complications" OR MESH descriptor: "Follow-Up Studies" OR MESH descriptor: "Heart Failure" OR MESH descriptor:"Ventricular Function, Left" OR MESH descriptor:" Ventricular Dysfunction "Length of stay " : ti,ab,kw OR "Duration of inotropic support" : ti,ab,kw OR "Exercise capacity" : ti,ab,kw OR Safety: ti,ab,kw OR Mortality: ti,ab,kw OR Effectiveness: ti,ab,kw OR "return-to-work" " : ti,ab,kw OR "Back-to-Work" " : ti,ab,kw OR Complication: ti,ab,kw OR Complications: ti,ab,kw OR pain: ti,ab,kw OR "Adverse events" : ti,ab,kw OR "side effects" : ti,ab,kw OR morbility" : ti,ab,kw OR survival : ti,ab,kw OR morbility: ti,ab,kw OR effectiveness : ti,ab,kw
"mitral valve" and transcatheter" : ti,ab,kw				

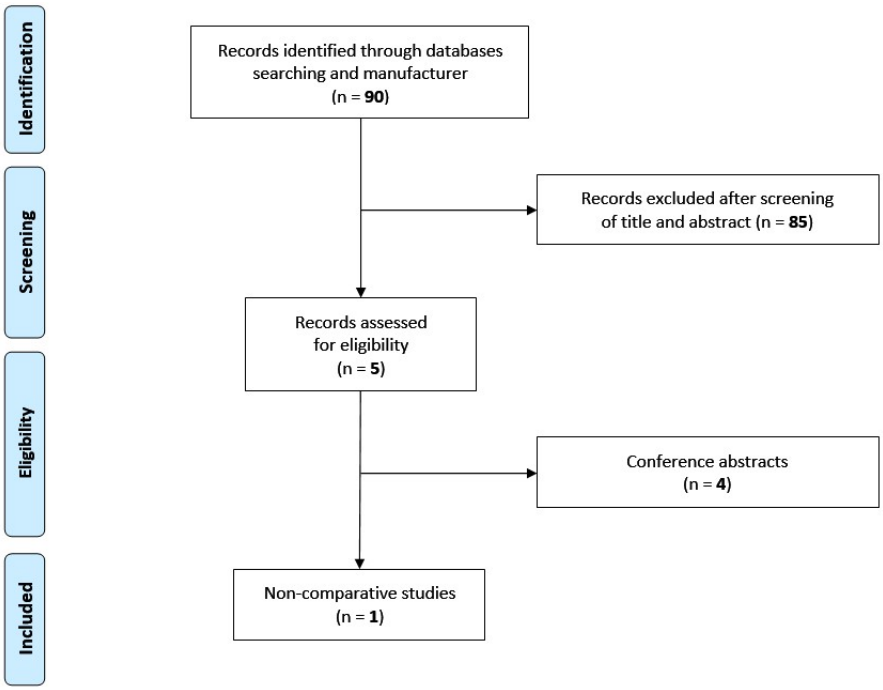
Economic studies

Searches of the databases were carried out on 21st September 2017 using the following keywords to indicate:

- ***the technology:*** *Neochord; Neochord* and chordal.*
- ***the pathology:*** *transapical mitral valve repair"; "transapical chordal repair"; "transapical chordal replacement".*
- ***the study design:*** *Costs and cost analysis"; "Health Care Economics and Organizations"; "Economics, Medical"; Cost* OR cost-analysis; "Health care costs"; Cost-effectiveness OR "cost effectiveness analysis" OR CEA; Cost-utility OR "cost utility analysis" OR CUA; Cost-minimization OR "cost minimization analysis" OR CMA; Cost-benefit OR "cost benefit analysis" OR CBA.*

Flow-chart of studies

Figure 1: Flow-chart of studies on NeoChord DS1000 according to PRISMA (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097. www.prisma-statement.org).



Glossary

AML: anterior mitral leaflet.

CE: Conformité Européen.

CND: Classificazione Nazionale dei Dispositivi Medici.

ePTFE: expanded polytetrafluoroethylene.

EU: European Union.

FDA: Food and Drug Administration.

HF: heart failure.

ICS: isolated central segment.

IDE: investigational device exemption.

LCV: leaflet capture verification.

MR: mitral regurgitation.

MS: multisegment.

NYHA: New York Heart Association.

PML: posterior mitral leaflet.

RCT: randomised controlled trial.

RDM: Italian National medical device database (RDM) (http://www.salute.gov.it/dispositivi/paginainternasf.jsp?id=499&menu=repertorio).

TEE: trans-esophageal echocardiography.